Machine Learning Prediction of Pre-Clinical Drug Induced QT Prolongation Liability and Pathway Analysis

BY

DENNIS MICHAEL BERGAU
B.S., Northeastern University, Boston, 1991
M.A., Boston University, Boston, 1993

THESIS
Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Bioengineering
in the Graduate College of the
University of Illinois at Chicago, 2018

Chicago, Illinois

Defense Committee:
Hui Lu, Ph.D., Chair and Advisor
Yang Dai, Ph.D., University of Illinois-Chicago Bioengineering
Richard Magin, Ph.D., University of Illinois-Chicago Bioengineering
Beata Wolska, Ph.D., University of Illinois-Chicago Physiology in Medicne
Jack Clifton, MD, Abbvie
Gary Gintant, Ph.D., Abbvie

ii

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF TABLES (continued)

LIST OF TABLES (continued)

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

LIST OF ABBREVIATIONS

Term	**Definition**
ACh	Acetylcholine
ADME	Absorption, Distribution, Metabolism, and Excretion
ANS	Autonomic nervous system
AP	Action potential
AV	Atriaoventricular
AVN	Atrioventricular node
cAMP	Cyclic adenosine monophosphate
CiPA	Comprehensive *in vitro* Proarrhythmia Assay
cLQTS	Contenital Long QT Syndrome
CNS	Central nervous system
CPI	Critical Path Initiative
DE	Differentially expressed
diLQTS	Drug induced Long QT Syndrome
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EKG	Electrokardiogramm
Epi	Epinephrine
FDA	Food and Drug Administration
GPCR	G protein coupled receptor
GWAS	Genome Wide Association Study
hERG	Human ether-a-go-go
HRV	Heart rate variability

LQTS	Long QT Syndrome
MAPK	Mitogen activated protein kinase
MCC	Matthews Correlation Coefficient
mV	Millivolt
NCBI	National Center for Biotechnology Information
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NE	Norepinephrine
OMIM	Online Mendelian Inheritance in Man
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
SA	Sinoatrial
SAN	Sinoatrial Node
SMOTE	Synthetic Minority Oversampling Technique
SNP	Single Nucleotide Polymorphism
SVM	Support Vector Machine
TdP	Torsade de Pointes
TQT	Thourough QT

SUMMARY

Prolongation of ventricular repolarization in the heart is widely accepted as a biomarker for potentially life-threatening cardiac arrhythmias; however, it is also widely accepted to be an imperfect biomarker. Current pre-clinical cardiac safety evaluations during the drug development process rely on patch clamping experiments and animal testing to assess ion channel activity. The Comprehensive *in Vitro* Proarrhythmia Assay (CiPA) initiative is a somewhat recent collaboration between industry, regulatory agencies, and academia to improve cardiac safety assessments during drug discovery and development. The current direction suggestion from the CiPA initiative is to look beyond single ion channel assays to include ion channels not previously studied, gene expression changes, and *in silico* modeling.

This investigation used machine learning techniques to predict drug-induced ventricular repolarization delays and explore gene expression changes based on drug-treated rat liver RNA expression microarray data from the GEO Datasets collection. The intended goal was not to replace the existing paradigms, but rather to use machine learning results to augment the current patch clamp experiments and whole animal experiments used in pre-clinical cardiac safety assessments since each has their respective strengths and weaknesses.

Supervised machine learning in the form of Support Vector Machine (SVM) classifiers using rat liver RNA microarray data from drugs known to prolong the QT interval versus those that do not, and 76 additional sub-classifications showed improved sensitivity and specificity ranges compared to recently reported patch clamp sensitivities and specificities.

Unsupervised machine learning in the form of clustering based on expression profile similarities in each of the 77 classifications showed that while drugs known to prolong QT interval do not always cluster into "pure" groups, the number of groups was limited. Clustering results help to support the

classifier predictions and may also serve as an alternative method to predict ventricular repolarization

delays based on gene expression similarities.

An association between gene expression profiles and ventricular repolarization does not

necessarily imply a causal relationship; however, an attempt was made to link physiological phenomena

using genes associated with congenital Long QT Syndrome, genes associated with autonomic activity,

and drug-induced gene expression changes using the most significantly differentially expressed probes

in each of the 77 classes. The most common network connections involved changes in fatty acid

metabolism, associations with G proteins, associations with glutathione, immune responses and

apoptosis, mitochondrial activity and electron transport, and mitogen activated protein kinases

(MAPKs).

These results of this project suggest that machine learning of gene expression profiles to predict

QT liability may be used as a surrogate biomarker to augment the current paradigm of testing ion

channel activities as part of the pre-clinical safety assessment of drugs during drug discovery and

development. Further investigation based on these findings may help to elucidate previously

undescribed gene expression changes that may contribute to ventricular repolarization delays which

may in turn help to support the safety of a particular drug, or to confirm a drug having the potential for

higher risk.

CHAPTER 1: INTRODUCTION

<u>Section 1.1: Background</u>

When reviewing an electrocardiogram (ECG), the QT interval represents electrical depolarization and repolarization of the ventricles of the heart. A QT interval of greater than 500 milliseconds (msec) is widely accepted as a biomarker for the potential of ventricular tachyarrhythmias such as Torsade de Pointes (TdP), and is considered to be a risk factor for sudden death [1,2] although the QT interval is also acknowledged to be an imperfect biomarker [3]. TdP in some cases may degenerate into ventricular fibrillation, which is sometimes colloquially referred to as a "heart attack". Visually, a heart in ventricular fibrillation looks similar to shaking a bowl of gelatin. In more scientific terms, the usual directed electrical depolarization sequence is replaced by random, non-sequential depolarization and repolarization, and the coordinated muscle contractions that would normally pump blood throughout the body no longer occur and blood flow stops. Without oxygen being delivered to the brain by circulating blood, the brain tissue begins to die after approximately 5-6 minutes.

The duration of the QT interval can be influenced by several factors, one of which may be broadly categorized as gene mutations. The Online Mendeilan Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/omim) database describes 15 different types of congenital Long QT Syndromes (cLQTS) associated with a total of 16 different genes, all of which are summarized in Table I. The prevalence of cLQTS in the United States is 1:7000 causing 2000-3000 sudden deaths in children and young adults annually [4]. The administration of drugs known to prolong the QT interval to individuals with cLQTS is generally avoided or the patient is closely monitored clinically.

Secondly, there is increasing evidence that QT interval prolongation is a heritable trait in healthy individuals [5,6], and genetic variants may be important for predisposing individuals to a higher risk from drugs that cause QT prolongation. These genetic variants in total explain more of the QT variation (except heart rate) than any other factor including gender, which is also a predisposing factor [6].

Table I: Types of Congenital Long QT Syndrome and Associated Genes, Proteins, and Online Mendelian Inheritance in Man (OMIM) Links

cLQT Type	Gene Symbol	Protein Name	OMIM Link
LQTS Type 1	KCNQ1	KQT-like voltage-gated potassium channel-1	http://omim.org/entry/192500
LQTS Type 2	KCNH2	Potassium voltage-gated channel subfamily H member 2	http://omim.org/entry/613688
LQTS Type 2	ALG10	Putative Dol-P-Glc: Glc(2)Man(9) GlcNAc(2)-PP-Dol alpha-1,2-glucosyltransferase	http://omim.org/entry/613688
LQTS Type 3	SCN5A	Sodium channel protein type 5 subunit alpha	http://omim.org/entry/603830
LQTS Type 4	ANK2	Ankyrin-2	http://omim.org/entry/600919
LQTS Type 5	KCNE1	Potassium voltage-gated channel subfamily E member 1	http://omim.org/entry/613695
LQTS Type 6	KCNE2	Potassium voltage-gated channel subfamily E member 2	http://omim.org/entry/613693
LQTS Type 7	KCNJ2	Inward rectifier potassium channel 2	http://omim.org/entry/170390
LQTS Type 8	CACNA1C	Voltage-dependent L-type calcium channel subunit alpha-1C	http://omim.org/entry/601005
LQTS Type 9	CAV3	Caveolin-3	http://omim.org/entry/611818
LQTS Type 10	SCN4B	Sodium channel subunit beta-4	http://omim.org/entry/611819
LQTS Type 11	AKAP9	A-kinase anchor protein 9	http://omim.org/entry/611820
LQTS Type 12	SNT1	Alpha-1-syntrophin	http://omim.org/entry/612955
LQTS Type 13	KCNJ5	G protein-activated inward rectifier potassium channel 4	http://omim.org/entry/613485
LQTS Type 14	CALM1	Calmodulin	http://omim.org/entry/616247
LQTS Type 15	CALM2	Calmodulin 2 (phosphorylase kinase, delta)	http://omim.org/entry/616249

However, these same patients are likely to have normal ECG morphology and normal or near normal QT interval off the drug making identification of this group difficult without exposing them to a particular drug [1].

Thirdly, a November 2014 estimate from the Tufts University Center for the Study of Drug Development (http://csdd.tufts.edu) claims the cost to develop a new drug is between $1.7 - 2.6 billion dollars and the time required to bring a new drug to market is approximately 10-15 years.

During the drug development process, assessment of the QT interval is an important safety

consideration which can influence the decision to either continue with development or discontinue

development. Careful decision making during drug development is essential to avoid costly failures [7]

and better tools are necessary to streamline the analysis of large volumes of data to expedite the

decision making process. The US Food and Drug Administration (FDA) recognized this, and in 2004

launched the Critical Path Initiative (CPI) as a strategy to drive innovation in the scientific processes

through which medical products are developed, evaluated, and manufactured [8]. As new data

sources and computing power continue to grow, the potential for a more granular understanding of

how pharmaceuticals impact genetic expression becomes possible. An improved understanding of

gene expression and associated molecular mechanisms can lead to a reduction in time and cost to

bring a drug to market, and can help with novel drug target identification.

In the absence of having a genetic predisposition, prolongation of the QT interval may also be

drug-induced (diLQTS) with the administration of particular drugs being contraindicated in certain

clinical conditions. An undesirable property commonly referred to as a "side effect" or "off-target effect"

of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization which is thought to

produce an electrophysiological environment that increases the chance of developing TdP. Assessment

of QT prolongation liability in humans is a necessary part of the drug development process described in

the *International Conference on Harmonisation of Technical Requirements for Registration of*

Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline E14 (ICH E14) [3]. In cases of

positive QT prolongation findings for a drug with a favorable overall risk/benefit profile, the label of a

marketed drug must disclose a finding of significant QT prolongation. In other cases, QT prolongation

may completely stop development of a new drug, or may be the basis for market removal for previously

approved drugs.

Many anti-arrhythmic drugs target the action of ion channels in they myocardium. Titrated antagonism of one or more ion channels may produce a beneficial clinical condition which prevents arrhythmias, while enough of the channels in the plasma membrane remain unblocked and active to still allow the required basic functionality. Different chemical compounds have different effects on ion channels, hence the need for dosing levels and dosing frequencies. Metabolism of many compounds occurs in the liver, which contributes to the removal of the pharmaceutical products from the body.

Some non-antiarrhythmic drugs may have an undesirable property of being able to delay cardiac repolarization. Delayed repolarization of cardiomyocites is thought to produce an electrophysiological environment wich increases the likelihood of developing a potentially lethal arrhythmia called Torsade de Pointes (TdP). The antihistamine terfenadine (Seldane) is an example of a non-antiarrhythmic drug that was removed from the commercial market in the United States because of the associated QT prolongation risk due to potassium channel blockade and association with TdP. Terfenadine (Seldane), was a commonly prescribed antihistamine. To increase the efficacy, ketoconazole, an inhibitor of CYP3A4 (an enzyme which breaks down many drugs in the liver) was co-administered therapeutically. It was found that there were low levels of terfenadine's metabolite, fexofenadine. Terfenadine was found to be a potent blocker of the potassium (hERG) channel and it was eventually removed from the US market and replaced by its metabolite, fexofenadine (Allegra) which does not have clinically relevant K^+ channel blocking properties and was thus found to be a safer alternative. A summary of the terfenadine case study is as follows:

1981: Marketed in Europe - Overdoses linked to cardiotoxicity, which was thought to be idiosyncratic at the time.
1985: US FDA Approval, despite case reports of syncope with overdose.
1990: Case report of rare arrhythmia (TdP) when terfenadine (metabolized by CYP3A4) was co-administered with ketoconazole (CYP3A4 inhibitor). High buildup of parent drug, low concentrations of metabolite found:
- Labeling change to include drug interaction warnings.
- "Safe and effective when used properly".

1992: 10th most prescribed medication in US - 83 serious cardiovascular events.
July 1992 FDA proposed a Black Box warning. Prescriptions & use continued.

Jan 1997 – Market removal proposed.
February 1998 – Withdrawn from United States market.

Lastly, not all conditions associated with QT prolongation involve pharmaceuticals or obvious

channelopathies. In addition to the scenarios described above, QT prolongation may be associated with

diurnal variations, increasing age, female gender, hyperthyroidism, hypokalemia, hypomagnesimia,

hypocalcemia [1], diabetes [9], and changes in autonomic tone [10]. Prolongation of the QT interval is

also common in cirrhosis of the liver, with a prevalence that exceeds 60% in patients with an advanced

disease [11]. Similar to individuals having cLQTS, individuals having advanced cirrhosis are often advised

to avoid using drugs known to prolong the QT interval, or be closely monitored clinically. The

pathophysiology of QT prolongation in cirrhosis has not been identified [11,12].

Considerations beyond ion channels reinforce the need for a better understanding of biological

pathways which may at least in part be explained and driven by changes in gene expression. The

healthy rat liver tissue used in this investigation may help to lay the groundwork for future studies

comparing a rat model with advanced cirrhosis and potentially a better understanding of the link

between cirrhosis and QT prolongation.

Regarding the mechanism of diLQTS, almost all drugs that have been associated with QT

prolongation block the rapid component of the delayed rectifier potassium channel (I_{Kr}) encoded by the

human ether-a-go-go related gene (hERG, or KCNH2). However, it still remains unclear why certain

drugs that are potent blockers of I_{Kr} and cause QT prolongation, rarely cause TdP such as amiodarone

[1]. Shi, et al. [13] demonstrated a gene expression profile similarity between amiodarone

administration and hypothyroidism in rats which suggests that gene expression changes associated with

drug administration may mimic physiological conditions. Verapamil is an example of a drug which blocks

the hERG channel, but more strongly blocks calcium, which is associated with the plateau phase of the

cardiac action potential, and has a low risk for TdP [14].

Pre-clinical evaluations occur before and during clinical testing of drugs, including tests described in the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use, S7B, The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (ICH S7B) [15]. diLQTS is known to occur in rats, although as stated in ICH S7B, it is known to be mechanistically different from humans and thus not a recommended model for electrophysiological safety testing.

Patch clamp hERG channel assays are routinely conducted as part of pre-clinical safety assessments during drug development. Babcock [16] described clustering methods for drugs that prolong the QT interval with other drugs based on gene expression in three cancer cell lines (breast cancer, prostate cancer, and leukemia); however, the focus was on an association with patch clamp results from only the hERG channel, which is encoded by the gene KCNH2. diLQTS is known to occur in rats, although due to differences in ion channel activities between rat and human cardiomyocytes, *in vivo* testing of drugs in rats also has limitations. Until 2014, the primary focus of QT prolongation assessments was on the potassium rectifier current associated with the human ether-a-go-go (hERG) channel, encoded by KCNH2. The 2013 Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative (http://cipaproject.org/) expanded the focus to other ion channels and other physiological factors such as membrane capacitance and ion concentrations, with a blended approach of *in vitro* and *in silico* assessments to predict QT liability. In 2016, Gintant [17] described the evolution of preclinical safety assessments in the CiPA initiative which proposes the inclusion of patch clamp assessments for other ion channels, and the addition of *in silico* ion channel modeling. At the time of this writing, analysis of an association between epigenetic changes and the administration of a chemical entity on the QT interval as a predictive biomarker has not been proposed in the literature.

A drug-induced decrease in expression of the KCNH2 gene may also be associated with prolongation of the QT interval [17], with pentamidine being one such example. Fewer ion channel

openings in the plasma membrane mean that fewer K$^+$ ions can diffuse out of the cytoplasm, thereby prolonging the time required for repolarization. While gene expression changes associated with a prolongation of the QT interval may not always be directly responsible for QT prolongation, an association between gene expression profiles and QT prolongation might be identified which could potentially be used for predictive purposes to augment existing pre-clinical assessments of QT prolongation liability, and perhaps propose starting points for studies to enhance our understanding of underlying mechanisms.

Many anti-arrhythmic drugs target the action of ion channels in the myocardium, so an effect such as a titrated antagonism may produce a desirable effect to prevent arrhythmias but enough of the channels remain unblocked to still allow the required basic functionality. Hence the need for dosing levels, and dosing frequency as organs such as the liver break down, and contribute to the removal of the pharmaceutical products from the body.

Section 1.2: Pharmaceutical Development Considerations

The drug development process may be described as having three stages, as depicted in Figure 1. Stage 1 is the drug discovery process where drugs are designed to chemically address a physiological condition. Stage 2 is pre-clinical development, where in vitro and in vivo testing in animal models takes place. Stage 3 is clinical development where testing in humans takes place. Phase 3 is further subdivided into 5 phases. Phase 0 evaluates the effect on the human body by administering a single, sub-therapeutic dose in small numbers of subjects (approximately 10-15). Phase 0 studies may also be called "microdosing" studies because their purpose is to determine if the body responds as expected to a very low level of exposure to the drug. Phase 1 Studies are often called "first in human" studies and typically involve roughly 20-100 subjects, and the study may last for several days, weeks or months. The purpose of Phase 1 trials is to verify safety in humans and to determine safe dose ranges. Some studies use "healthy" subjects (i.e. those without any major underlying condition), while others, such as in an

oncology setting, may use subjects with a particular target condition because the drug or drug combination may be toxic, thus it would be unethical to administer the treatment to a subject without the targeted condition. Phase 2 studies are designed to test how effective the drug is in treating a particular condition. These studies are conducted in up to several hundred subjects, all of whom have the targeted condition, and these studies typically last on the order of several months to approximately 2 years. Phase 3 studies are also designed to test efficacy and any potential side effects in a larger population which typically ranges from 300-3000 subjects and typically last for approximately 1-4 years. Phase 4 studies are meant to study the safety and efficacy of the drug in populations of several thousand people for durations of 2 years or longer after the drug has been granted permission by regulatory agencies to be sold. For this reason, Phase 4 studies are sometimes referred to as "post-market" studies.
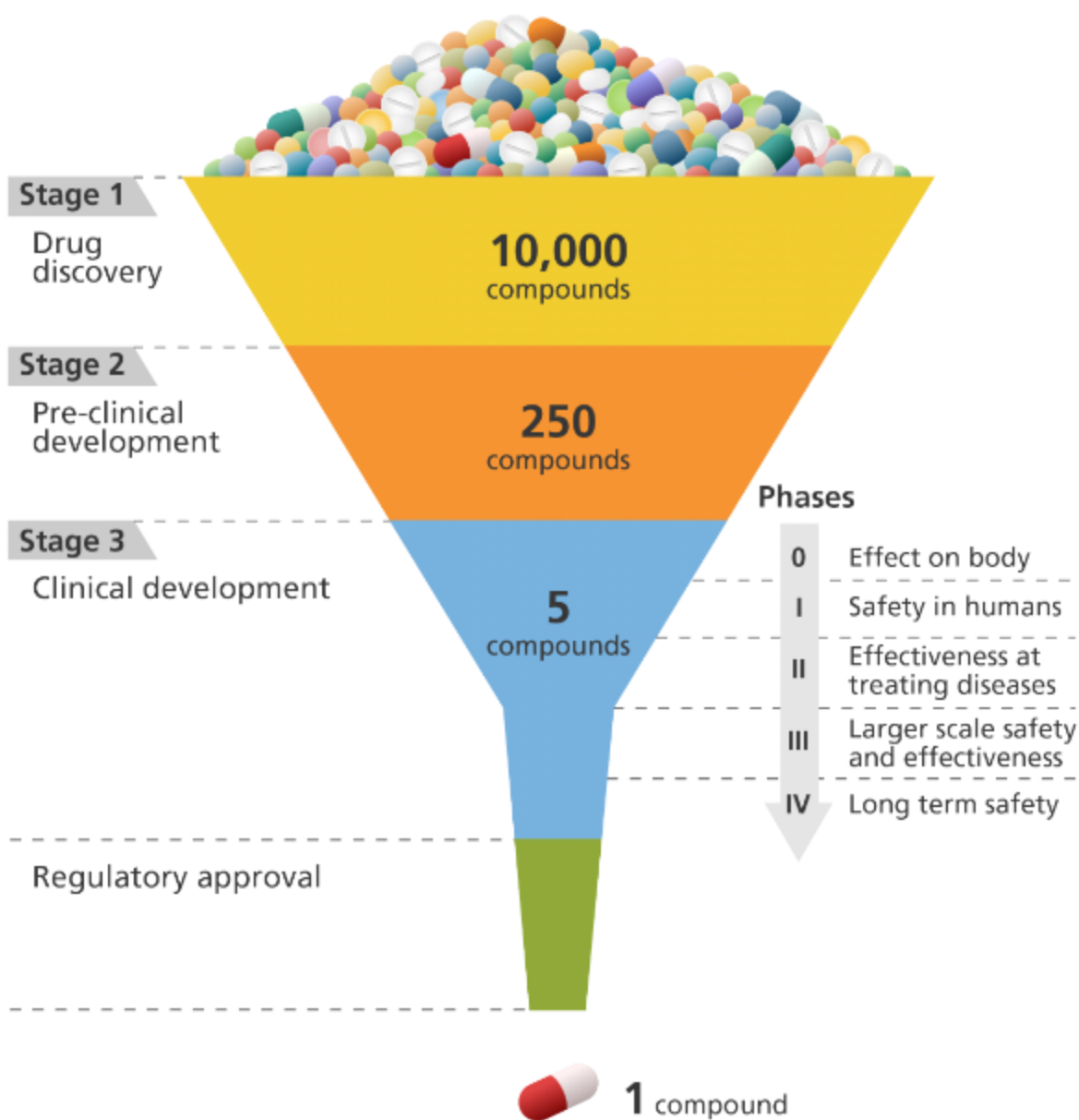
Figure 1: Stylistic representation of the stages in drug development. Image reused with permission courtesy of Genome Research Limited [18].

A Thorough QT (TQT) study is an ECG-intensive study designed for rigorous assessment of changes in the QT interval, although assessment of other intervals and morphology changes are also required. This type of study is a required part of the application to bring a new drug to market and

typically occurs before or during the time a compound reaches a Phase 3 clinical trial. Although the US

FDA commonly requires information on all standard interval durations (PR, QRS, RR, QT, and QTc) and a

description of any changes in T waveform morphology, one of the primary focuses of a TQT study is to

evaluate changes in the QT interval after receiving the drug being studied. As previously discussed, the

RR interval is the duration between the R wave of a particular heart beat and the R wave in either the

previous or subsequent beat. RR values are typically represented as an average of all RR intervals in a

signal segment. QTc a QT measurement "corrected" for heart rate. Several correction formulas exist

and will be described in more detail below. Recommendations about design, conduct, analysis, and

interpretation of clinical studies to delay cardiac repolarization can be found in the *International*

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human

Use: ICH Harmonised Tripartite Guideline E14 (ICH E14) [3].

The QT interval in inversely related to the underlying heart rate. For this reason, measured QT

intervals are often corrected to take heart rate into account to better determine if a change has

occurred compared to baseline measurement. It is especially important to apply the most accurate

correction formula available during trials early in the development process where the effects of a new

drug on the QT/QTc intervals in healthy volunteers is being evaluated to detect relatively small changes

(e.g., on the order of 5 ms) [3]. Several correction formulae have been proposed, however, Bazett's and

Fridericia's methods are most commonly used. Other alternatives such as population-based and

individualized correction correction formulae are further described in the ICH E14 guidance.

QT correction formulae and what is meant by delta and double delta QT corrections are as

follows:

Bazette: $QTcB = QT / RR^{1/2}$ (Eq. 1)
Fridericia: $QTcF = QT / RR^{1/3}$ (Eq. 2)
Framingham: $QTc = QT + 1.54(1-RR)$ (Eq. 3)
Hodges: $QTc = QT + 1.75(\text{heart rate} - 60)$ (Eq. 4)
Individualized: QTcI is determined by linear regression using different HRs for same person.

QTcB is thought to over-correct at HR > 100, under-correct at HR < 60.

The Friedericia and Framingham corrections are considered to be more accurate at HRs outside of 60-100. If an ECG is captured while the patient's heart rate is 60 bpm, the absolute QT interval should be used instead.

When reporting changes in the QT interval, it is common to see "Delta QTc" and "Double Delta QTc" reported in the literature, and the method used for calculation is typically provided. Delta QTc (ΔQTc) means a "change from baseline". There are two common ways to calculate ΔQTc illustrated in Figure 2, where:

ΔQTc Definition 1 Formula: Treatment Arm (T1) – Placebo Arm (T2)   (Eq. 5)
ΔQTc Definition 2 Formula: Pre-Dose (T1) – [n time] Post-Dose (T0)   (Eq. 6)
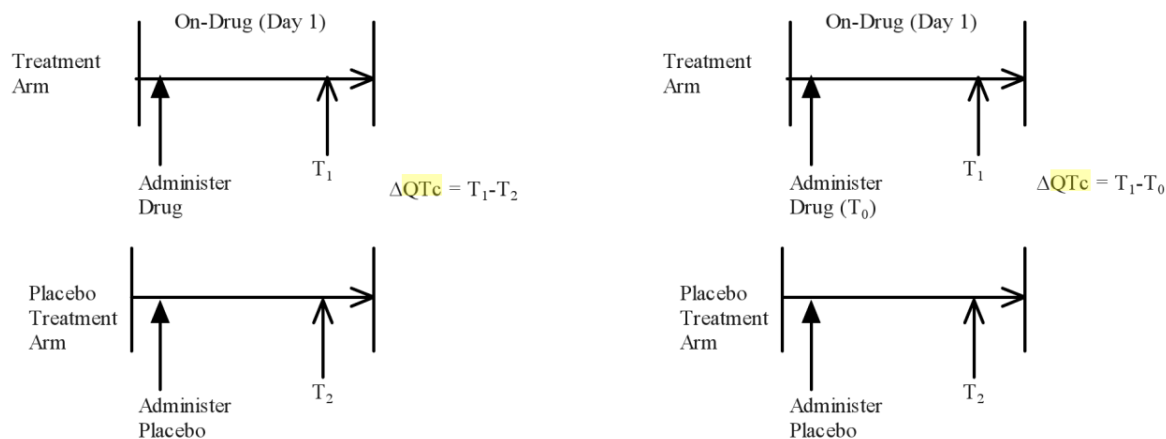
Figure 2: Graphical representations of two methods for calculating ΔQTc [19].

Double Delta QTc ($\Delta\Delta$QTc) refers to a "placebo adjusted change from baseline" where both placebo and baseline measurements are taken into consideration. The $\Delta\Delta$QTc logic is depicted in Figure 3. Similar to ΔQTc, $\Delta\Delta$QTc may also be calculated in two ways, where:

$\Delta\Delta$QTc Definition 1 =   (Eq. 7)
       [(Day 1) Post-Dose Treatment Arm (T2) – (Day 1) Pre-Dose Treatment Arm (T1)]
        – [(Day 1) Post-Dose Placebo Arm (T4) – (Day 1) Pre- Dose Placebo Arm (T3)]

$\Delta\Delta$QTc Definition 2 =   (Eq. 8)

[Post-Dose Treatment Arm (T2) – (Day -1 same time) Treatment Arm (T1)]
– [Post-Dose Placebo Arm (T4) – (Day -1 same time) Placebo Arm (T3)]
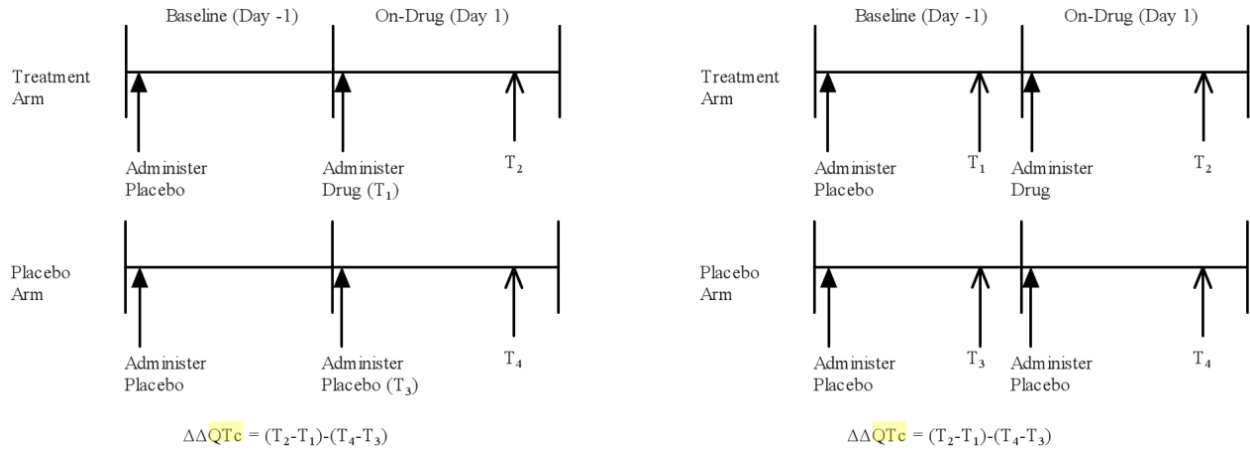
Figure 3: Two methods for calculating ΔΔQTc [19].

When reviewing an electrocardiogram (ECG), the QT interval represents electrical depolarization and repolarization of the ventricles of the heart. A QT interval of greater than 500 milliseconds (msec) is widely accepted as a biomarker for the potential of ventricular tachyarrhythmias such as Torsade de Pointes (TdP), and is considered to be a risk factor for sudden death [1,2] although the QT interval is also acknowledged to be an imperfect biomarker [3]. Prolongation of cardiomyocyte repolarization, the manifestations of ventricular repolarization, and normal rhythm degenerating into Torsade des Pointes is stylistically illustrated in Figure 4 (A-D):
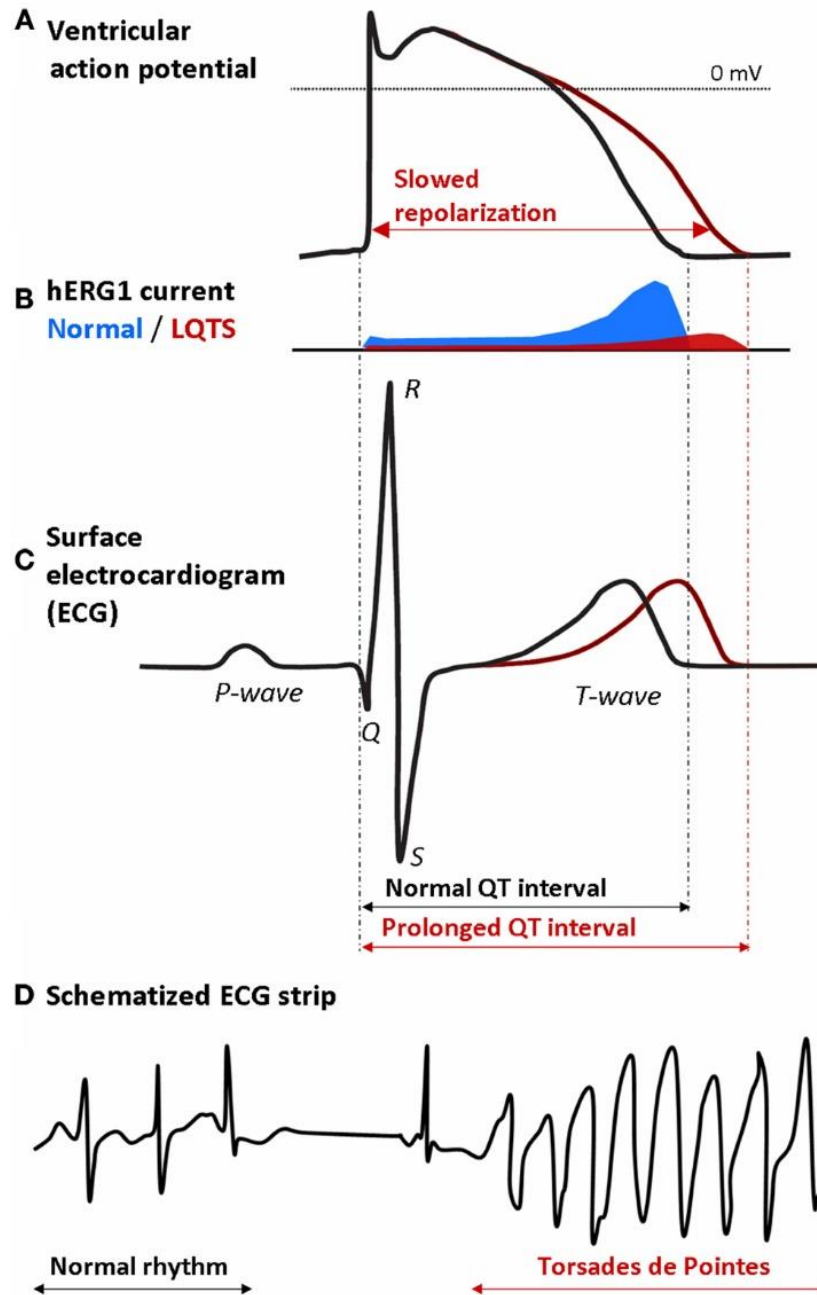
Figure 4: Relationship between single cardiomyocyte physiology and Torsades de Pointes. (A) Normal and prolonged ventricular action potential. (B) Reduction of hERG1 currents in LQTS. (C) ECG recording with lengthening of the QT interval which is a biomarker for Torsades de Pointes. (D) ECG recording showing the onset of Torsade de Pointes in a patient with long QT syndrome. Image reused with permission [20].

Section 1.3: Study Aims

Given the CiPA initiative's aims to expand cardiac safety assessments beyond potassium

channels and to include other physiological factors, the question being addressed in this investigation is

whether or not the available expression profiles from whole-animal experiments in the rat model can be

used as an associative biomarker to augment existing prediction methods for QT prolongation in

humans; and furthermore, if the changes in gene expression might help to further explain existing

mechanisms of action or elucidate previously undescribed mechanisms that might lead to prolongation

of the QT interval. Although prolongation of the QT interval in the rat by a particular compound may be

interesting, it is not clinically relevant given the known differences described in ICH S7B. However, such

predictions based on associations could be taken into consideration with other pre-clinical safety

assessments, including the current paradigm of patch clamp testing for channel blockage by the drug or

one of its metabolites. Expression changes may also suggest future studies to determine if expression

changes might impact intracellular protein expression which, by extension might impact ion channel

activity, intracellular or extracellular ion concentrations, or a combination of these factors. It is

important to mention that association does not imply causality, so it is possible that if a correlation is

found between the rat liver expression profiles used and QT prolongation in humans, the expression

changes may or may not be directly or indirectly responsible for QT prolongation in rats or humans.

With all of these considerations, none of the current guidance documents related to QT liability

assessments including ICH S7B and ICH E14 describe the use of pre-clinical gene expression profiles to

predict QT prolongation in humans.

In clinical practice, pharmaceuticals can impact the autonomic nervous system in a variety of

applications including but not limited to anesthesia, psychiatry, and cardiac medications as target

indications, although off target effects, sometimes also referred to as "side effects" may also be seen

when used in other clinical settings. Knowing that a drug which influences receptors of norepinephrine

(NE) or acetylchonline (Ach) means it could potentially impact the autonomic nervous system which by extension may have electrophysiological effects on the heart.

In this study, rat liver tissue serves as a surrogate tissue for suggesting expression changes that may be associated with changes in autonomic tone such as expression changes in receptors associated with the autonomic nervous system or potentially proteins associated with downstream mechanisms. More definitive studies would require autonomic monitoring, perhaps through circulating levels of catecholamines (epinephrine and norepinephrine) and acetylcholine, along with telemetry monitoring of the heart and heart rate variability under control and treatment conditions. Signal data was not collected in conjunction with the gene expression datasets used in this project, thus analysis of ECGs collected during control and drug treatment conditions is beyond the scope of the current project.

The first aim of this investigation was to use drug-treated and vehicle treated (control) rat liver RNA microarray expression data from the public domain and open-source software to train machine learning algorithms for the prediction of diLQTS pre-clinically, based on available rat liver RNA expression profiles. At the time of data selection in this study, there were 171 drugs defined in CredibleMeds (https://crediblemeds.org). Drugs are occasionally added, removed, or reclassified in this list so this project represents a point in time. Of the drugs listed in CredibleMeds at the time of this investigation, 28 of these drugs had microarray data in the dataset used for this study. The drugs known to prolong the QT interval (QT drugs) with microarray data available, and drugs sharing a target, metabolizing enzyme, or transporter which do not prolong the QT interval (NQT drugs) with microarray data available that were used for this study are listed in Tables 2.1 and 2.2, respectively, in the Methods section. An extension of this aim was to use the pentamidine example of impacting QT duration through downregulation of important ion channels, and assess expression profiles of genes associated with congenital Long QT Syndrome (cLQTS) in the QT drugs versus NQT drug groups to study ion channel expression changes in the available data beyond the hERG channel.

15

The second aim was to perform cluster analyses on differentially expressed genes. Clustering of drug treated was done to 1) predict QT prolongation for drugs currently not classified to do so, 2) suggest novel uses for existing drugs, 3) propose potentially safer alternatives for clusters containing a mix of QT and NQT drugs, and 4) serve as a validity check of the SVM model, assuming QT prolonging drugs cluster together, which was the case in this study.

The third aim of this investigation was to use the differentially expressed probes from the individual drug classes to determine whether or not interactions between the top differentially expressed probes are known to be linked to the genes currently known to cause QT prolongation in the literature. It is acknowledged that changes in expression levels for some physiologically important genes such as those which encode promotor or suppression proteins may be expressed at a level that is not statistically significant but may be biologically and clinically significant. The list of drugs used in this investigation are chemically diverse and have many different indications; thus, it is also possible that the same end result of QT prolongation may be reached by more than one mechanistic pathway. For this reason, further sub-classification of the drugs tested by their indication may unveil expression profiles within the same classification to suggest the possibility of multiple, separate expression profiles which may predict QT prolongation. Existing links may suggest previously undescribed mechanisms, while missing links may suggest future experiments. Rat liver tissue has long been known to have a membrane potential, with the work by Claret [21] being one such example. *In vitro* patch clamp testing of rat liver tissue electrophysiology in conjunction with gene expression assessments may be leveraged along with similar *in vitro* testing in cardiac tissue for comparative and translational studies.

The question being asked in this investigation is whether or not the available expression profiles from whole-animal experiments in the rat model, not limited to ion channel expression can be used as an associative surrogate biomarker to augment predictions for QT prolongation in humans.

Machine learning predictions could be taken into consideration with other pre-clinical safety assessments, including the current paradigm of patch clamp testing for channel blockage by the drug or one of its metabolites. Expression changes may also suggest future studies to determine if expression changes might impact intracellular protein expression which, by extension might impact ion channel activity or ion concentrations inside and outside of the cell. While gene expression changes associated with ion channels directly involved with cardiac action potentials has been described, we believe the proposal for the use of expression profiles not limited to ion channels as a surrogate biomarker is a novel proposal in response to the CiPA initiative to look "beyond hERG" channels [17].

The next sections describe the approach taken in this project as a proof of concept which suggests that machine learning methods may be considered as viable options for future use.

CHAPTER 2: METHODS

A central concept related to the classifier predictions presented here is that an association (i.e. a correlation) does not imply a cause. The classifier predictions from expression profile changes described here may be thought of as a correlated "surrogate biomarker" for QT prolongation in humans with potentially useful implications, for example, in the drug development process. Any association found is intended to be used for predictive purposes only, based on the association. The use of a surrogate tissue model is common in the field of Translational Medicine when the desired tissue model is not available, as was the case in this investigation.

At the time of this investigation, large groups of open-source *in vivo* drug treated gene expression data from human cardiomyocytes was not available; however, during the drug development process, extensive pre-clinical testing is conducted *in vitro* and *in vivo*, with rats being a common animal model used to help make choices about which chemical entities to further develop. The use of surrogate tissue models is common in the field of Translational Medicine when the desired tissue is not available.

It is acknowledged that the microarray data used was derived from rat liver, and different tissues may have different expression profiles so one must use caution when making claims of causality. The suggestions made below are based on an assumption that expression profiles would be conserved in rat heart tissue. By extension, the hope is that expression may be conserved across species to humans, but testing would be required for unequivocal confirmation. This underscores the importance of biological testing.

A benefit of *in vitro* testing is that it provides an investigator with more control over the physiological environment, and the experiments can be done at a comparatively lower cost than *in vivo* testing. A drawback of in vitro testing is that cells and organs do not exist alone in nature and it is reasonable to assume that other bodily functions such as neuronal and humoral influences might

18

produce different results, knowing that whole-body physiology is currently impossible to reproduce in an *in vitro* setting. A benefit of *in vivo* testing is that the whole-body influences are more accurately represented. Drawbacks of *in vivo* testing include comparatively higher costs and logistics related to maintaining animals during the study period. Considering *in vivo* human studies, acquiring human heart tissue under experimental circumstances for assessments of gene expression profiles is limited by both ethical and technical challenges so animal models are currently the most realistic approach for *in vivo* studies, and such in vivo animal studies are common, as described in the ICH guidance documents mentioned previously.

In addition to cardiovascular assessments, hepatic effects of drug treatment are also extensively studied during the drug development process. While not the focus of this study, pre-clinical *in vivo* liver expression data may also be used for *in silico* hepatotoxicity assessments to gain more information from the same data and reduce animal use.

Using publicly available RNA expression profiles of control and drug-treated rat liver from the same investigator (28 drugs known to prolong QT as defined in the CredibleMeds database and 166 drugs not considered to have a QT liability sharing targets, transporters, and metabolizing enzymes), this investigation consists of three parts which are described in more detail below:

1) Support Vector Machine (SVM) classification for prediction purposes;
2) Clustering of expression profiles for prediction and further study of expression signatures; and
3) The use of differentially expressed genes to search existing biological databases to identify potential mechanistic links between gene expression and QT prolongation.

Microarray datasets were downloaded from the GEO datasets website (https://www.ncbi.nlm.nih.gov/gds) from the Natsoulis experiment [22] (GSE 8858). In addition to the practical considerations of having *in vivo* liver expression data for hepatotoxicity assessments, further *in silico* analysis of the same data for potential cardiotoxicity could help to reduce the cost of the drug development process by getting more information out of the same data and also reduce the number of

animals required for pre-clinical testing. This data source was chosen for the reasons listed above, and

because of the large number and diversity of classifications of drugs tested, the same animal model

being used, and a level of consistency implied by having the studies conducted by the same investigator

using the same methods and same microarray platform. Corresponding ECG recording data for each rat

at the time of liver expression data collection was not part of the study design of the Natsoulis

investigation and therefore not available for heart rate variability analyses.

For the purpose reproducibility, the normalized expression values described in the individual

microarray data files were used. Normalization methods are described within the dataset file.

Expression profiles for drugs in the dataset known to cause diLQTS as listed in CredibleMeds at the time

of the investigation (n=28) were compared to those having common targets, enzymes, or transporters as

defined in DrugBank (http://www.drugbank.ca/) (n=166) referred to here as the non-QT prolonging

(NQT) drugs. Specifics of the methods used for data processing and model training are as follows:

Section 2.1: Dataset Pre-Processing Steps

1. Drugs known to prolong the QT interval were identified from CredibleMeds.org, summarized in Table II.
2. Drugs sharing targets, enzymes and transporters with the available drugs were identified in Drugbank.ca, summarized in Table III.
3. Available microarray data was downloaded GEO (GSE 8858) and loaded into the R platform. No attempt was made to further classify drugs based on dose or duration, only by generic drug name.
4. Normalization was already performed in GSE 8858 data, and published normalized data values were used for reproducibility.
5. Control probes were removed because they are not expression related.
6. Mean fold changes (2-4 samples) were calculated from the mean of control probes (15-20) for each probe.

Section 2.2: Choice of Features

Differentially expressed (DE) probes were identified based on the difference between the fold

change of the QT group vs. the NQT group using a t-Test ($p \leq 0.05$), and then further refined by

calculating the False Discovery rate and selecting probes with $p \leq 0.05$ and $q \leq 0.05$ to reduce the

potential for a DE probe being a false positive. Probes meeting these criteria were selected as input features to the SVM.

In addition to the QT versus Non-QT grouping, 76 additional sub-classes were identified based on drug classification annotations in Drugbank, and then DE probes were again identified between QT and NQT groups as having a $p \leq 0.05$ and $q \leq 0.05$. All datasets for drugs having more than one classification were included in all classifications defined in DrugBank and therefore were in as many classes as there were annotations for the drug.

Table II: Drugs Known to Prolong QT Interval in Humans with Rat Liver Microarray Data Available

Amantadine	Clomipramine	Ketoconazole	Sertraline
Amiodarone	Erythromycin	Pantoprazole	Sotalol
Azithromycin	Fluconazole	Primaquine	Sparfloxacin
Chlorpromazine	Fluoxetine	Promazine	Sulfisoxazole
Ciprofloxacin	Granisetron	Promethazine	Tamoxifen
Citalopram	Isoproterenol	Quetiapine	Torsemide
Clarithromycin	Itraconazole	Roxithromycin	Venlafaxine

Table III: Chemical Entities Defined in DrugBank Sharing a Target, Enzyme, or Transporter with Drugs Known to Prolong the QT Interval in Humans Having Rat Liver Microarray Data Available

Acetaminophen	Diazepam	Lomefloxacin	Procarbazine
Acetazolamide	Diclofenac	Lomustine	Progesterone
Albendazole	Diethylstilbestrol	Lovastatin	Pyrazinamide
Alprazolam	Digoxin	Mebendazole	Rabeprazole
Aminoglutethimide	Dimenhydrinate	Mefenamic Acid	Raloxifene
Amlodipine	Dipyridamole	Megestrol Acetate	Rifabutin
Amoxicillin	Disulfiram	Melatonin	Rofecoxib
Anastrozole	Doxorubicin	Meloxicam	Rosiglitazone
Artemether	Doxycycline	Mestranol	Salicylic Acid
Aspirin	Econazole	Methimazole	Secobarbital
Atorvastatin	Enoxacin	Methotrexate	Sildenafil
Atropine	Epirubicin	Metronidazole	Simvastatin
Benzocaine	Ergocalciferol	Mevastatin	Sulconazole
Beta Napthoflavone	Estriol	Miconazole	Sulfadiazine
Bezafibrate	Ethanol	Mifepristone	Sulfaphenazole
Bupropion	Ethinylestradiol	MitomycinC	Sulfathiazole
Busulfan	Etodolac	Modafinil	Sulindac
Capsaicin	Etoposide	Naloxone	Tacrine
Carbamazepine	Famciclovir	Naproxen	Temafloxacin
Carbimazole	Fenofibrate	Neostigmine Bromide	Terbinafine
Carboplatin	Finasteride	Nevirapine	Testosterone
Carmustine	Fluphenazine	Niacin	Tetracycline
Carvedilol	Fluvastatin	Nisoldipine	Thalidomide
Celecoxib	Gemfibrozil	Nitrazepam	Thiabendazole
Cerivastatin	Genistein	Nitrofurantoin	Ticlopidine
Chlorambucil	Gentian Violet	Norethindrone	Ticrynafen
Chlorzoxazone	Glimepiride	Olanzapine	Tinidazole
Cholecalciferol	Glipizide	Omeprazole	Tocainide
CholicAcid	Griseofulvin	Oxiconazole	Tretinoin
Cinnarizine	Hydralazine	Oxymetazoline	Troglitazone
Cisplatin	Hydrocortisone	Oxymetholone	Trovafloxacin
Clofibrate	Hydroxyurea	Oxytetracycline	Valproic Acid
Clomiphene	Ifosfamide	Pentobarbital	Vinblastine
Clonazepam	Imatinib	Pergolide	Vinorelbine
Clotrimazole	Indomethacin	Perhexiline	Warfarin
Cyclandelate	Insulin	Phenacetin	Zaleplon
Cyclosporin A	Isoniazid	Phenobarbital	Zidovudine
Cyproterone Acetate	Ivermectin	Pioglitazone	Zileuton
Cytarabine	Lamivudine	Pralidoxime	Zomepirac
Danazol	Lansoprazole	Praziquantel	Zopiclone
Daunorubicin	Leflunomide	Prednisolone	
Dexamethasone	Letrozole	Primidone	

Section 2.3: Bias-Variance Tradeoff

The bias–variance tradeoff is a central problem in supervised learning. Ideally, one wants to choose a model that both accurately captures the regularities in its training data, but also generalizes well to unseen data. Unfortunately, it is typically difficult or impossible to do both simultaneously. Figure 5 illustrates the difference between bias and variability.
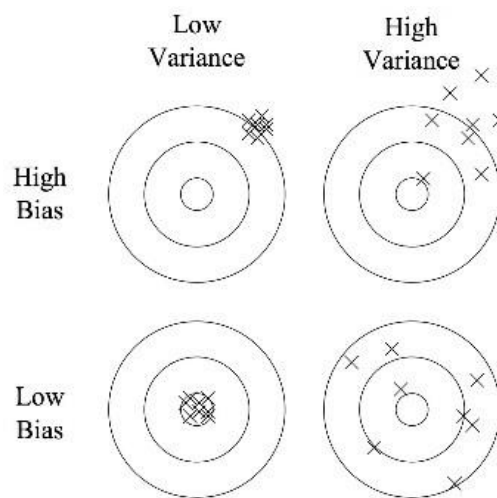
Figure 5: Stylistic representation of the difference between bias and variance. Image reused with permission [23].

Figure 6 illustrates common outcomes in cases where there is high bias on the left, high variance on the right which can lead to overfitting, and a balance between bias and variance to attain the desired prediction model.

$$\theta_0 + \theta_1 x \qquad \theta_0 + \theta_1 x + \theta_2 x^2 \qquad \theta_0 + \theta_1 x + \theta_2 x^2 + \theta_3 x^3 + \theta_4 x^4$$

High bias (underfit)   "Just right"   High variance (overfit)
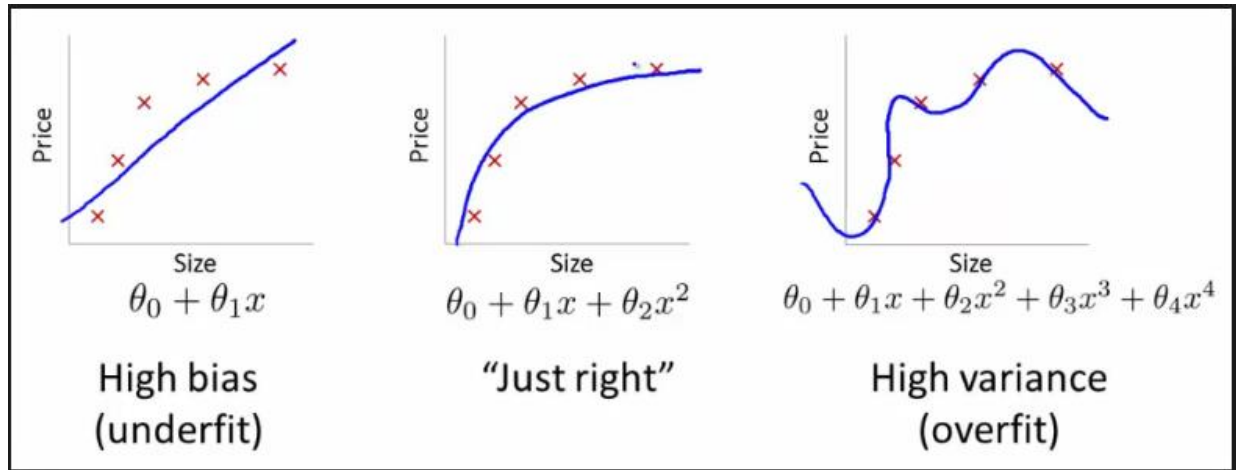
Figure 6: Stylistic representation of the balance of over- and under-fitting a model, with the desired outcome in the center. Image reused with permission [24].

Another challenge associated with training machine learning classification models is

dimensionality which may lead to an over-fit model. This is overcome using regularization during

training of the model. Regularization may be thought of as "putting on the breaks when making a turn"

to make the turns more gradual, which is illustrated in the middle graph of Figure 6.

Section 2.4: Classifier Selection

A Support Vector Machine (SVM) was chosen for binary classification because of the following

characteristics:

- Supervised learning model to optimize class differences.
- Ease of implementation in R (e1071 package).
- SVMs were developed by Cortes & Vapnik [25] for binary classification, which is the central theme for the classification part of this project.
- SVMs are a good option for regression, outlier detection, and general (nonlinear) classification which was the focus of this project. Furthermore, the model representation is intuitive.
- Binary (yes/no) prediction of QT liability is easily available.
- Support Vector Machines define decision boundaries with what is referred to as a "soft margin" so that misclassified points contribute less to the model. A decision plane separates between inputs form different pre-defined classes.
- Hyperplanes are expandable to infinite dimensions, assuming regularization parameter is tuned carefully so the number of dimensions (i.e. RNA probes) used in the model is not a limitation.

The Cortes & Vapnik classification approach is as follows [25]:

- Class separation – essentially creating a hyperplane to separate classes by maximizing the distance between closest points from each of the classes. Support vectors refer to points which lie on the outer boundaries. The optimal separating hyperplane is in the middle of the support vectors as illustrated in Figure 7.
- Overlapping classes – points on the "wrong" side of the discriminant line have a reduced influence during the model training process(soft margin).
- Nonlinearity – when linear separation is not possible, data points are mathematically projected into a higher-dimensional space to make data points linearly separable in the new space. This conversion process is accomplished using mathematical processes, sometimes referred to as "kernel tricks" which are sometimes denoted using the greek letter φ.
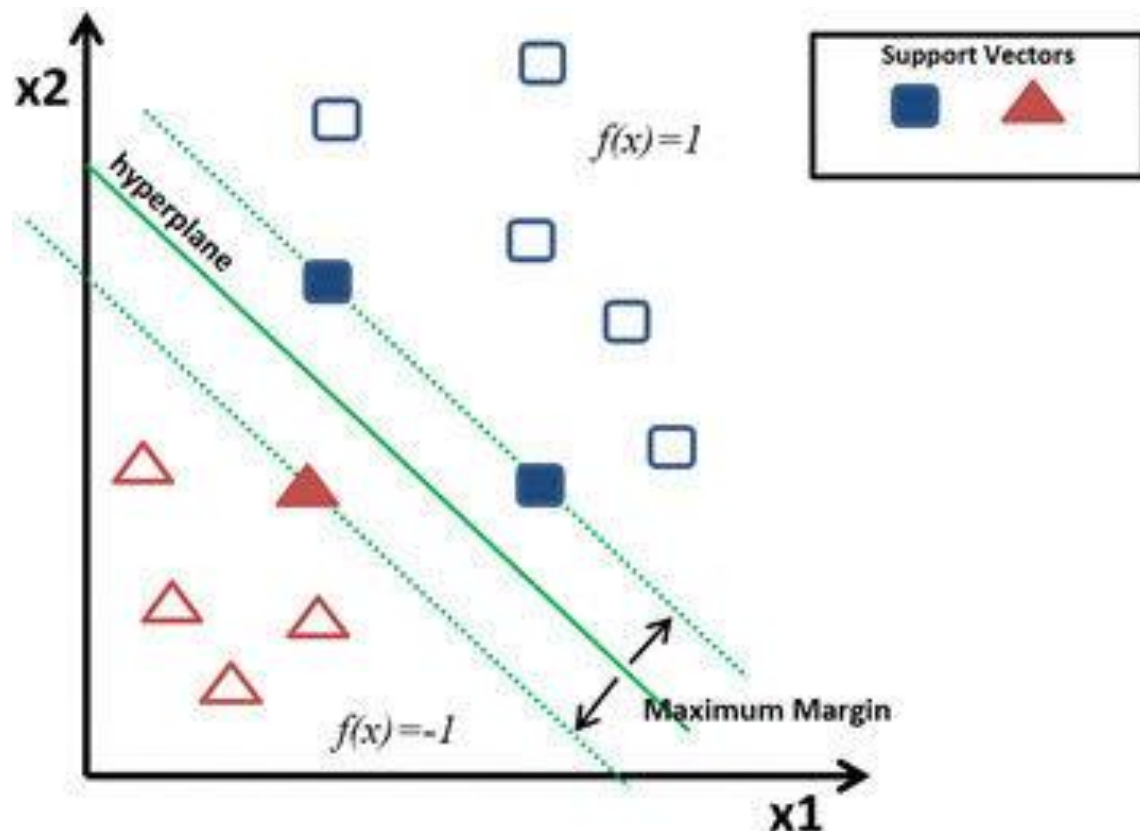
Figure 7: Illustration of a separating hyperplane with a margin and support vectors lying on the margin [26].

In some cases, classes are not linearly separable in 2 dimensions as illustrated in Figure 8. The basic idea behind Support Vector Machines is the input space is rearranged using a set of mathematical

functions, known as kernels to a feature space. The process of rearranging the objects is known as

mapping (a.k.a. transformation) as illustrated in Figure 36. In the new feature space, the mapped

objects are linearly separable, so instead of constructing a complex curve, the SVM finds an optimal

plane line that can best separate the red and blue data points.
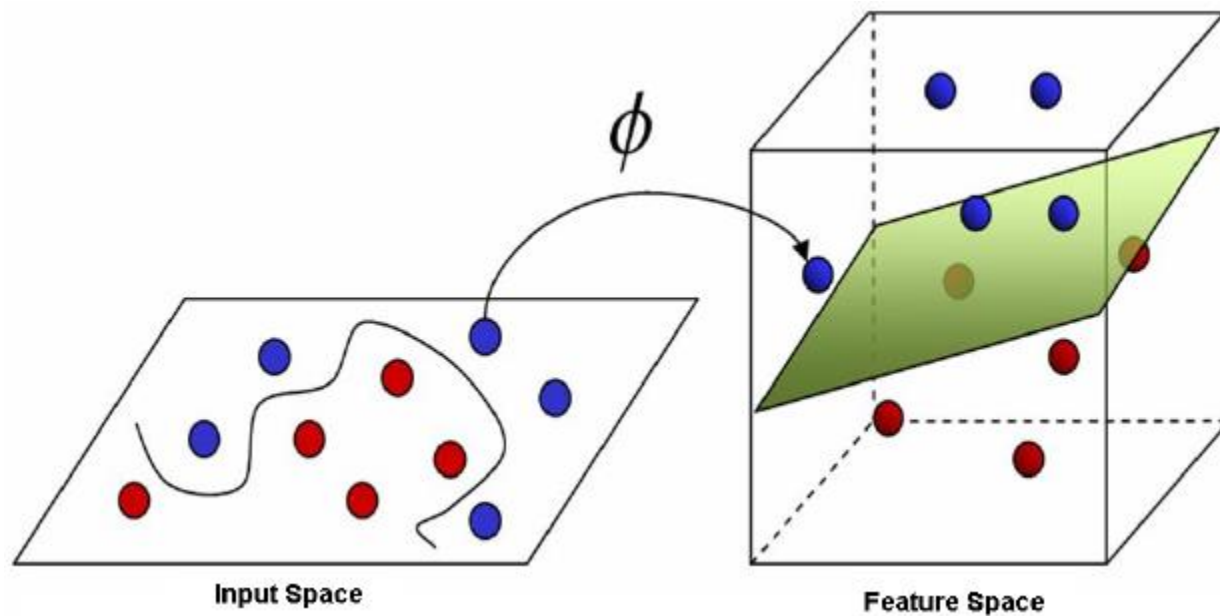
Figure 8: Mapping data points which are not linearly separable into a higher dimensional space using a kernel function φ which allows data points to be separated by a hyperplane [27].

An SVM model must be tuned to perform optimally. This is done by tuning two parameters,

which are "gamma" and "C". These are described in an open forum discussion [28] in the following way:

Gamma is the parameter of a Gaussian kernel (to handle non-linear classification). To "raise" the points, gamma controls the shape of the "peaks" where points are raised. A small gamma gives you a pointed bump in the higher dimensions, a large gamma gives you a softer, broader bump. A small gamma gives low bias and high variance (may overfit model). A large gamma will give you higher bias and low variance (may underfit model). When classes are not linearly separable in 2 dimensions such as the example in Figure 9, transform them to a higher

dimension where they will be linearly separable. Imagine "raising" the green points, then you can separate them from the red points with a plane (hyperplane).
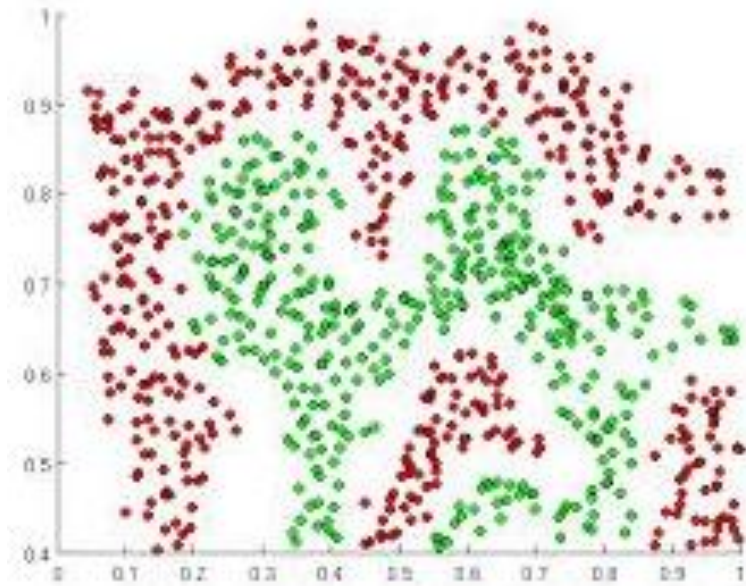
Figure 9: Data which are not linearly separable that would be impacted by tuning the parameter "gamma" [28].

Input **C** is the parameter for the soft margin cost function (regularization), which controls the influence of each individual support vector; this process involves trading error penalty for stability. A large **C** gives low bias and high variance (too high leads to overfitting). Low bias because you penalize the cost of misclassification a lot. A small **C** gives higher bias and lower variance. The results are illustrated in Figure 10.
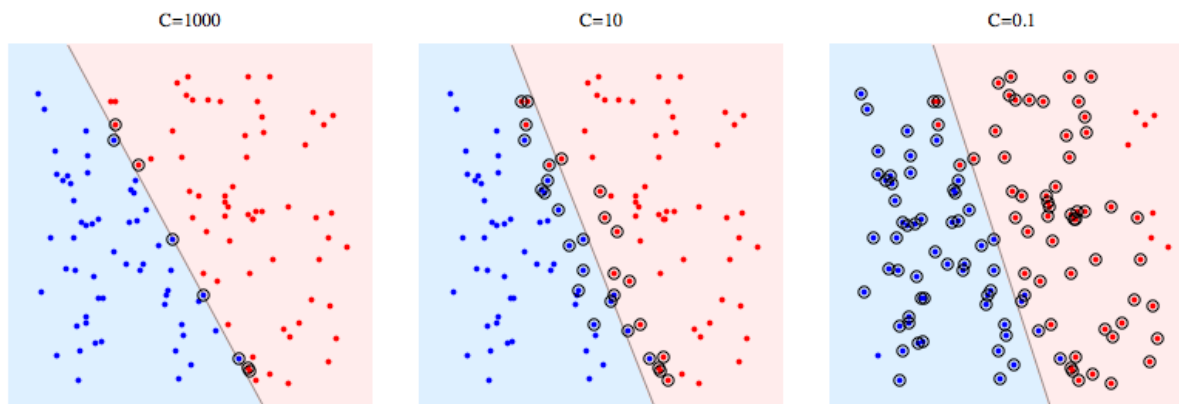
Figure 10: Illustration of the impact of setting the C parameter too high (C=1000) giving too little room for variability, reasonably (C=10) allowing some margin for variability, and too low (C=0.1) allowing for too much variability [28].

Section 2.5: Training, Validation and Testing of Support Vector Machine Models

For QT vs. NQT classification predictions, a support vector machine (SVM) classifier was implemented in R (http://bioconductor.org) using the *e1071* package [29] using all available samples from all available drug categories to determine whether or not the available QT and NQT datasets could be classified based on fold change differences between differentially expressed probes in each of the respective groups alone. Datasets were then further sub-classified based on drug categorization annotations in the DrugBank database and an SVM was trained for each sub-classification yielding a total of 77 SVMs. Drugs having multiple categorizations were used in all available categories large enough to train an SVM. In cases where there was an overt imbalance between QT and NQT datasets (*n* QT datasets ≤ 10% *n* NQT datasets), the R *unbalanced* package [30] was used to help equalize the number of samples in each group using the Synthetic Minority Over-sampling TEchnique (SMOTE) algorithm to impute additional synthetic samples for the minority class. In all cases, 10% of the available data for each group were reserved for use as "unseen" data for testing. The remaining 90% of the data was used to train the respective SVM models. Cost and Regularization parameters were systematically

adjusted to train the respective models. The procedure was repeated 10 times (i.e. 10-fold cross-validation), with the best sensitivity and specificity results being chosen for the final model. A confusion matrix was generated for the testing results from each of the 77 SVM models created. Matthews Correlation Coefficient (MCC) was also calculated for each of the SVM models because of the comparatively rare QT data observations versus the more frequent NQT data observations.

Section 2.6: Clustering Methods

The drugs used in this investigation are chemically diverse, have a large number of therapeutic indications, and in some cases, have multiple indications. Given the number of different drug classifications, trying to determine the best number of clusters to use for K-means clustering seemed cumbersome. This is the primary reason that *APCluster* [31] was chosen as a starting point. The model was relatively intuitive, implementation was fast and straightforward, and during proof of concept testing, *APCluster* ran very quickly and results were as expected.

The fold change features used as inputs to the SVMs were then clustered using the *APCluster* package in R to determine whether or not drugs clustered together into QT and NQT clusters in an attempt to identify an expression signature in the rat liver data that may be associated with prolongation of the QT interval in humans as a possible biomarker using an unsupervised machine learning method and allow the data to ultimately drive the outcome based on a pre-specified similarity level. Bodenhofer [31] describes affinity propagation in the following way (reused with permission):

> Affinity Propagation, much like agglomerative clustering does not require a prototype and works for any measure of similarity between samples. Affinity propagation (AP) is a relatively new clustering algorithm that has been introduced by Frey and Dueck (2007). AP clustering determines a so-called *exemplar* for each cluster, that is, a sample that is most representative for this cluster. Like agglomerative clustering, AP has the advantage that it works for any meaningful measure of similarity between data samples. Unlike most prototype-based clustering algorithms (like, e.g. k-means), AP does not require a vector space structure and the exemplars are chosen among the observed data samples and not computed as hypothetical averages of cluster samples. These characteristics make AP clustering particularly suitable for applications in bioinformatics: (i) many similarity measures used in bioinformatics cannot be linked

to explicit vectorial descriptions (e.g. sequence or structure alignment scores); (ii) the opportunity to identify a small set of exemplars provides new potentials for exploratory analysis of biological data. AP clustering has been used successfully for clustering microarray/gene expression data.

The *apcluster()* function first computes a similarity matrix for the input data using the

percentage passed into the function, with the default similarity being 50%, which was used in this

project. The standard similarity measure is the negative squared distances. Clustering was performed

with the following goals in mind:

1) Clustering to serve as an additional tool to predict QT prolongation liability based on expression profiles.
2) Expression profiles from individual clusters could be further investigated to help clarify and narrow expression profiles associated with QT prolongation.
3) Clusters may suggest potentially new uses or safer alternatives for QT and NQT drugs having a similar expression profile, depending on the indication.
4) Clustering results would help to validate the SVM results. If groupings cluster reasonably well together or even partially, it could help to explain SVM results.

Section 2.7: Biological Networks

Certain knowledge bases such as Gene Ontology (GO) and the Molecular Signatures Database

(MSigDB) commonly only provide information about a particular gene. Several publicly available

pathway knowledge bases exist which can be used to find gene products which interact with a given list

of genes in a given physiological pathway, how they interact with each other such as inhibition,

activation, acting in the capacity of a cofactor , and in which locations interactions may take place such

as within the nucleus, the cytoplasm, sarcoplasmic reticulum, etc. These knowledge bases include but

are not limited to:

- DAVID (https://david.ncifcrf.gov/)
- ConsensusPathDB (http://cpdb.molgen.mpg.de/)
- Reactome (http://www.reactome.org/
- g:Profiler (http://biit.cs.ut.ee/gprofiler/index.cgi)
- Enrichr (http://amp.pharm.mssm.edu/Enrichr/)
- EnrichNet (http://www.enrichnet.org/index.php)
- String (https://string-db.org/)

Challenges exist with open-source databases. Some of these challenges include, but are not limited

to the following:

- The same pathway may be defined differently in different knowledge bases. This can impact the statistical power related to performance assessments, as well as the number of true neagtives and true positives.
- Certain knowledge databases may have a low resoution. For example, a genome-wide association study (GWAS) may identify a large number of SNPs thought to be involved in different conditions and diseases. A low resolution knowledge base might only specify which genes are active in a particular pathway and give no additional information about the relationship to a particular condition.
- Annotations may be inaccurate or incomplete**.**
- Condition-specific and cell-specific information may be missing. A pathway knowledge base may be built based on curated experiments from different cell types at different time points under different conditions; however the details may not be consistently provided in the knowledge bases.

For the purposes of this investigation, the String database was chosen. The results from each of

the 77 groupings and proposals for how QT prolongation may be mechanistically caused are described in

more detail in the Results section, which are based on differential expression between QT and NQT

drugs. The String database allows for users to go to higher level connections, but for clarity and

simplicity, only first level connections are described in the Results section.

CHAPTER 3: RESULTS

Section 3.1: Support Vector Machine Results

Using all available dataset inputs only classified as those known to prolong the QT interval (drugs defined in CredibleMeds) and NQT drugs (those not defined in CredibleMeds), ten-fold cross validation resulted in an average sensitivity of 85.46% and average specificity of 90.01%, compared to the previously mentioned sensitivities and specificities of 64-82% and 75-88%, respectively, from patch clamp predictions. Further sub-classification of drugs based on drug category annotations in the DrugBank database resulted in 76 sub-categories, each having its own SVM. Ten-fold cross validation results for each of the sub-categories varied by class, but considering the 77 classes together, including all classes together, the median sensitivity and specificity (± Median Absolute Deviation) were 91.92(±4.08)% and 93.84(±2.67)%, respectively, and the mean sensitivity and specificity (± Standard Deviation) were 92.03(±5.70)% and 94.02(±3.42)% respectively. Results are summarized in Table IV and the corresponding Receiver Operating Characteristic (ROC) curve showing model performance is shown in Figure 11 for illustrative purposes. Individual SVM results and corresponding ROC curves are listed in Appendix A.

Table IV: Summary of Support Vector Machine Testing Results after 10-Fold Cross-Validation

QT vs. NQT Classification Only	Sensitivity (%)	Specificity (%)	Matthews Correlation Coefficient
All Drugs	85.46	90.01	0.8102
Individual Classifications Including All Classes (n = 77 SVMs)			
Median	91.92	93.84	0.8782
Median Absolute Deviation	4.08	2.67	0.0561
Mean	92.03	94.02	0.8765
Standard Deviation	5.70	3.42	0.0874
Minimum	75.86	83.83	0.6358
Maximum	100.00	100.00	1.0000
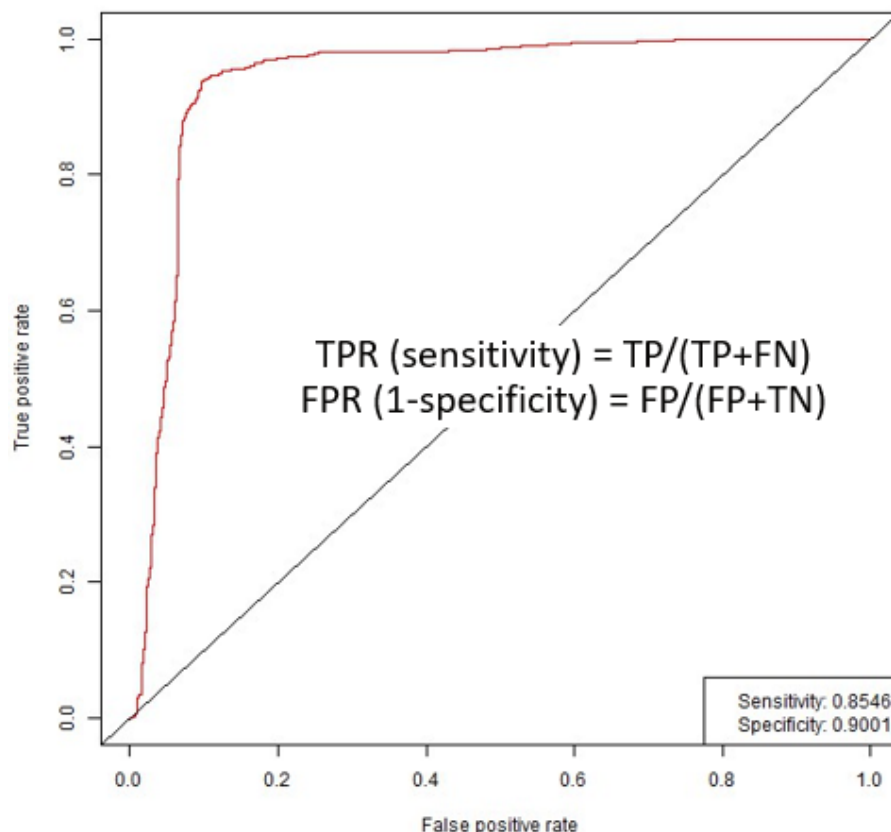
Figure 11: Receiver Operating Characteristic Curve – Support Vector Machine model for All Drug Classes

Section 3.1.1: Expression Changes for Genes Associated with Congenital Long QT Syndrome

In addition to channel blockade, a reduction in the expression of ion channel proteins may produce a similar effect of repolarization delay and QT prolongation by reducing the number of openings in the plasma membrane which can allow ions to cross the plasma membrane and thereby slowing changes to the transmembrane potential.

The results summarized in Table V from the available data did not show an overwhelming preponderance of expression differences in the genes associated with cLQTS, with the exception of CACNA1C, which was downregulated in the NQT group approximately 2.4 times more frequently than in the QT group. Prolongation of the QT interval by a reduction in KCNH2 expression for a drug such as

pentamidine has been previously described [17], which supports the possibility of more than one

mechanism being responsible for a delay in cardiomyocyte repolarization; however, microarray data

from the full group of QT drugs and additional efforts would be required to make any claims about

changes in expression being categorically related to QT prolongation. The results presented here show

that not all drugs which prolong the QT interval reduce the expression of ion channel proteins.

Table V: Percentages of Drugs in the Available Dataset which Increase or Decrease Expression of Genes Associated with Congenital Long QT Syndrome

LQTS Type	Gene	QT Drug % Downregulated n=121	QT Drug % Upregulated n=121	NQT Drug % Downregulated n=921	NQT Drug % Upregulated n=921
Type 1	KCNQ1§	N/A	N/A	N/A	N/A
Type 2	KCNH2	8.3	0.8	8.8	0.3
Type 2	ALG10§	N/A	N/A	N/A	N/A
Type 3	SCN5A§	N/A	N/A	N/A	N/A
Type 4	ANK2	2.5	0.8	4.7	0.7
Type 5	KCNE1	0.0	3.3	1.6	0.7
Type 6	KCNE2	2.5	1.7	2.5	0.5
Type 7	KCNJ2	1.7	0.0	2.7	0.5
Type 8	CACNA1C	5.8	0.0	13.9	1.0
Type 9	CAV3	0.8	0.0	1.3	0.4
Type 10	SCN4B	14.0	0.0	17.9	1.0
Type 11	AKAP9	0.0	2.5	3.5	2.4
Type 12	SNT1§	N/A	N/A	N/A	N/A
Type 13	KCNJ5	9.1	0.0	8.9	1.6
Type 14	CALM1§	N/A	N/A	N/A	N/A
Type 15	CALM2	0.8	3.3	3.4	4.7

§ Probes for Type 1 (KCNQ1), Type 2 (ALG10), Type 3 (SCN5A), Type 12 (SNT1), and Type 14 (CALM1) were not included in the available microarray probe set and therefore not available for assessment.

Section 3.2: Clustering Results by DrugBank Classification

Generally speaking, the clustering results suggest that clustering by expression profiles may be another useful tool, although it depends heavily on the grouping. The clustering results also appear to be consistent with the SVM results. In cases where QT drugs did not cluster together into one cluster, they commonly clustered together in a limited number of the total clusters within a particular classification.

A complete listing of all representative cluster outputs are listed in Appendix B, however a summary description of the findings is described in Table 3.2 for each of the 77 classifications.

Table VI: Summary of Clustering Results at 50% Similarity Level

DrugBank Classification	Samples	Clusters	"All QT" Clusters	Partial QT Clusters
All Drugs	1045	214	0	3
Alimentary Tract and Metabolism	150	39	0	1
Amides	86	16	0	1
Antifungal Agents	81	18	1	1
Antifungals Dermatological	68	11	0	3
AntiInfective Agents	246	44	4	1
Antiinfectives for Systemic Use	160	26	2	4
Antineoplastic Agents	248	53	0	1
Azoles	170	31	1	3
BCRP/ABCG2 Substrates	85	13	0	1
Benzimidazoles	29	5	1	0
Cardiovascular Agents	143	30	0	2
Cardiovascular System	187	34	0	1
Central Nervous System Agents	283	72	0	2
Central Nervous System Depressants	112	29	0	2
Chemically Induced Disorders	127	18	1	3
Combined Inducers of CYP3A4 and P-Glycoprotein	55	11	0	1
Combined Inhibitors of CYP3A4 and P-Glycoprotein	211	36	2	7
CYP2D6 Inhibitors (Weak)	123	25	0	1
CYP3A4 Inhibitors (Weak)	59	12	0	1
Cytochrome P450 CYP1A2 Inhibitors	274	64	0	4
Cytochrome P450 CYP1A2 Inhibitors (Moderate)	39	6	0	1
Cytochrome P450 CYP1A2 Inhibitors (Weak)	164	26	1	4
Cytochrome P450 CYP1A2 Substrates	193	37	0	3
Cytochrome P450 CYP2A6 Inhibitors	106	23	0	2

Table VI: Summary of Clustering Results at 50% Similarity Level (continued)

DrugBank Classification	Samples	Clusters	"All QT" Clusters	Partial QT Clusters
Cytochrome P450 CYP2A6 Substrates	77	19	0	1
Cytochrome P450 CYP2B6 Substrates	91	16	2	3
Cytochrome P450 CYP2C8 Inhibitors	221	51	0	1
Cytochrome P450 CYP2C8 Substrates	178	37	0	1
Cytochrome P450 CYP2C9 Inhibitors	329	71	0	4
Cytochrome P450 CYP2C9 Substrates	304	68	0	3
Cytochrome P450 CYP2C19 Inhibitors	255	61	0	5
Cytochrome P450 CYP2C19 Substrates	201	46	0	3
Cytochrome P450 CYP2D6 Inhibitors	296	70	3	6
Cytochrome P450 CYP2D6 Substrates	168	26	1	4
Cytochrome P450 CYP2E1 Inhibitors	114	21	0	1
Cytochrome P450 CYP2E1 Substrates	85	16	0	2
Cytochrome P450 CYP3A4 Substrates	566	135	0	10
Cytochrome P450 CYP3A Inducers	214	49	0	1
Cytochrome P450 CYP3A Inhibitors	403	87	0	6
Cytochrome P450 Enzyme Inhibitors	97	16	2	4
Dermatologicals	130	21	0	2
Drugs for Acid Related Disorders	38	8	0	2
Drugs for Peptic Ulcer and Gastro Oesophageal Reflux Disease (GORD)	38	8	0	2
Enzyme Inhibitors	399	83	1	5
Estrogen Antagonists	37	5	0	1
Fluoroquinolones	32	3	1	0
Gastrointestinal Agents	51	10	1	2
Heterocyclic Compounds	553	107	0	9
Heterocyclic Compounds – 1 Ring	362	64	2	5
Heterocyclic Compounds – 2 Ring	225	54	0	3
Hormone Antagonists	117	19	2	1
Hormones, Hormone Substitutes, and Hormone Antagonists	196	32	0	2
Hydrocarbons	251	48	0	1
Hydrocarbons, Aromatic	193	32	0	1
Hydrocarbons, Cyclic	222	39	0	1
Hyperglycemia Associated Agents	74	12	0	1
Hypotensive Agents	67	10	0	2
Imidazole Derivatives	48	6	0	1
Inorganic Chemicals	203	38	0	3
Nervous System	171	33	0	4
Neurotransmitter Agents	154	25	1	5
Ophthalmologicals	115	28	1	2
Peripheral Nervous System Agents	187	48	0	3
P-Glycoprotein/ABCB1 Inducers	86	16	0	1
P-Glycoprotein/ABCB1 Inhibitors	338	69	0	12
P-Glycoprotein/ABCB1 Substrates	244	62	1	4
Piperazines	40	6	3	0
Polycyclic Compounds	240	57	0	2
Psycholeptics	55	8	0	2
Respiratory System	32	8	1	1
Sensory Organs	123	28	0	2
Steroid Synthesis Inhibitors	72	10	3	1
Sulfonamides	41	6	0	1
Sulfones	49	7	0	2
Sulfur Compounds	179	32	0	5
Topoisomerase II Inhibitors	54	11	0	1

Section 3.2.1: All Drugs (QT versus Non-QT)

There were no large "All QT" clusters identified, although cluster 3 shows a "mostly QT" cluster.

Section 3.2.2: Alimentary Tract and Metabolism

No "All QT" clusters were found. The closest was cluster 1 which contained all of the QT drug samples and approximately the same number of NQT samples.

Section 3.2.3: Amides

No "All QT" clusters were found. The closest was cluster 1 which contained all of the QT drug samples and slightly more than the same number of NQT samples.

Section 3.2.4: Antifungal Agents

Cluster 2 was an "All QT" cluster. Cluster 8 had QT drugs making up slightly less than half of the cluster.

Section 3.2.5: Antifungals for Dermatological Use

There were no "All QT" clusters. Cluster 1 was mostly QT, Cluster 4 was less than half QT, and Cluster 10 was also slightly less than half QT.

Section 3.2.6: Anti-Infective Agents

Clusters 2, 3, 5 and 10 were "All QT" clusters. Cluster 11 was about half QT and half NQT.

Section 3.2.7: Antiinfectives for Systemic Use

Clusters 2 and 9 were "All QT". Cluster 1 was mostly QT, Cluster 11 was slightly more than half QT, Cluster 12 was all QT except for 1 entry, and Cluster 15 was approximately ¼ QT.

Section 3.2.8: Antineoplastic Agents

There were no "All QT" clusters. Cluster 1 contained all of the QT samples, which were approximately 1/3 of the samples in the cluster.

Section 3.2.9: Azoles

Cluster 1 was "All QT". Clusters 2 and 3 contained a small portion, less than ¼ QT, and Cluster 4

was "Mostly QT".

Section 3.2.10: BCRP/ABCG2 Substrates

There were no "All QT" clusters. Cluster 1 contained all of the QT samples, which comprised

slightly less than half of the samples in the cluster.

Section 3.2.11: Benzamidazoles

Cluster 1 was "All QT" and it contained all of the possible QT samples in this sub-class.

Section 3.2.12: Cardiovascular Agents

There were no "All QT" clusters. Custer 1 contained approximately half QT and half NQT. Cluster

2 was approximately 1/8 QT samples and the remainder were NQT.

Section 3.2.13: Cardiovascular System

No "All QT" clusters were found. Cluster 3 contained all of the QT samples, which comprised

approximately ¼ of the samples in the cluster.

Section 3.2.14: Central Nervous System Agents

No "All QT" clusters were found. Cluster 1 was comprised of approximately 1/3 QT samples.

Cluster 2 was also comprised of approximately 1/3 QT samples.

Section 3.2.15: Central Nervous System Depressants

No "All QT" clusters were found. Both Clusters 1 and 2 were comprised of slightly more than

half QT samples.

Section 3.2.16: Chemically-Induced Disorders

Cluster 5 was "All QT" and Cluster 6 was all but one QT. Cluster 1 was comprised of

approximately 2/3 QT samples. Cluster 8 was comprised of approximately 1/3 QT samples.

Section 3.2.17: Combined Inducers of CYP3A4 and P-Glycoprotein

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¾ QT samples.

Section 3.2.18: Combined Inhibitors of CYP3A4 and P-Glycoprotein

Clusters 2 and 3 were "All QT". Clusters 1 and 33 were comprised of mostly QT samples. Cluster 10 was comprised of approximately 2/3 QT samples. Clusters 4, 9, 10 and 16 were comprised of approximately half QT samples.

Section 3.2.19: CYP2D6 Inhibitors (Weak)

No "All QT" clusters were found. Cluster 1 was comprised of slightly more than half QT samples.

Section 3.2.20: CYP3A4 Inhibitors (Weak)

No "All QT" clusters were found. Cluster 1 was comprised of approximately 1/3 QT samples.

Section 3.2.21: Cytochrome P-450 CYP1A2 Inhibitors

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¼ QT samples. Cluster 2 was comprised of approximately 2/3 QT samples. Clusters 56 and 57 were comprised of approximately 1/3 and ¼ QT samples, respectively.

Section 3.2.22: Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

No "All QT" clusters were found. Cluster 1 was comprised of approximately 2/3 QT samples.

Section 3.2.23: Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Cluster 1 was "All QT". Cluster 2 was comprised of approximately ½ QT samples. Cluster 3 contained approximately 3/4 QT samples. Clusters 9 and 22 were comprised of approximately ½ QT samples.

Section 3.2.24: Cytochrome P-450 CYP1A2 Substrates

No "All QT" clusters were found. Cluster 1 contained approximately ¾ QT samples. Cluster 2 contained approximately ½ QT samples. Cluster 4 contained approximately 1/3 QT samples.

Section 3.2.25: Cytochrome P-450 CYP2A6 Inhibitors

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples. Cluster 2 contained all but 2 QT samples.

Section 3.2.26: Cytochrome P-450 CYP2A6 Substrates

No "All QT" clusters were found. Cluster 1 contained approximately ¾ QT samples.

Section 3.2.27: Cytochrome P-450 CYP2B6 Substrates

Clusters 2 and 4 were "All QT" clusters. Clusters 1 and 3 contained all but 1 QT sample. Cluster 5 contained all but 2 QT samples.

Section 3.2.28: Cytochrome P-450 CYP2C8 Inhibitors

No "All QT" clusters were found. Cluster 21 was comprised of approximately 1/3 QT samples.

Section 3.2.29: Cytochrome P-450 CYP2C8 Substrates

No "All QT" clusters were found. Cluster 1 contained approximately ¼ QT samples.

Section 3.2.30: Cytochrome P-450 CYP2C9 Inhibitors

No "All QT" clusters were found. Cluster 1 contains approximately ½ QT samples. Cluster 3 contains all but 1 QT sample. Cluster 6 contains approximately 1/3 QT samples. Cluster 66 contains approximately ¼ QT samples.

Section 3.2.31: Cytochrome P-450 CYP2C9 Substrates

No "All QT" clusters were found. Cluster 1 contained approximately ½ QT samples, and Clusters 19 and 47 contained all but one of the remaining QT Samples.

Section 3.2.32: Cytochrome P-450 CYP2C19 Inhibitors

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¼ QT samples. Cluster 2 was approximately ½ QT samples. Cluster 34 was approximately ½ QT samples. Cluster 44 was approximately 1/5 QT samples. Cluster 50 was approximately 1/6 QT samples.

Section 3.2.33: Cytochrome P-450 CYP2C19 Substrates

No "All QT" clusters were found. Cluster 1 contained all but 2 QT samples. Cluster 4 contained approximately 2/3 QT clusters. Cluster 5 contained 3 QT samples.

Section 3.2.34: Cytochrome P-450 CYP2D6 Inhibitors

Cluster 1 was slightly more than ½ QT samples. Cluster 3 was an "All QT" cluster. Cluster 4 was approximately 1/5 QT samples. Clusters 5 and 6 were "All QT". Cluster 7 contained all but 1 QT sample. Cluster 8 contained approximately ½ QT samples. Cluster 9 was "All QT". Cluster 10 was approximately 1/3 QT samples. Cluster 52 was slightly less than ½ QT samples.

Section 3.2.35: Cytochrome P-450 CYP2D6 Substrates

Cluster 1 contained all but 2 QT samples. Cluster 2 was approximately 2/3 QT samples. Cluster 3 was an "All QT" cluster. Cluster 4 was approximately ½ QT samples. Cluster 14 was approximately 1/3 QT samples.

Section 3.2.36: Cytochrome P-450 CYP2E1 Inhibitors

No "All QT" clusters were found. Cluster 1 contained slightly more than ½ QT samples.

Section 3.2.37: Cytochrome P-450 CYP2E1 Substrates

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples. Cluster 2 contained approximately 2/3 QT samples.

Section 3.2.38: Cytochrome P-450 CYP3A4 Substrates

No "All QT" clusters except for those having only one sample were found. Cluster 1 contained slightly more than ½ QT samples. Cluster 2 contained slightly less than ½ QT samples. Cluster 3 contained approximately 1/3 QT samples. Cluster 5 contained all but one QT sample. Cluster 8 contained slightly less than 1/3 QT samples. Cluster 9 contained approximately 1/3 QT samples. Cluster 88 contained approximately ¼ QT samples. Cluster 107 contained approximately ¼ QT samples. Cluster 116 contained approximately ¼ QT samples. Cluster 119 contained approximately 1/3 QT samples.

Section 3.2.39: Cytochrome P-450 CYP3A Inducers

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples.

Section 3.2.40: Cytochrome P-450 CYP3A Inhibitors

No "All QT" clusters were found except for one cluster containing only one sample. Cluster 1 contained approximately ½ QT samples. Cluster 5 contained 2 out of 3 QT samples. Cluster 6 contained slightly less than ½ QT samples. Cluster 26 contained 2 out of 5 QT samples. Cluster 30 contained approximately 1/3 QT samples. Cluster 53 contained approximately ¼ QT samples.

Section 3.2.41: Cytochrome P-450 Enzyme Inhibitors

Cluster 1 contained all but 1 QT sample. Clusters 5 and 6 were "All QT" samples. Cluster 7 contained all but 1 QT sample. Cluster 9 contained approximately ¼ QT samples. Cluster 13 contained slightly more than ¼ QT samples.

Section 3.2.42: Dermatologicals

No "All QT" clusters were found. Cluster 2 contained slightly less than ½ QT samples. Cluster 3 contained approximately 2/3 QT samples.

Section 3.2.43: Drugs for Acid Related Disorders

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was comprised of ½ QT samples.

Section 3.2.44: Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was comprised of ½ QT samples.

Section 3.2.45: Enzyme Inhibitors

Cluster 1 was comprised of approximately 1/3 QT samples. Cluster 2 was comprised of approximately 2/3 QT samples. Cluster 3 was comprised of approximately 2/3 QT samples. Cluster 4 was

comprised of approximately 1/10 QT samples. Cluster 5 was an "All QT" cluster. Cluster 6 contained 2 out of 3 QT samples.

Section 3.2.46: Estrogen Antagonists

No "All QT" clusters were found. Cluster 1 was comprised of approximately ½ QT samples.

Section 3.2.47: Fluoroquinolones

Cluster 1 was an "All QT" cluster.

Section 3.2.48: Gastrointestinal Agents

Cluster 1 was an "All QT" cluster. Cluster 2 was comprised of all but 2 QT samples. Cluster 7 was ½ comprised of QT samples.

Section 3.2.49: Heterocyclic Compounds

No "All QT" clusters were found. Cluster 2 contained 3 out of 5 QT samples. Cluster 4 was approximately 1/5 comprised of QT samples. Cluster 5 contained all but 1 QT sample. Cluster 6 was 1/3 comprised of QT samples. Cluster 10 was approximately ¼ comprised of QT samples. Cluster 16 was approximately ½ comprised of QT samples. Cluster 38 contained 4 QT samples of 53 total. Cluster 74 was approximately ¾ comprised of QT samples. Cluster 77 was approximately ¼ comprised of QT samples.

Section 3.2.50: Heterocyclic Compounds – 1 Ring

Cluster 1 was ½ comprised of QT samples. Clusters 2 and 3 were "All QT" clusters. Cluster 4 was approximately ¼ comprised of QT samples. Cluster 9 was approximately 1/3 comprised of QT samples. Cluster 10 was approximately ¼ comprised of QT samples. Cluster 57 was approximately 1/8 comprised of QT samples.

Section 3.2.51: Heterocyclic Compounds – 2 Ring

Cluster 2 was comprised of slightly less than ½ QT samples. Cluster 4 was comprised of slightly more than ½ QT samples. Cluster 50 was approximately 1/7 comprised of QT samples.

Section 3.2.52: Hormone Antagonists

Clusters 2 and 3 were "All QT" clusters. Cluster 4 was approximately ½ comprised of QT samples.

Section 3.2.53: Hormones, Hormone Substitutes, and Hormone Antagonists

No "All QT" clusters were found. Cluster 1 was 1/3 comprised of QT samples. Cluster 2 was approximately ½ comprised of QT samples.

Section 3.2.54: Hydrocarbons

No "All QT" clusters were found. Cluster 3 was approximately 1/7 comprised of QT samples.

Section 3.2.55: Hydrocarbons, Aromatic

No "All QT" clusters were found. Cluster 4 was approximately 1/10 comprised of QT samples.

Section 3.2.56: Hydrocarbons, Cyclic

No "All QT" clusters were found. Cluster 3 was approximately 1/6 comprised of QT samples.

Section 3.2.57: Hyperglycemia-Associated Agents

No "All QT" clusters were found. Cluster 1 was approximately ¼ comprised of QT samples.

Section 3.2.58: Hypotensive Agents

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was 1/3 comprised of QT samples.

Section 3.2.59: Imidazole Derivatives

No "All QT" clusters were found. Cluster 1 was approximately ½ comprised of QT samples.

Section 3.2.60: Inorganic Chemicals

No "All QT" clusters were found. Cluster 1 contained all but 2 QT samples. Cluster 2 contained all but 2 QT samples. Cluster 3 was approximately 1/5 comprised of QT samples.

Section 3.2.61: Nervous System

No "All QT" clusters were found. Cluster 1 was approximately 1/3 comprised of QT samples. Cluster 2 was comprised of slightly less than ½ QT samples. Cluster 24 was slightly more than 1/3 comprised of QT samples. Cluster 28 was comprised of slightly less than 1/3 QT samples.

Section 3.2.62: Neurotransmitter Agents

Cluster 1 was approximately 4/5 comprised of QT samples. Cluster 2 was 2/3 comprised of QT samples. Cluster 3 contained all but 1 QT sample. Cluster 4 was an "All QT" cluster. Cluster 15 was approximately 1/5 comprised of QT samples. Cluster 25 was approximately ¼ comprised of QT samples.

Section 3.2.63: Ophthalmologicals

Cluster 1 was an "All QT" cluster. Cluster 2 was slightly more than ½ comprised of QT samples. Cluster 23 was ½ comprised of QT samples.

Section 3.2.64: Peripheral Nervous System Agents

No "All QT" clusters were found. Cluster 1 contained 2 QT samples of 5 total samples. Cluster 2 was approximately 1/8 comprised of QT samples. Cluster 29 was approximately 1/3 comprised of QT samples.

Section 3.2.65: P-Glycoprotein/ABCB1 Inducers

No "All QT" clusters were found. Cluster 1 was slightly more than 1/3 comprised of QT samples.

Section 3.2.66: P-Glycoprotein/ABCB1 Inhibitors

No "All QT" clusters were found. Cluster 2 was approximately 2/3 comprised of QT samples. Cluster 3 contained 2 QT samples of 3 total. Cluster 5 was approximately 4/5 comprised of QT samples. Cluster 6 was slightly more than ½ comprised of QT samples. Cluster 8 contained 5 QT samples out of 7 total. Cluster 12 contained 3 QT samples of 4 total. Cluster 14 was slightly less than 1/3 comprised of QT samples. Cluster 37 was approximately 1/6 comprised of QT samples. Cluster 38 was 1/3 comprised of

QT samples. Cluster 47 was slightly more than ½ comprised of QT samples. Cluster 56 was slightly more than ¼ comprised of QT samples. Cluster 64 was slightly less than 1/3 comprised of QT samples.

Section 3.2.67: P-Glycoprotein/ABCB1 Substrates

Cluster 1 was an "All QT" cluster. Cluster 6 was approximately ¾ comprised of QT samples. Cluster 7 was slightly less than ½ comprised of QT samples. Cluster 9 was slightly more than 1/3 comprised of QT samples. Cluster 58 was approximately 1/10 comprised of QT samples.

Section 3.2.68: Piperazines

Clusters 1, 2, and 3, respectively, were "All QT" clusters.

Section 3.2.69: Polycyclic Compounds

No "All QT" clusters were found. Cluster 1 was slightly more than 1/3 comprised of QT samples. Cluster 2 was comprised of slightly more than 1/6 of QT samples.

Section 3.2.70: Psycholeptics

No "All QT" clusters were found. Cluster 1 was comprised of all but 1 QT sample. Cluster 2 was 1/3 comprised of QT samples.

Section 3.2.71: Respiratory System

Cluster 1 contained 3 QT samples of 4 total. Cluster 2 was an "All QT" cluster.

Section 3.2.72: Sensory Organs

No "All QT" clusters were found. Cluster 1 was slightly less than ¾ comprised of QT samples. Cluster 21 was slightly more than 1/3 comprised of QT samples.

Section 3.2.73: Steroid Synthesis Inhibitors

Clusters 1, 2, and 3, respectively were "All QT" clusters. Cluster 9 was slightly less than ¼ comprised of QT samples.

Section 3.2.74: Sulfonamides

No "All QT" clusters were found. Cluster 1 was ¾ comprised of QT samples.

Section 3.2.75: Sulfones

No "All QT" clusters were found. Cluster 1 was ¾ comprised of QT samples. Cluster 3 was slightly more than ¼ comprised of QT samples.

Section 3.2.76: Sulfur Compounds

No "All QT" clusters were found. Cluster 1 was more than ¾ comprised of QT samples. Cluster 2 was slightly more than ¼ comprised of QT samples. Cluster 9 was comprised of slightly less than ¼ QT samples. Cluster 23 was comprised of slightly less than 1/6 QT samples. Cluster 32 was comprised of slightly less than 1/6 QT samples.

Section 3.2.77: Topoisomerase II Inhibitors

No "All QT" clusters were found. Cluster 1 contains all but 1 QT sample.

Section 3.3: Molecular Pathways and Networks Associated with Genes Linked to the Autonomic Nervous System and Congenital Long QT Syndrome

A maximum of the top 50 differentially expressed probes from each of the classifications were identified. In some groups, there were fewer than 50 probes which were differentially expressed. In those cases, all available probes were used. Some of the differentially expressed genes were annotated as "transcribed locus" and did not correspond to a particular gene in the annotation file. Such probes were excluded from the list of genes that was ultimately entered into the String database search. The intention of the search was to look for links between cLQTS genes, genes associated with the autonomic nervous system, and the differentially expressed genes from the microarray data. The confirmed genes were loaded into the String database along with the genes associated with cLQTS and the genes known to be associated with the autonomic nervous system. For brevity, the cLQTS genes and ANS genes will be listed once, but for reproducibility, these genes in Table VII would be added to the group-specific genes listed for each respective group.

Since statistical significance (i.e. differential expression), or the lack thereof, does not always imply biological or clinical significance, so it is reasonable to expect that not all genes entered into the database search will return a connection. As time progresses, new information will likely be added to the String database, so connections identified using the group-specific list of genes today may return different results in the future. Similarly, if different databases are searched, it would be reasonable to expect somewhat different results from the same inputs. When provided by String, a link to the results in String is also provided. In all cases that follow, regardless of molecular activity, expression differences may still serve as a surrogate biomarker to predict QT prolongation.

Figure 12 is a legend from the String database describing the significance of node colors and contents and the significance of the colors of the edges connecting the nodes in the network connection output results for each of the groups that follow.

Figure 12: Legend from String Database which Applies to all String Output Displays
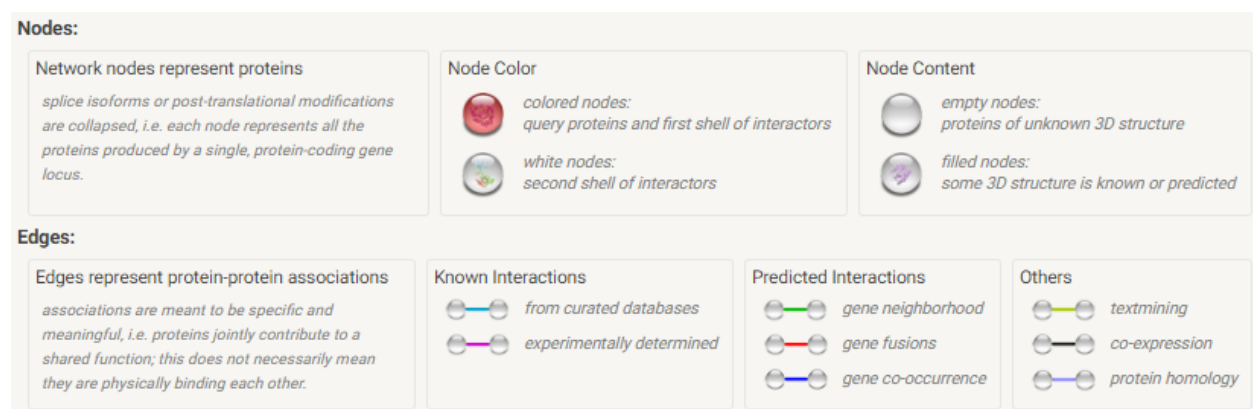
Table VII: Genes Associated with cLQTS and the Autonomic Nervous System Used as Inputs to String for All 77 Drug Classifications

Association	Gene Symbol
cLQTS Type 1	KCNQ1
cLQTS Type 2	KCNH2
cLQTS Type 2	ALG10
cLQTS Type 3	SCN5A
cLQTS Type 4	ANK2
cLQTS Type 5	KCNE1
cLQTS Type 6	KCNE2
cLQTS Type 7	KCNJ2
cLQTS Type 8	CACNA1C
cLQTS Type 9	CAV3
cLQTS Type 10	SCN4B
cLQTS Type 11	AKAP9
cLQTS Type 12	SNT1
cLQTS Type 13	KCNJ5
cLQTS Type 14	CALM1
cLQTS Type 15	CALM2
Autonomic Nervous System	ADRA1A
Autonomic Nervous System	ADRA1B
Autonomic Nervous System	ADRA1D
Autonomic Nervous System	ADRA2A
Autonomic Nervous System	ADRA2B
Autonomic Nervous System	ADRA2C
Autonomic Nervous System	ADRB1
Autonomic Nervous System	ADRB2
Autonomic Nervous System	ADRB3
Autonomic Nervous System	CHRM1
Autonomic Nervous System	CHRM2
Autonomic Nervous System	CHRM3
Autonomic Nervous System	CHRM4
Autonomic Nervous System	CHRM5
Autonomic Nervous System	CHRNA1
Autonomic Nervous System	CHRNA2
Autonomic Nervous System	CHRNA3
Autonomic Nervous System	CHRNA4
Autonomic Nervous System	CHRNA5
Autonomic Nervous System	CHRNA6
Autonomic Nervous System	CHRNA7
Autonomic Nervous System	CHRNA9
Autonomic Nervous System	CHRNA10
Autonomic Nervous System	CHRNB1
Autonomic Nervous System	CHRNB2
Autonomic Nervous System	CHRNB3
Autonomic Nervous System	CHRNB4
Autonomic Nervous System	CHRND
Autonomic Nervous System	CHRNE

Section 3.3.1: All Drugs (QT versus Non-QT)

Table VIII: Differentially Expressed Genes Used as Input from All Drugs (QT versus Non-QT)

Probe ID	Gene Symbol	Human Equivalent Gene Name
M30596_PROBE1	ME1	Malic enzyme 1
J02752_PROBE1	ACOX1	Acyl-CoA oxidase 1
AF111268_PROBE1	CD36	CD36 molecule
NM_019157_PROBE1	AQP7	Aquaporin 7
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
AA944380_PROBE1	NUDT7	Nudix hydrolase 7
AW141928_PROBE1	VNN1	Vanin 1
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
AW918222_PROBE1	TOR3A	Torsin family 3 member A
NM_012600_PROBE1	ME1	Malic enzyme 1
AF051561_PROBE1	SLC12A2	Solute carrier family 12 member 2
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
D00569_PROBE1	DECR1	2,4-dienoyl-CoA reductase 1
X13295_PROBE1	LCN2	Lipocalin 2
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
NM_017243_PROBE1	PRPS1	Phosphoribosyl pyrophosphate synthetase 1
AF034577_PROBE1	PDK4	Pyruvate dehydrogenase kinase 4
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
D87839_PROBE1	ABAT	4-aminobutyrate aminotransferase
AW918255_PROBE1	DGAT2	Diacylglycerol O-acyltransferase 2
Y00497_PROBE1	SOD2	Superoxide dismutase 2
BE104266_PROBE1	KNTC1	Kinetochore associated 1
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
NM_013200_PROBE1	CPT1B	Carnitine palmitoyltransferase 1B
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
NM_019179_PROBE1	TYMS	Thymidylate synthetase
NM_017208_PROBE1	LBP	Lipopolysaccharide binding protein
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
L18948_PROBE1	S100A9	S100 calcium binding protein A9

Figure 13: String Database Results for Top Differentially Expressed Genes from All Drugs (QT versus Non-QT)

Permanent Link: http://bit.ly/2xnogC4
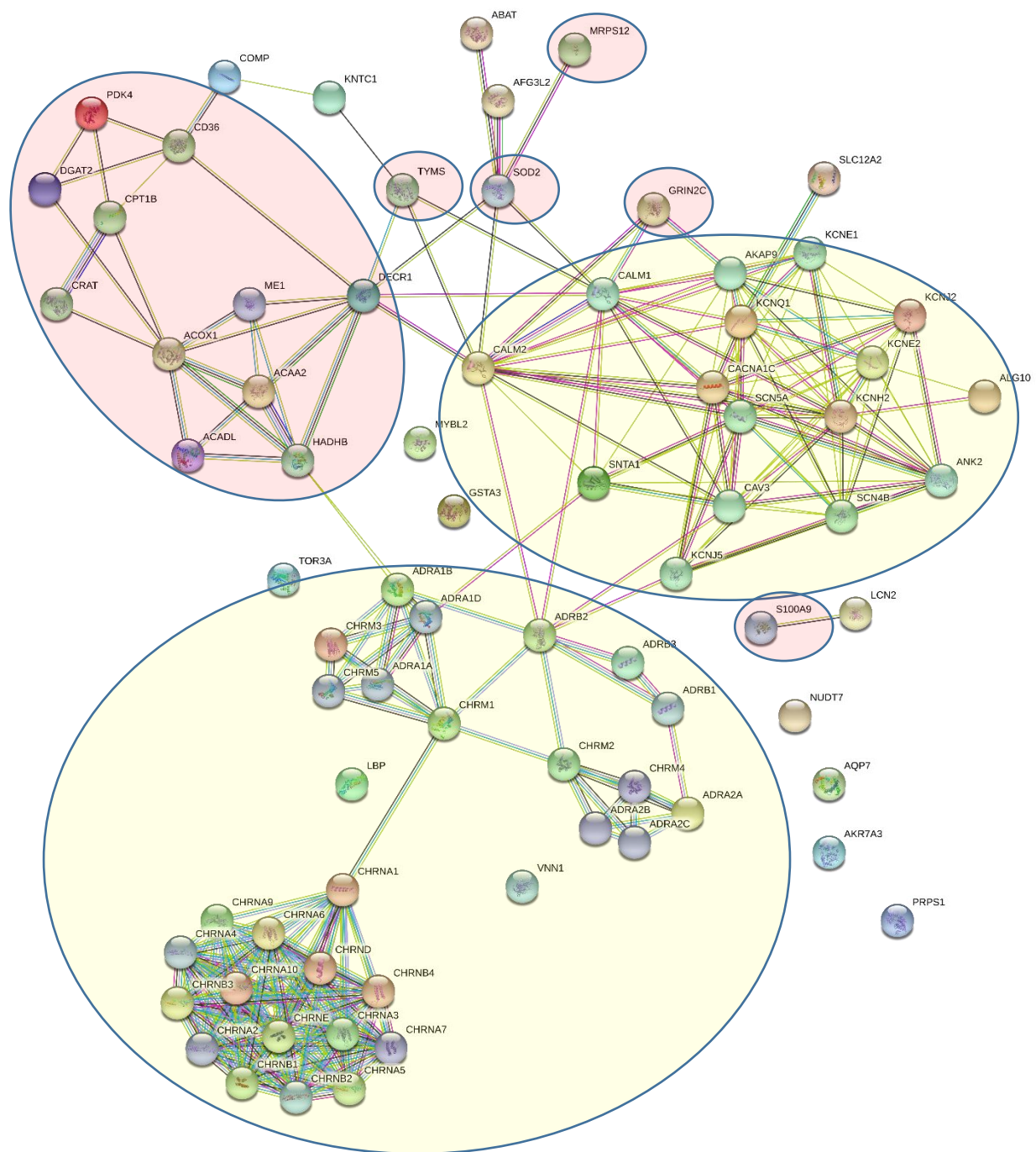
Section 3.3.1.1: Observations from String and Proposed Mechanisms from All Drugs (QT versus Non-QT)

In Figure 13, genes highlighted in yellow at the top right are associated with cLQTS. The group highlighted in yellow at the bottom represents genes associated with the autonomic nervous system.

PDK4, **DGAT2**, **CD36**, **CPT1B**, **CRAT**, **ME1**, **ACOX1**, **ACAA2**, **ACADL**, **DECR1**, and **HADHB** are associated with fatty acid metabolism. Mean expression of all of thes genes was lower in the QT group compared to the same probes in the NQT group.

SOD2 removes superoxide radicals which suggests a link to oxidative metabolism. Mean expression of SOD2 was lower in the QT group than the NQT group.

GRIN2C is a glutamate receptor and ion channel in nerve cells impacted by many pharmaceuticals, which might suggest a possible link to the autonomic nervous system. Mean expression of GRIN2C was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

S100A9 is associated with inflammatory and immune responses. Mean expression of S100A9 was lower in the QT group compared to the NQT group.

Section 3.3.2: Alimentary Tract and Metabolism

Table IX: Differentially Expressed Genes Used as Input using Drugs Classified in DrugBank as Alimentary Tract and Metabolism

Probe ID	Gene Symbol	Human Equivalent Gene Name
U02983_PROBE1	SCG3	Secretogranin III
L22558_PROBE1	HTR7	5-hydroxytryptamine receptor 7
D38072_PROBE1	PTPN12	Protein tyrosine phosphatase, non-receptor type 12
AF084975_PROBE1	P2RX3	Purinergic receptor P2X 3
AF070065_PROBE1	CIT	Citron rho-interacting serine/threonine kinase
X61925_PROBE1	PNLIPRP1	Pancreatic lipase related protein 1
NM_012886_PROBE1	TIMP3	TIMP metallopeptidase inhibitor 3
NM_021858_PROBE1	GNB3	G protein subunit beta 3
D38261_PROBE1	PPP2R2C	Protein phosphatase 2 regulatory subunit B gamma
D44481_PROBE1	CRK	CRK proto-oncogene, adaptor protein
AI170665_PROBE1	CHAC1	ChaC glutathione specific gamma-glutamylcyclotransferase 1
AF111268_PROBE1	CD36	CD36 molecule
J00696_PROBE1	ORM1	Orosomucoid 1
BE113656_PROBE1	TBX3	T-box 3
NM_012803_PROBE1	PROC	protein C, inactivator of coagulation factors Va and VIIIa
D00575_PROBE1	CGA	Glycoprotein hormones, alpha polypeptide
NM_017364_PROBE1	ZNF260	Zinc finger protein 260
AA818120_PROBE1	SLN	Sarcolipin
NM_012678_PROBE1	TPM4	Tropomyosin 4
X97831_PROBE1	SLC25A20	Solute carrier family 25 member 20
BF417292_PROBE1	KCNMA1	Potassium calcium-activated channel subfamily M alpha 1
NM_021841_PROBE1	GABRA6	Gamma-aminobutyric acid type A receptor alpha6 subunit
U89280_PROBE1	HSD17B6	Hydroxysteroid 17-beta dehydrogenase 6
Y15068_PROBE1	STIP1	Stress induced phosphoprotein 1
U02315_PROBE1	NRG1	Neuregulin 1
AB035722_PROBE1	NEU1	Neuraminidase 1
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2

Figure 14: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Alimentary Tract and Metabolism

Permanent Link: http://bit.ly/2xn2Wwy
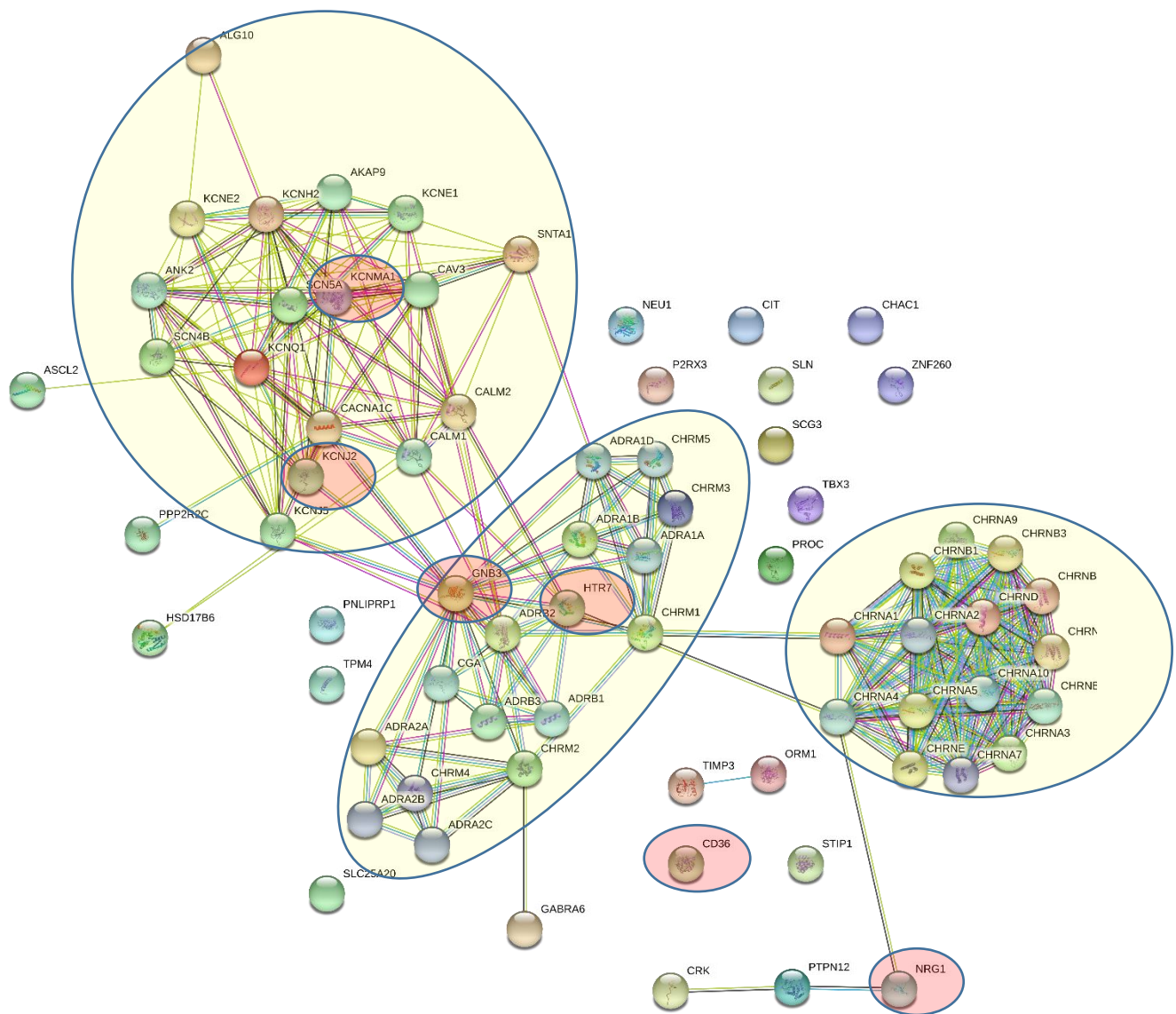
Section 3.3.2.1: Observations from String and Proposed Mechanisms from using Drugs Classified in DrugBank as Alimentary Tract and Metabolism

In Figure 14, genes highlighted in yellow in the top left are associated with cLQTS. Genes highlighted in the two yellow groups towards the bottom correspond to the ANS.

KCNMA1 is a potassium channel mediated by Ca^{2+}, which in turn might impact action potential duration in cardiomyocytes. Mean expression of KCNMA1 was lower in the QT group compared to the NQT group.

GNB3 modulates G protein messenger signal systems. Mean expression of GNB3 was lower in the QT group than the NQT group.

HTR7 is associated with G proteins. Mean expression of HTR7 was lower in the QT group compared to the NQT group.

CD36 is associated with immune responses and fatty acid metabolism. Mean expression of CD36 was lower in the QT group compared to the NQT group.

NRG1 is associated with MAPK processes. Mean expression of NRG1 was lower in the QT group compared to the NQT group.

Section 3.3.3: Amides

Table X: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Amides

Probe ID	Gene symbol	Human Equivalent Gene Name
U86635_PROBE1	GSTM5	Glutathione S-transferase mu 5
U94856_PROBE1	PON1	Paraoxonase 1
M22642_PROBE1	TK1	Thymidine kinase 1
AW251213_PROBE1	IPO7	Importin 7
AF092091_PROBE1	TSGA10	Testis specific 10
NM_017284_PROBE1	PSMB2	Proteasome subunit beta 2
U78889_PROBE1	DLL1	Delta like canonical Notch ligand 1
AI454418_PROBE1	IGSF1	Immunoglobulin superfamily member 1
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
U94709_PROBE1	PTGER4	Prostaglandin E receptor 4
AW916095_PROBE1	UBE4B	Ubiquitination factor E4B
AW253367_PROBE1	RNF10	Ring finger protein 10
NM_017063_PROBE1	KPNB1	Karyopherin subunit beta 1
AF020346_PROBE1	PDXK	Pyridoxal kinase
L38644_PROBE1	KPNB1	Karyopherin subunit beta 1
M30596_PROBE1	ME1	Malic enzyme 1
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
AB006137_PROBE1	FUT1	Fucosyltransferase 1 (H blood group)
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
BF544951_PROBE1	DDHD1	DDHD domain containing 1
NM_012739_PROBE1	ADRA2A	Adrenoceptor alpha 2A
NM_019179_PROBE1	TYMS	Thymidylate synthetase
AF222712_PROBE1	CTBP2	C-terminal binding protein 2
AF087696_PROBE1	MPP2	Membrane palmitoylated protein 2
NM_013078_PROBE1	OTC	Ornithine carbamoyltransferase
U40188_PROBE1	TAF9	TATA-box binding protein associated factor 9
AI170351_PROBE1	DUS4L	Dihydrouridine synthase 4 like
AA800803_PROBE1	DCAKD	Dephospho-CoA kinase domain containing
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
AF094609_PROBE1	SPATA7	Spermatogenesis associated 7
NM_012839_PROBE1	CYCS	Cytochrome c, somatic
U53512_PROBE1	MRPL17	Mitochondrial ribosomal protein L17
AI070123_PROBE1	SLURP1	Secreted LY6/PLAUR domain containing 1
U04808_PROBE1	CX3CR1	C-X3-C motif chemokine receptor 1
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
AJ011608_PROBE1	PRIM1	DNA primase subunit 1

Figure 15: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Amides
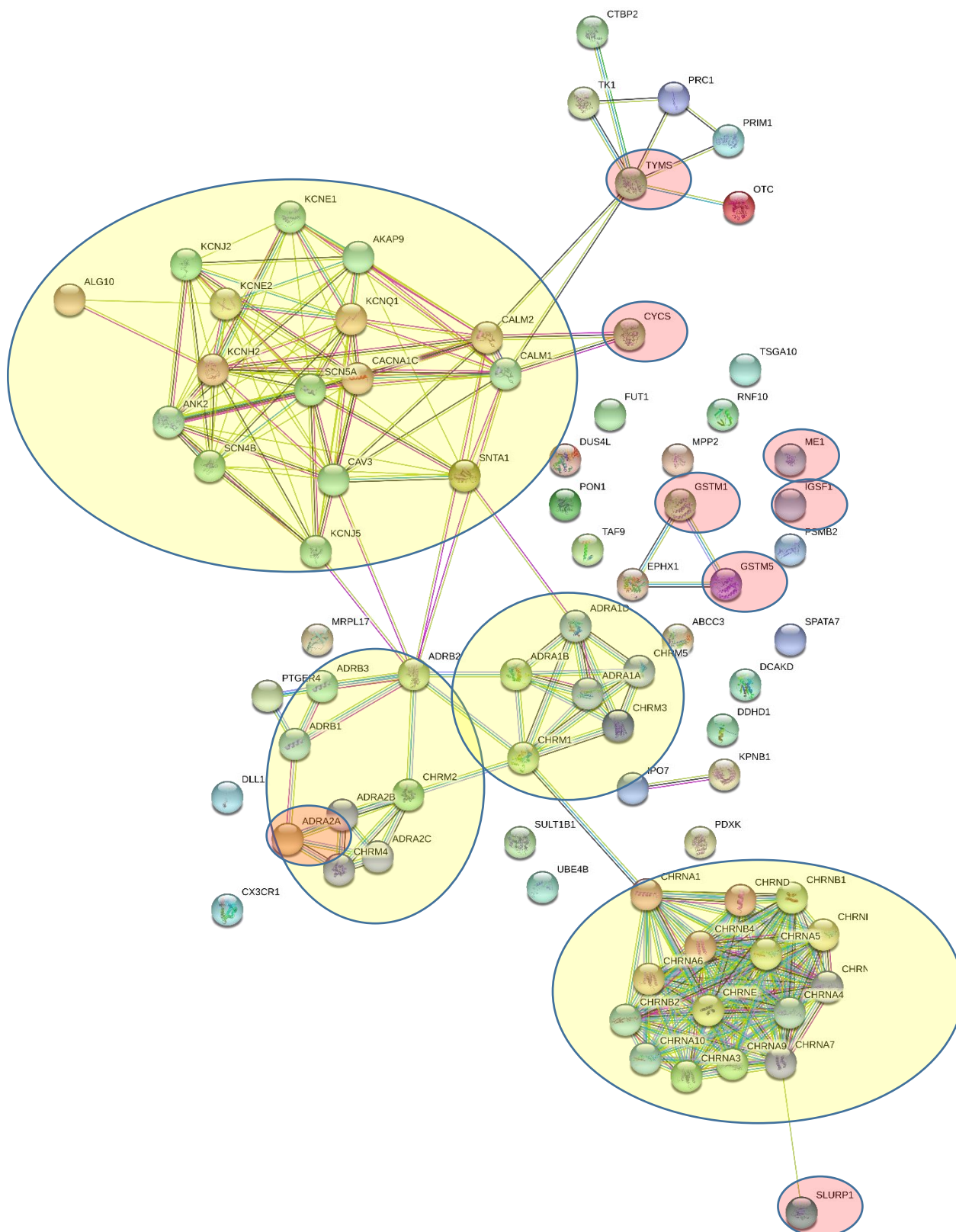
Section 3.3.3.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Amides

In Figure 15, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are highlighted yellow in the two sections towards the bottom.

CYCS has a role in electron transfer in the mitochondria and plays a role in apoptosis. Mean expression of CYCS was higher in the QT group compared to the NQT group.

GSTM1 and **GSTM5** are associated with glutathione. Mean expression of GSTM1 was lower in the QT group compared to the NQT group, while mean expression of GSTM5 was higher in the QT group compared to the same probes in the NQT group.

IGSF1 and **SLURP1** are associated with immune responses. Mean expression of IGSF1 was higher in the QT group compared to the NQT group. Mean expression of SLURP1 was lower in the QT group compared to the same probes in the NQT group.

ADRA2A is an adrenergic receptor which is part of the autonomic nervous system. Mean expression of ADRA2A was higher in the QT group compared to the NQT group.

TYMS is associated with mitochondrial metabolism. Mean expression of TYMS was less in the QT group compared to the NQT group.

ME1 is involved with fatty acid metabolism. Mean expression of ME1 was higher in the QT group compared to the NQT group.

Section 3.3.4: Antifungal Agents

Table XI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Antifungal Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012903_PROBE1	ANP32A	Acidic nuclear phosphoprotein 32 family member A
AA891834_PROBE1	COL4A5	Collagen type IV alpha 5 chain
AW916201_PROBE1	SCCPDH	Saccharopine dehydrogenase (putative)
NM_013027_PROBE1	SELENOW	Selenoprotein W
NM_013069_PROBE1	CD74	CD74 molecule
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
NM_017092_PROBE1	TYRO3	TYRO3 protein tyrosine kinase
BF557572_PROBE1	FGFR2	Fibroblast growth factor receptor 2
NM_017313_PROBE1	RAB3IP	RAB3A interacting protein
AI172272_PROBE1	TCEA3	Transcription elongation factor A3
NM_019206_PROBE1	STK10	Serine/threonine kinase 10
BE103543_PROBE1	RFC1	Replication factor C subunit 1
M63991_PROBE1	SERPINA7	Serpin family A member 7
AA850909_PROBE1	NECTIN2	Nectin cell adhesion molecule 2
AB012759_PROBE1	PREP	Prolyl endopeptidase
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
AW921149_PROBE1	C2	Complement C2
BF405883_PROBE1	DHX16	DEAH-box helicase 16
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
BE111773_PROBE1	TARBP2	TARBP2, RISC loading complex RNA binding subunit
AF004811_PROBE1	MSN	Moesin
AB001982_PROBE1	GHSR	Growth hormone secretagogue receptor
AI229684_PROBE1	TSEN34	tRNA splicing endonuclease subunit 34
AI406275_PROBE1	CBX7	Chromobox 7
AW918493_PROBE1	PGLS	6-phosphogluconolactonase
BF282646_PROBE1	SMPDL3A	Sphingomyelin phosphodiesterase acid like 3A
X55995_PROBE1	DMGDH	Dimethylglycine dehydrogenase
AI232098_PROBE1	CRYZ	Crystallin zeta
NM_012758_PROBE1	SYK	Spleen associated tyrosine kinase

Figure 16: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Antifungal Agents

Permanent Link: http://bit.ly/2xntHkw
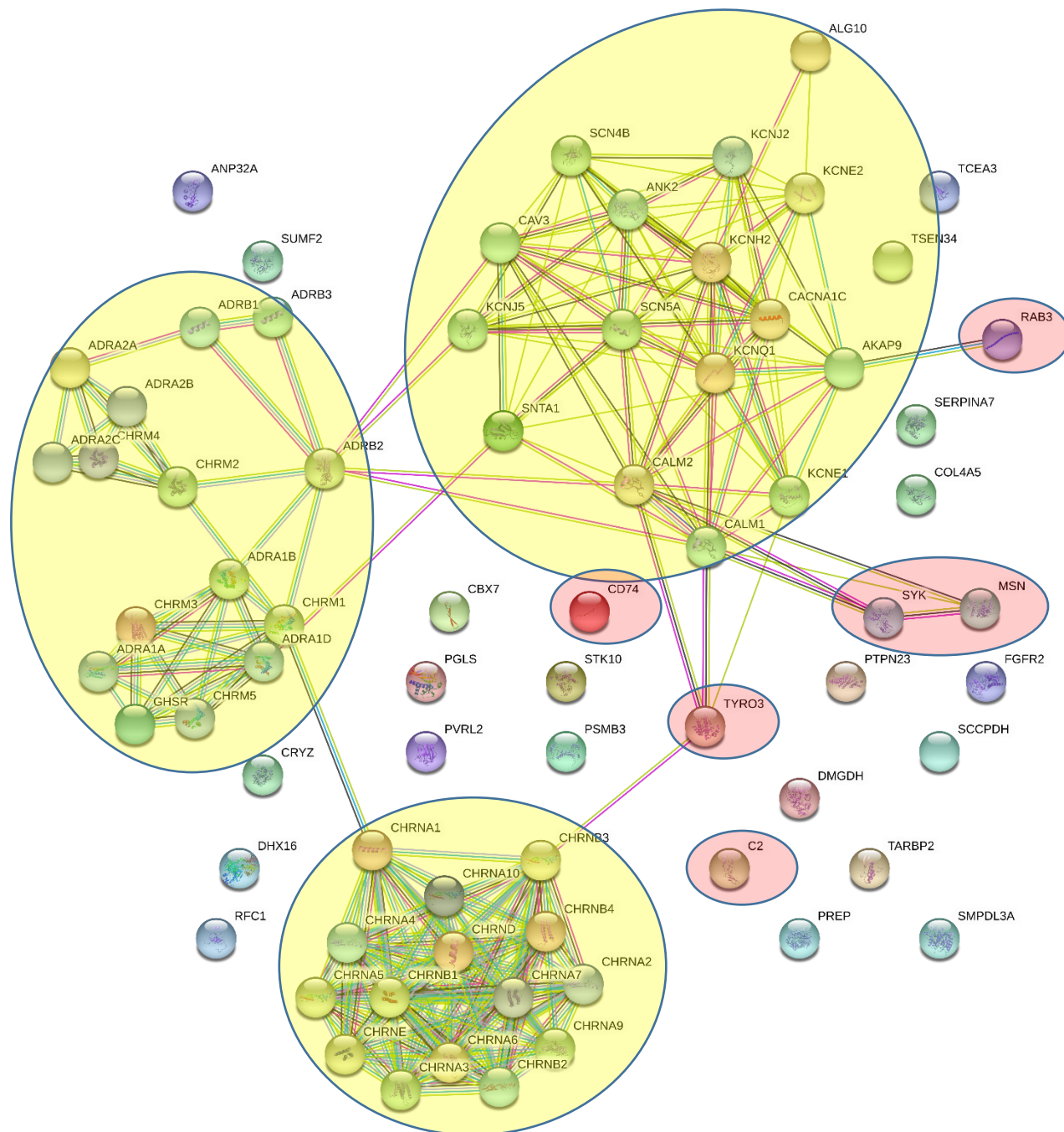
Section 3.3.4.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Antifungal Agents

In Figure 16, connected genes associated with cLQTS are highlighted in yellow at the top right.

Genes associated with the ANS are highlighted in the two yellow sections at the left and bottom.

CD74, **TYRO3**, **C2**, **SYK**, and **MSN** are associated with immune responses. Mean expression of all

of these was lower in the QT group compared to the same probes in the NQT group.

RAB3IP is associated with G protein activity. Mean expression of RAB3IP was higher in the QT

group compared to the NQT group.

Section 3.3.5: Antifungals for Dermatological Use

Table XII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Antifungals for Dermatological Use

Probe ID	Gene Symbol	Human Equivalent Gene Name
AA874881_PROBE1	ADNP	Activity dependent neuroprotector homeobox
AI044638_PROBE1	SERTAD2	SERTA domain containing 2
NM_012758_PROBE1	SYK	Spleen associated tyrosine kinase
D70816_PROBE1	CPLX2	Complexin 2
D90035_PROBE1	PPP3CA	Protein phosphatase 3 catalytic subunit alpha
AA945062_PROBE1	ARHGAP8	Rho GTPase activating protein 8
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
D86557_PROBE1	CAMK1G	Calcium/calmodulin dependent protein kinase IG
AF004811_PROBE1	MSN	Moesin
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
AW921149_PROBE1	C2	Complement C2
BF544320_PROBE1	KIF2A	Kinesin family member 2A
BF544703_PROBE1	CPLX1	Complexin 1
AA891834_PROBE1	COL4A5	Collagen type IV alpha 5 chain
AW916201_PROBE1	SCCPDH	Saccharopine dehydrogenase (putative)

Figure 17: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Antifungals for Dermatological Use

Permanent Link: http://bit.ly/2xn1jPt

Section 3.3.5.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Antifungals for Dermatological Use

In Figure 17, genes associated with cLQTS are highlighted in yellow at the top left. Genes

associated with the ANS are highlighted yellow in the sections at the center and lower right corner.

CAMK1G might suggest that calcium dependencies may play a role. Mean expression of

CAMK1G was lower in the QT group compared to the NQT group.

C2, **SKY**, and **MSN** are associated with immune responses. Mean expression of all three was

lower in the QT group compared to the same probes in the NQT group.

Section 3.3.6: Anti-Infective Agents

Table XIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Anti-Infective Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012545_PROBE1	DDC	Dopa decarboxylase
BF544703_PROBE1	CPLX1	Complexin 1
AW253895_PROBE1	BAP1	BRCA1 associated protein 1
AA892325_PROBE1	CEPT1	Choline/ethanolamine phosphotransferase 1
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
NM_021657_PROBE1	PHLPP1	PH domain and leucine rich repeat protein phosphatase 1
AW142847_PROBE1	HSF2	Heat shock transcription factor 2
AI169375_PROBE1	NUP93	Nucleoporin 93
AI408713_PROBE1	IMPACT	Impact RWD domain protein
BF283754_PROBE1	CASP7	Caspase 7
BF281319_PROBE1	TBCE	Tubulin folding cofactor E
AA819871_PROBE1	CDC16	Cell division cycle 16
AW143149_PROBE1	GNPDA2	Glucosamine-6-phosphate deaminase 2
L19698_PROBE1	RALA	RAS like proto-oncogene A
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
AA944079_PROBE1	ADAM8	ADAM metallopeptidase domain 8
AI103106_PROBE1	LMNB1	Lamin B1
AF017637_PROBE1	CPZ	Carboxypeptidase Z
AI176781_PROBE1	FDFT1	Farnesyl-diphosphate farnesyltransferase 1
AA799829_PROBE1	ATP5S	ATP synthase, H+ transporting, mitochondrial Fo complex subunit s (factor B)
BF544320_PROBE1	KIF2A	Kinesin family member 2A
AI009197_PROBE1	VKORC1	Vitamin K epoxide reductase complex subunit 1
AW534533_PROBE1	SPAST	Spastin
BF551318_PROBE1	HERC4	HECT and RLD domain containing E3 ubiquitin protein ligase 4
U09824_PROBE1	LGALS8	Galectin 8

Figure 18: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Anti-Infective Agents

Permanent Link: http://bit.ly/2xnuBxq
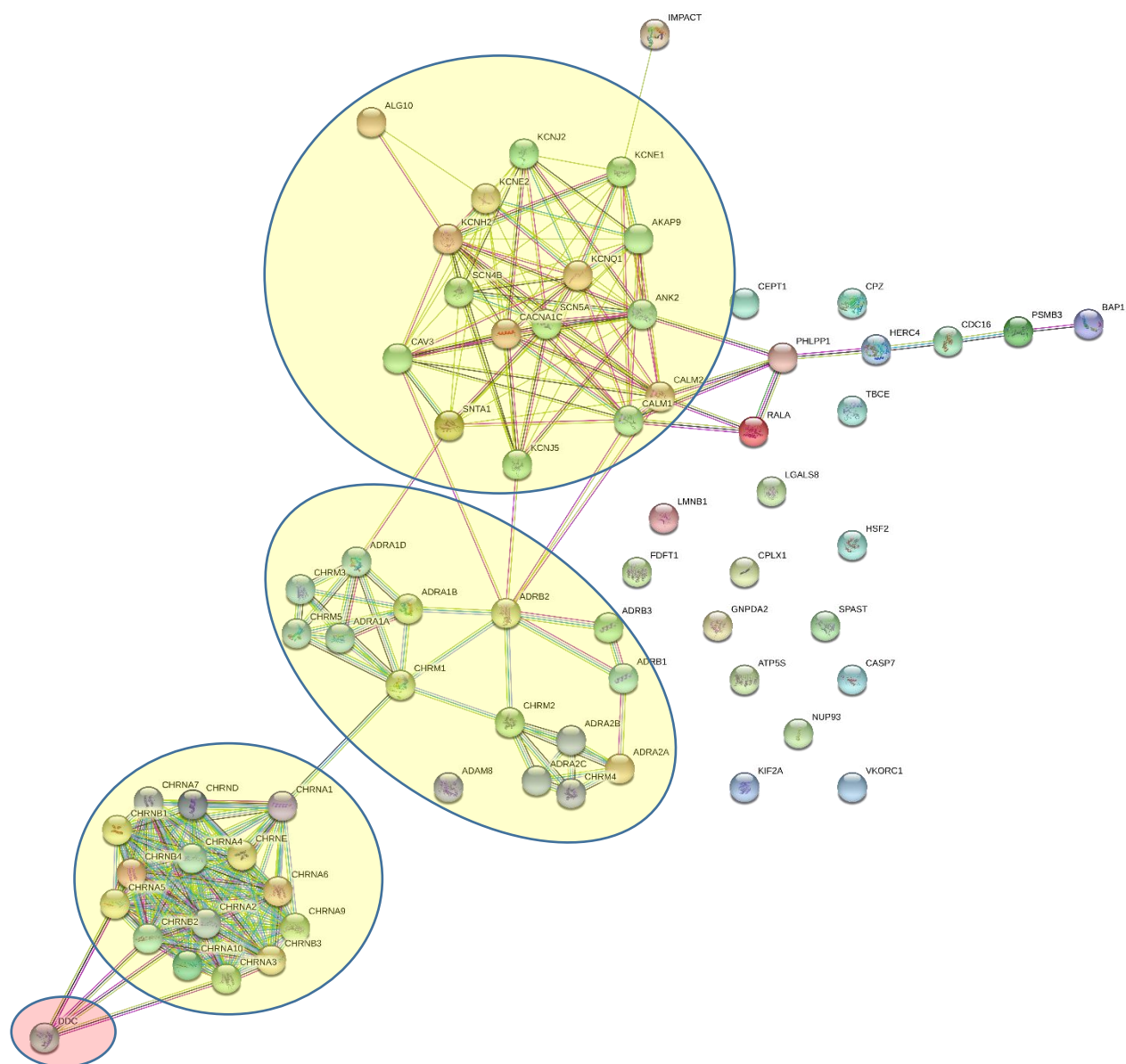
Section 3.3.6.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Anti-Infective Agents

Inf Figure 18, genes associated with cLQTS are highlighted in yellow at the top. Genes

associated with the ANS are highlighted yellow in the sections at the center and lower left corner.

DDC is a catalytic enzyme involved with catecholamines biosynthesis, which by extension, could

directly impact autonomic nervous system activity or the heart. Mean expression of DDC was lower in

the QT group compared to the NQT group.

Section 3.3.7: Antiinfectives for Systemic Use

Table XIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Antiinfectives for Systemic Use

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012545_PROBE1	DDC	Dopa decarboxylase
BF544703_PROBE1	CPLX1	Complexin 1
NM_021657_PROBE1	PHLPP1	PH domain and leucine rich repeat protein phosphatase 1
AA892325_PROBE1	CEPT1	Choline/ethanolamine phosphotransferase 1
AW253895_PROBE1	BAP1	BRCA1 associated protein 1
AW142847_PROBE1	HSF2	Heat shock transcription factor 2
M23601_PROBE1	MAOB	Monoamine oxidase B
AW143149_PROBE1	GNPDA2	Glucosamine-6-phosphate deaminase 2
AW534533_PROBE1	SPAST	Spastin
AB032178_PROBE1	COX17	COX17, cytochrome c oxidase copper chaperone
J04112_PROBE1	FBP1	Fructose-bisphosphatase 1
AI175030_PROBE1	MLH3	MutL homolog 3
BF281319_PROBE1	TBCE	Tubulin folding cofactor E
AI408713_PROBE1	IMPACT	Impact RWD domain protein
AI169375_PROBE1	NUP93	Nucleoporin 93
AF046886_PROBE1	AXL	AXL receptor tyrosine kinase
AI406275_PROBE1	CBX7	Chromobox 7
BE109075_PROBE1	ZFYVE21	Zinc finger FYVE-type containing 21
AA819871_PROBE1	CDC16	Cell division cycle 16
BF544320_PROBE1	KIF2A	Kinesin family member 2A
AA891746_PROBE1	EDF1	Endothelial differentiation related factor 1
AA946349_PROBE1	NUDT3	Nudix hydrolase 3
BF283754_PROBE1	CASP7	Caspase 7
BF415024_PROBE1	HIGD1B	HIG1 hypoxia inducible domain family member 1B
AW920527_PROBE1	ADHFE1	Alcohol dehydrogenase, iron containing 1
AW918154_PROBE1	MRPL51	Mitochondrial ribosomal protein L51

Figure 19: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Antiinfectives for Systemic Use

Permanent Link: http://bit.ly/2xnCIKf
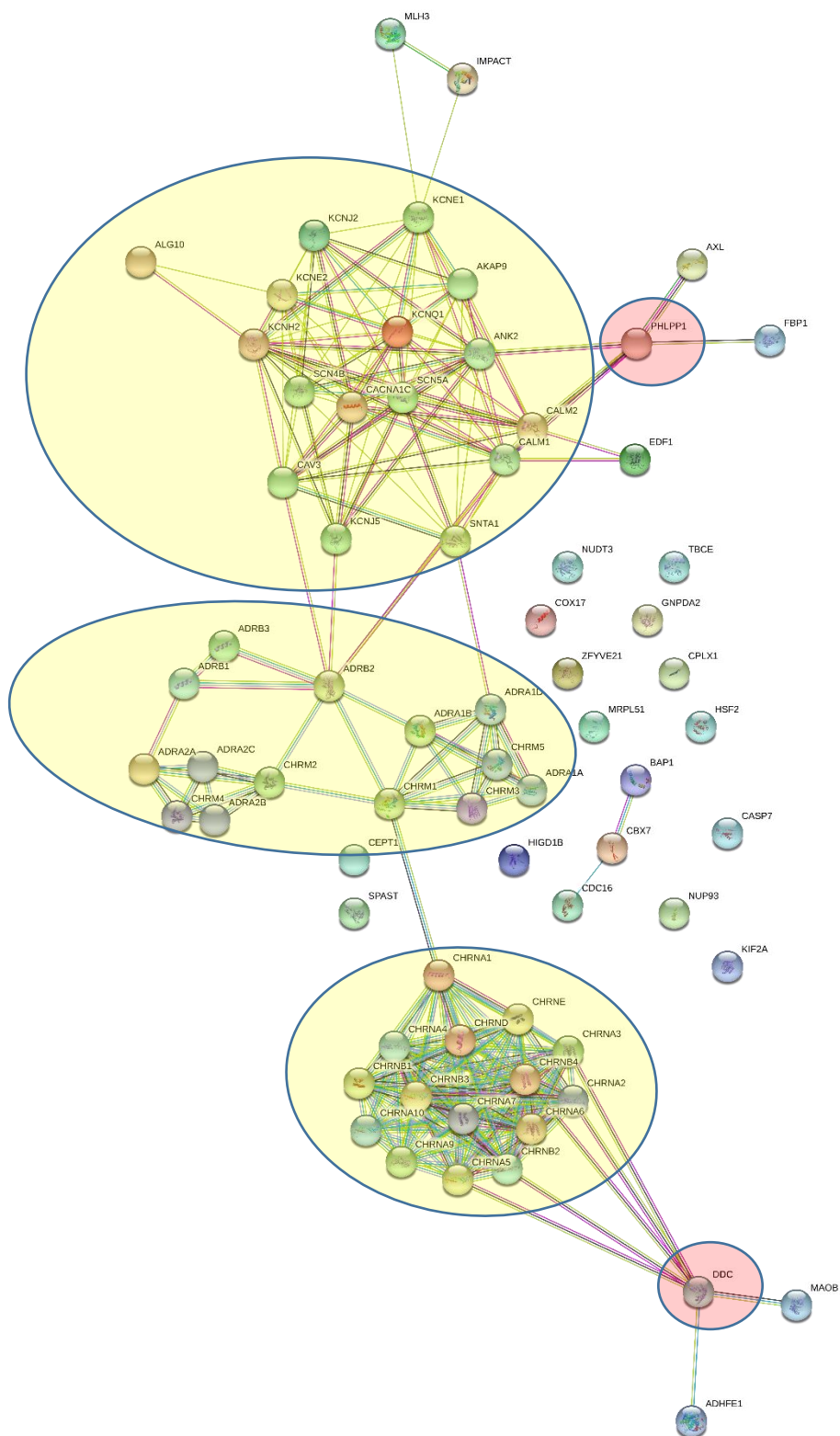
Section 3.3.7.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Antiinfectives for Systemic Use

In Figure 19, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the sections at the center and bottom.

DDC is a catalytic enzyme involved with catecholamines biosynthesis, which by extension, could directly impact autonomic nervous system activity. Mean expression of DDC was lower in the QT group compared to the NQT group.

PHLPP1 is involved with kinase activity, immune-related activities such as the regulation of apoptosis, cytokines, and the function and activity of T cells. Mean expression of PHLPP1 was lower in the QT group compared to the NQT group.

Section 3.3.8: Antineoplastic Agents

Table XV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Antineoplastic Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
NM_017034_PROBE1	PIM1	Pim-1 proto-oncogene, serine/threonine kinase
NM_021654_PROBE1	GJA4	Gap junction protein alpha 4
AF062402_PROBE1	VCAN	Versican
NM_021858_PROBE1	GNB3	G protein subunit beta 3
AI233199_PROBE1	FMO5	Flavin containing monooxygenase 5
AW144510_PROBE1	TAX1BP3	Tax1 binding protein 3
AF154114_PROBE1	PGLYRP1	Peptidoglycan recognition protein 1
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
D00833_PROBE1	GLRA1	Glycine receptor alpha 1
L33413_PROBE1	AGER	Advanced glycosylation end-product specific receptor
NM_012490_PROBE1	ACR	Acrosin
X70871_PROBE1	CCNG1	Cyclin G1
NM_012706_PROBE1	GRPR	Gastrin releasing peptide receptor
D28508_PROBE1	JAK3	Janus kinase 3
D10354_PROBE1	GPT	Glutamic--pyruvic transaminase
M84488_PROBE1	VCAM1	Vascular cell adhesion molecule 1
NM_012923_PROBE1	CCNG1	Cyclin G1
NM_017129_PROBE1	CTF1	Cardiotrophin 1
U90888_PROBE1	AMPD3	Adenosine monophosphate deaminase 3
AF013241_PROBE1	P2RX2	Purinergic receptor P2X 2
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
AW252096_PROBE1	FGF12	Fibroblast growth factor 12
L20900_PROBE1	ICA1	Islet cell autoantigen 1
AF016247_PROBE1	DDR2	Discoidin domain receptor tyrosine kinase 2
BF407531_PROBE1	RASL10B	RAS like family 10 member B
NM_012719_PROBE1	SSTR1	Somatostatin receptor 1
AI070394_PROBE1	BRINP2	BMP/retinoic acid inducible neural specific 2
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
L05435_PROBE1	SV2A	Synaptic vesicle glycoprotein 2A
AI012356_PROBE1	STAT3	Signal transducer and activator of transcription 3

Figure 20: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Antineoplastic Agents

Permanent Link: http://bit.ly/2w7NUvW
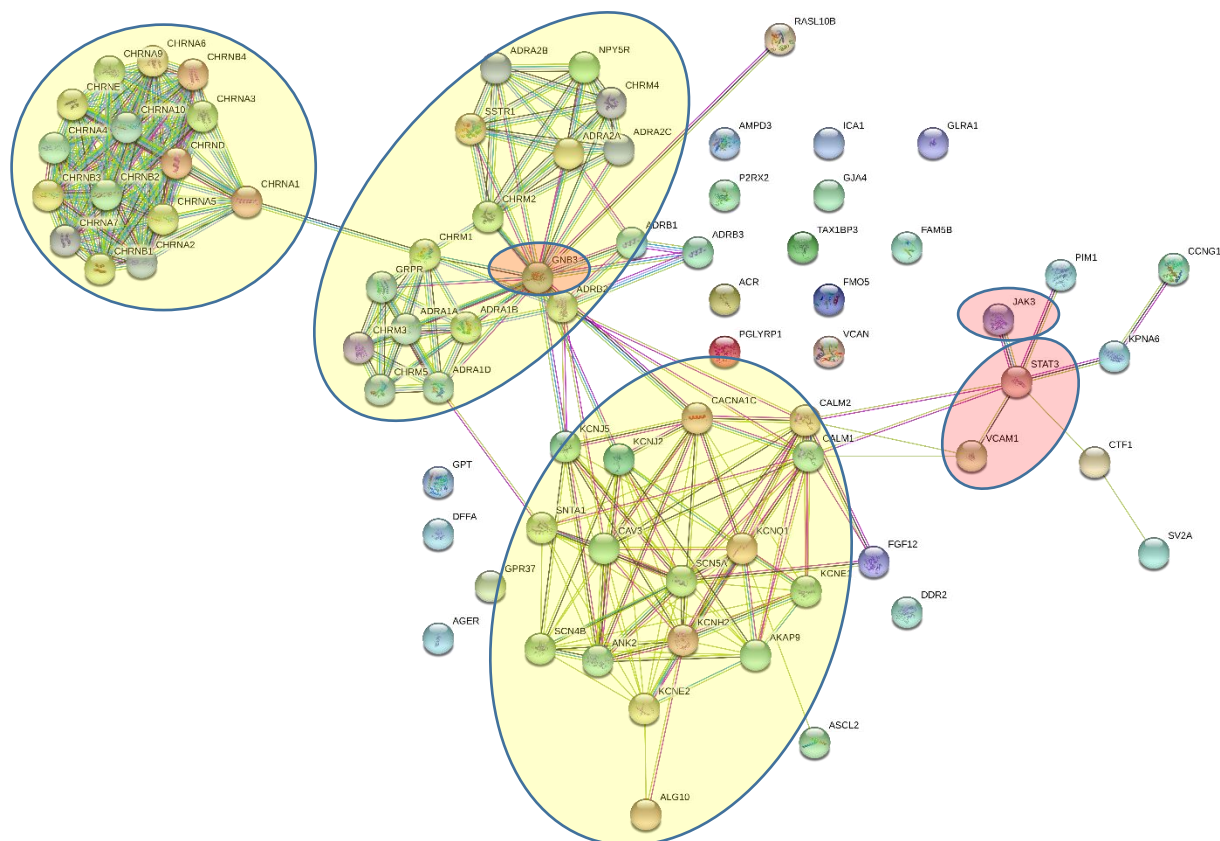
Section 3.3.8.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Antineoplastic Agents

In Figure 20, genes associated with cLQTS are highlighted in yellow in the center. Genes associated with the ANS are highlighted yellow in the sections at the top left and top center.

GNB3 is associated with G protein activity, signal transduction pathways, and second messengers. Mean expresrsion of GNB3 was lower in the QT group compared to the NQT group.

STAT3 suggests differences in immune responses related to interleukins and macrophages. Mean expression of STAT3 was lower in the QT group compared to the NQT group.

VCAM1 is associated with cell adhesion in immune responses. Mean expression of VCAM1 was lower in the QT group compared to the NQT group.

JAK3 is associated with immune responses. Mean expression of JAK3 was lower in the QT group compared to the NQT group.

Section 3.3.9: Azoles

Table XVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Azoles

Probe ID	Gene Symbol	Human Equivalent Gene Name
D00569_PROBE1	DECR1	2,4-dienoyl-CoA reductase 1
AF118816_PROBE1	ACKR3	Atypical chemokine receptor 3
AI137488_PROBE1	PGRMC2	Progesterone receptor membrane component 2
NM_017127_PROBE1	CHKA	Choline kinase alpha
NM_012846_PROBE1	FGF1	Fibroblast growth factor 1
NM_012627_PROBE1	PKIB	cAMP-dependent protein kinase inhibitor beta
NM_017136_PROBE1	SQLE	Squalene epoxidase
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
U10697_PROBE1	ESS2	Ess-2 splicing factor homolog
AF279918_PROBE1	RGS2	Regulator of G protein signaling 2
U02096_PROBE1	FABP7	Fatty acid binding protein 7
D50559_PROBE1	MSMO1	Methylsterol monooxygenase 1
NM_017268_PROBE1	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
M83107_PROBE1	TAGLN	Transgelin
AW916201_PROBE1	SCCPDH	Saccharopine dehydrogenase (putative)
AF218568_PROBE1	CYR61	Cysteine rich angiogenic inducer 61
NM_019124_PROBE1	RABEP1	Rabaptin, RAB GTPase binding effector protein 1
NM_012941_PROBE1	CYP51A1	Cytochrome P450 family 51 subfamily A member 1
BF555867_PROBE1	HTRA3	HtrA serine peptidase 3
AF003835_PROBE1	IDI1	Isopentenyl-diphosphate delta isomerase 1
NM_012878_PROBE1	SFTPD	Surfactant protein D
NM_012492_PROBE1	ADRB2	Adrenoceptor beta 2
AF013144_PROBE1	DUSP5	Dual specificity phosphatase 5
AI179443_PROBE1	MAN1C1	Mannosidase alpha class 1C member 1
NM_013127_PROBE1	CD38	CD38 molecule
D37885_PROBE1	CHKA	Choline kinase alpha
D38104_PROBE1	CTSE	Cathepsin E
AF075704_PROBE1	SLC38A1	Solute carrier family 38 member 1
AF163321_PROBE1	PGRMC1	Progesterone receptor membrane component 1
NM_012545_PROBE1	DDC	Dopa decarboxylase
AF004218_PROBE1	SIGMAR1	Sigma non-opioid intracellular receptor 1
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
AW141445_PROBE1	RAC2	Rac family small GTPase 2
BF558694_PROBE1	RAB27A	RAB27A, member RAS oncogene family

Figure 21: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Azoles

Permanent Link: http://bit.ly/2w8mGFx
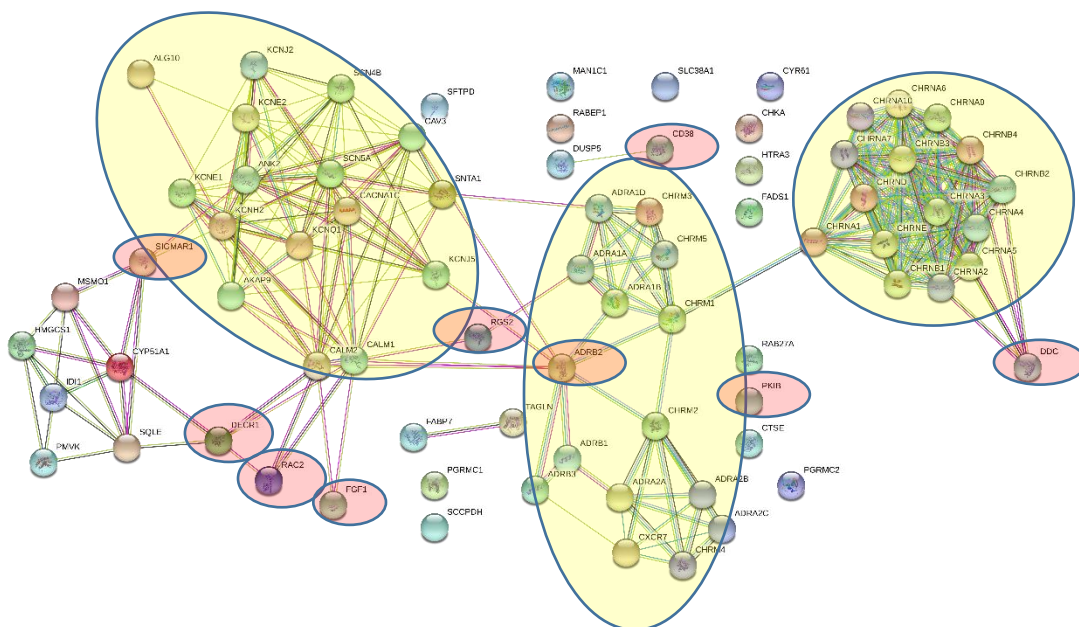
Section 3.3.9.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Azoles

In Figure 21, genes associated with cLQTS are highlighted in yellow on the left. Genes associated with the ANS are highlighted yellow in the sections at the center and right.

FABP7 and **FADS1** are involved with lipid metabolism. Mean expression of both FABP7 and FADS1 were lower in the QT group compared to the same probe in the NQT group.

DECR1 is associated with mitochondrial changes in electron transport. Mean expression of DECR1 was lower in the QT group compared to the NQT group.

ADRA2B is an adrenergic receptor associated with the ANS. Mean expression of ADRA2B was lower in the QT group compared to the NQT group.

75

DDC is associated with catecholamine biosynthesis. Mean expression of DDC was lower in the QT group compared to the NQT group.

RGS2 and **RAC2** are associated with G protein activity. RAC2 is also involved with the production of reactive oxygen species. Mean expression of both RGS2 and RAC2 were lower in the QT group compared to the same probe in the NQT group.

CD38 is associated with immune responses and insulin activity. Mean expression of CD38 was lower in the QT group compared to the NQT group.

SIGMAR1 is involved with calcium signaling and potassium ion channel regulation. Mean expression of SIGMAR1 was lower in the QT group compared to the NQT group.

FGF1 and **PKIB** are associated with MAPK activities. Mean expression of both FGF1 and PKIB were lower in the QT group compared to the same probe in the NQT group.

Section 3.3.10: BCRP/ABCG2 Substrates

Table XVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as BCRP/ABCG2 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
M34643_PROBE1	NTF3	Neurotrophin 3
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
U13253_PROBE1	COL4A1	Collagen type IV alpha 1 chain
AI233199_PROBE1	FMO5	Flavin containing monooxygenase 5
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36
AW917160_PROBE1	SLC19A2	Solute carrier family 19 member 2
AI235282_PROBE1	LRP1	LDL receptor related protein 1
X53003_PROBE1	ACACA	Acetyl-CoA carboxylase alpha
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
AA800232_PROBE1	NRBP1	Nuclear receptor binding protein 1
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
AI013474_PROBE1	ABHD2	Abhydrolase domain containing 2
AI136709_PROBE1	RND2	Rho family GTPase 2
M22631_PROBE1	PCCA	Propionyl-CoA carboxylase alpha subunit
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
AF036255_PROBE1	TRIM3	Tripartite motif containing 3
X76996_PROBE1	GZMB	Granzyme B
NM_012946_PROBE1	SPARCL1	SPARC like 1
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
NM_012931_PROBE1	BCAR1	BCAR1, Cas family scaffolding protein
AF154114_PROBE1	PGLYRP1	Peptidoglycan recognition protein 1
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3
AI556246_PROBE1	TRIM26	Tripartite motif containing 26
AW434978_PROBE1	KDELC2	KDEL motif containing 2
D11444_PROBE1	CXCL1	C-X-C motif chemokine ligand 1
D28508_PROBE1	JAK3	Janus kinase 3
AI070394_PROBE1	BRINP2	BMP/retinoic acid inducible neural specific 2

Figure 22: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as BCRP/ABCG2 Substrates

Permanent Link: http://bit.ly/2w8uB61
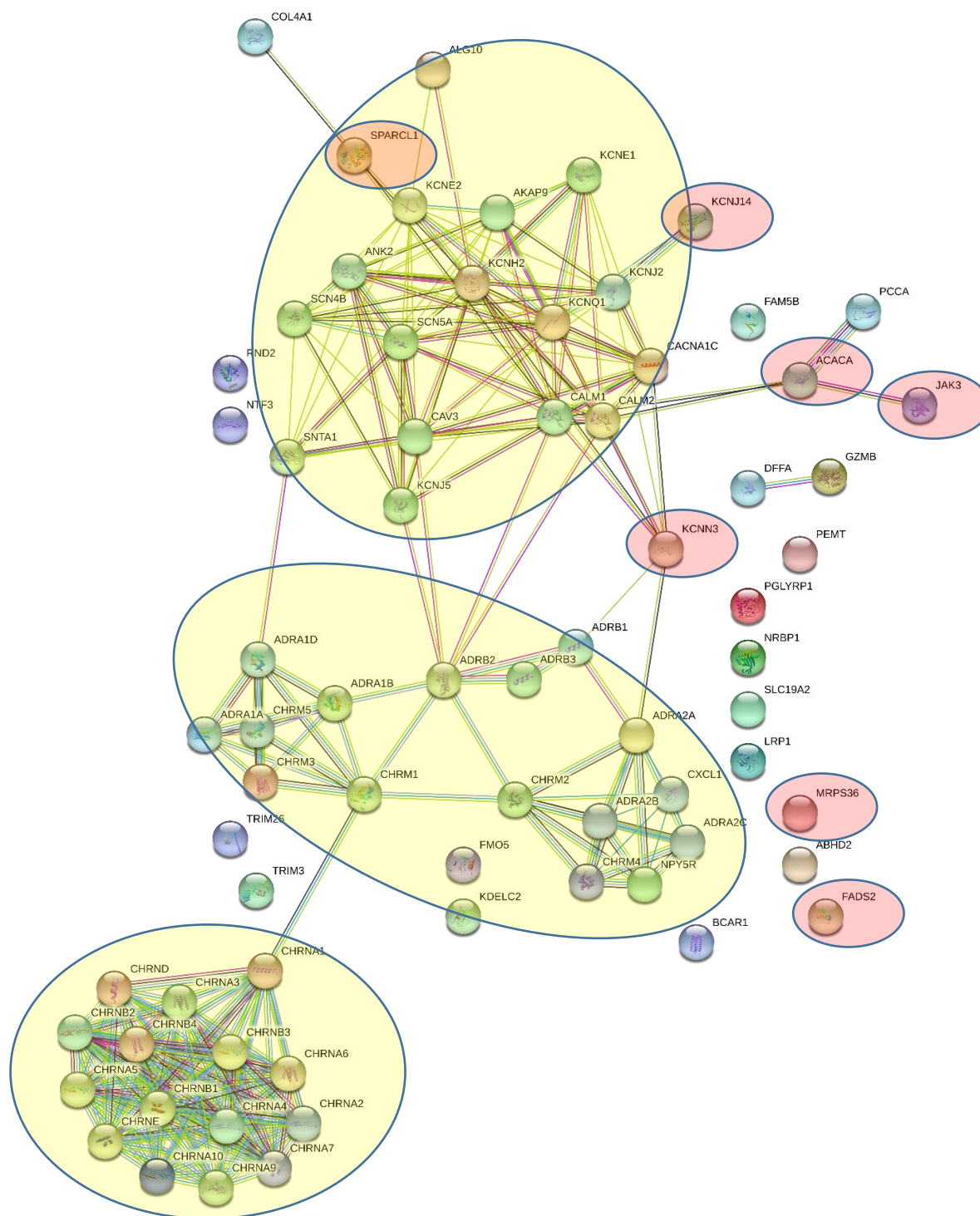
Section 3.3.10.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as BCRP/ABCG2 Substrates

In Figure 22, genes associated with cLQTS are highlighted in yellow at the top, except for SPARCL1, which is not a gene associated with cLQTS. Genes associated with the ANS are highlighted yellow in the sections at the center and bottom left.

SPARCL1 is associated with calcium ion binding. Mean expression of SPARCL1 was lower in the QT group compared to the NQT group.

KCNJ14 and **KCNN3** are potassium ion channels which were differentially expressed in this group. Mean expression of both KCNJ14 and KCNN3 were lower in the QT group compared to the same probes in the NQT group.

FADS2 and **ACACA** are associated with fatty acid metabolism. Mean expression of both FADS2 and ACACA were lower in the QT group compared to the same probes in the NQT group.

JAK3 is associated with an immune response. Mean expression of JAK3 was lower in the QT group compared to the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was lower in the QT group compared to the NQT group.

Section 3.3.11: Benzamidazoles

Table XVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Benzamidazoles

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB040804_PROBE1	GPR173	G protein-coupled receptor 173
NM_017119_PROBE1	GZMK	Granzyme K
AW144499_PROBE1	NXT1	Nuclear transport factor 2 like export factor 1
BE116768_PROBE1	RRAS2	RAS related 2
NM_017164_PROBE1	CAPZA3	Capping actin protein of muscle Z-line alpha subunit 3
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
BF412037_PROBE1	PEX2	Peroxisomal biogenesis factor 2
M84725_PROBE1	TAGLN3	Transgelin 3
NM_012725_PROBE1	KLKB1	Kallikrein B1
AF003944_PROBE1	NR2F2	Nuclear receptor subfamily 2 group F member 2
U78126_PROBE1	MAPKAP1	Mitogen-activated protein kinase associated protein 1
AI234142_PROBE1	IQCB1	IQ motif containing B1
AA942681_PROBE1	ATP6V1H	ATPase H+ transporting V1 subunit H
AI013800_PROBE1	TERF2	Telomeric repeat binding factor 2
AB011533_PROBE1	LRP4	LDL receptor related protein 4
U85512_PROBE1	GCHFR	GTP cyclohydrolase I feedback regulator
AI059234_PROBE1	LRBA	LPS responsive beige-like anchor protein
X52477_PROBE1	C3	Complement C3
NM_021578_PROBE1	TGFB1	Transforming growth factor beta 1
AW918408_PROBE1	CDC42EP5	CDC42 effector protein 5
U26397_PROBE1	INPP4A	Inositol polyphosphate-4-phosphatase type I A
NM_012920_PROBE1	CAMK2A	Calcium/calmodulin dependent protein kinase II alpha
NM_021841_PROBE1	GABRA6	Gamma-aminobutyric acid type A receptor alpha6 subunit
AF235993_PROBE1	BAX	BCL2 associated X, apoptosis regulator
AW916592_PROBE1	NDUFB7	NADH:ubiquinone oxidoreductase subunit B7
D84667_PROBE1	PI4KB	Phosphatidylinositol 4-kinase beta
M91597_PROBE1	NME2	NME/NM23 nucleoside diphosphate kinase 2
AI012598_PROBE1	TRMT2A	tRNA methyltransferase 2 homolog A
AI178938_PROBE1	CHCHD3	Coiled-coil-helix-coiled-coil-helix domain containing 3
BF389882_PROBE1	SHPRH	SNF2 histone linker PHD RING helicase
L16922_PROBE1	PGR	Progesterone receptor
NM_017271_PROBE1	NUDC	Nuclear distribution C, dynein complex regulator

Figure 23: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Benzamidazoles

Permanent Link: http://bit.ly/2w7VyGE
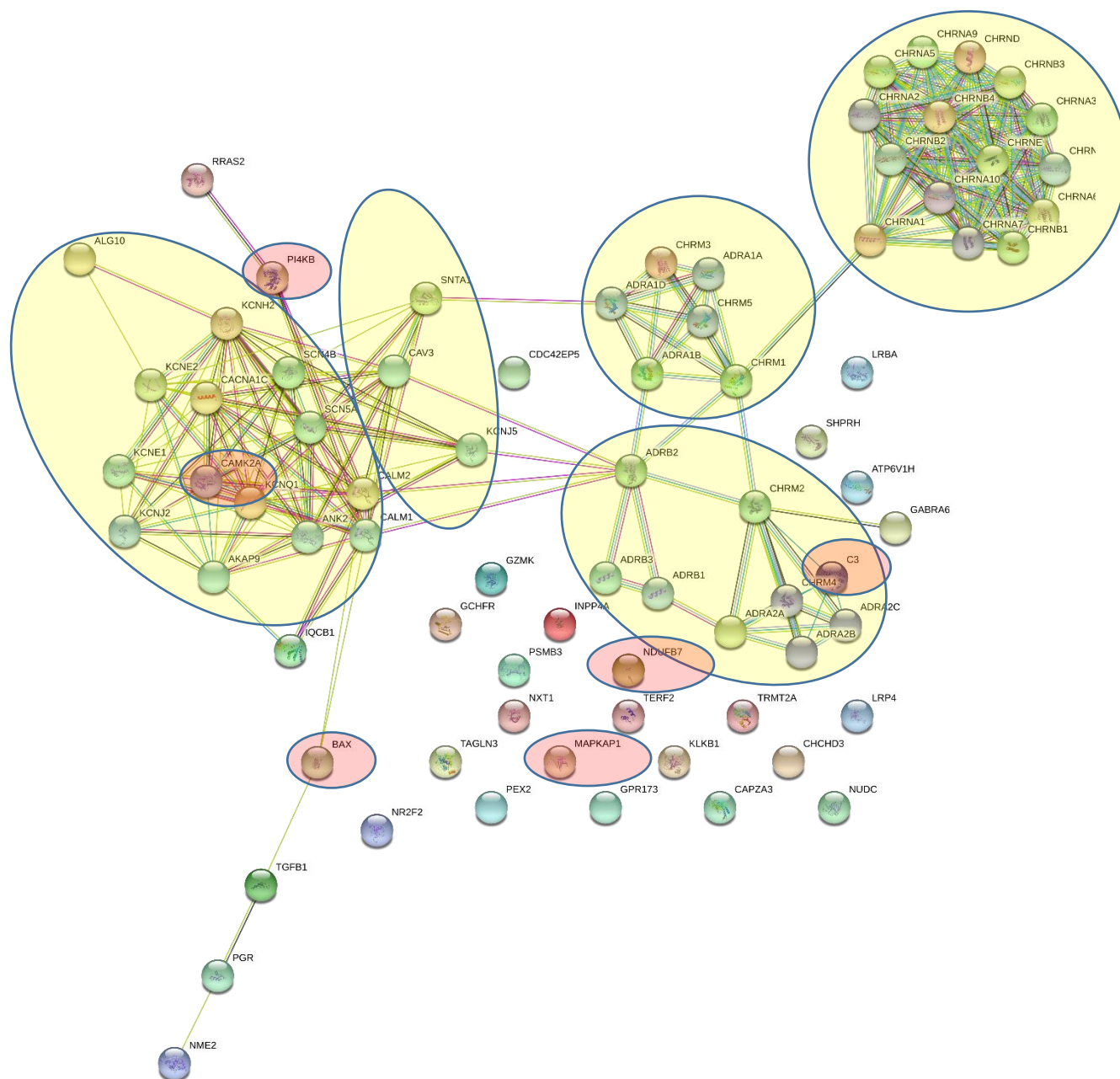
Section 3.3.11.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Benzamidazoles

In Figure 23, genes associated with cLQTS are highlighted in yellow in the two groups on the left. Genes associated with the ANS are highlighted yellow in the three sections on the left.

BAX is associated with apoptosis. Mean expression of BAX was higher in the QT group compared to the NQT group.

CAMK2A is a calcium-dependent protein kinase. Mean expression of CAMK2A was lower in the QT group compared to the NQT group.

MAPKAP1 is a differentially expressed MAPK. Mean expression of MAPKAP1 was lower in the QT group compared with the NQT group.

C3 is associated with immune responses and regulation of MAPKs. Mean expression of C3 was higher in the QT group compared to the NQT group.

PI4KB and **GPR173** are associated with G protein activity. Mean expression of PI4KB was higher in the QT group compared to the NQT group. Mean expression of GPR173 was lower in the QT group compared to the NQT group.

NDUFB7 is associated with NADH and electron transport. Mean expression of NDUFB7 was higher in the QT group compared to the NQT group.

Section 3.3.12: Cardiovascular Agents

Table XIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cardiovascular Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
M22642_PROBE1	TK1	Thymidine kinase 1
U66470_PROBE1	CGREF1	Cell growth regulator with EF-hand domain 1
AI101475_PROBE1	DCTPP1	dCTP pyrophosphatase 1
AW915563_PROBE1	SPC25	SPC25, NDC80 kinetochore complex component
U45986_PROBE1	MXD3	MAX dimerization protein 3
X74835_PROBE1	CHRND	Cholinergic receptor nicotinic delta subunit
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
AW914085_PROBE1	RPS19	Ribosomal protein S19
AW253880_PROBE1	KIFC1	Kinesin family member C1
BE099950_PROBE1	ADPRHL2	ADP-ribosylhydrolase like 2
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
AW921151_PROBE1	NHP2	NHP2 ribonucleoprotein
NM_012514_PROBE1	BRCA1	BRCA1, DNA repair associated
X97121_PROBE1	NTSR2	Neurotensin receptor 2
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
BE104266_PROBE1	KNTC1	Kinetochore associated 1
L02615_PROBE1	PKIA	cAMP-dependent protein kinase inhibitor alpha
NM_012597_PROBE1	LIPC	Lipase C, hepatic type
NM_017325_PROBE1	RUNX1	Runt related transcription factor 1
AF306458_PROBE1	STMN2	Stathmin 2
AW251335_PROBE1	SPC24	SPC24, NDC80 kinetochore complex component
U61261_PROBE1	LAMA3	Laminin subunit alpha 3
AW251213_PROBE1	IPO7	Importin 7
AW915824_PROBE1	CD302	CD302 molecule
D88190_PROBE1	STK39	Serine/threonine kinase 39
NM_019309_PROBE1	GRIK2	Glutamate ionotropic receptor kainate type subunit 2
AA850509_PROBE1	TRIP13	Thyroid hormone receptor interactor 13
AF220760_PROBE1	TXNRD1	Thioredoxin reductase 1
BE106888_PROBE1	CRELD2	Cysteine rich with EGF like domains 2
L02530_PROBE1	FZD2	Frizzled class receptor 2

Figure 24: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cardiovascular Agents
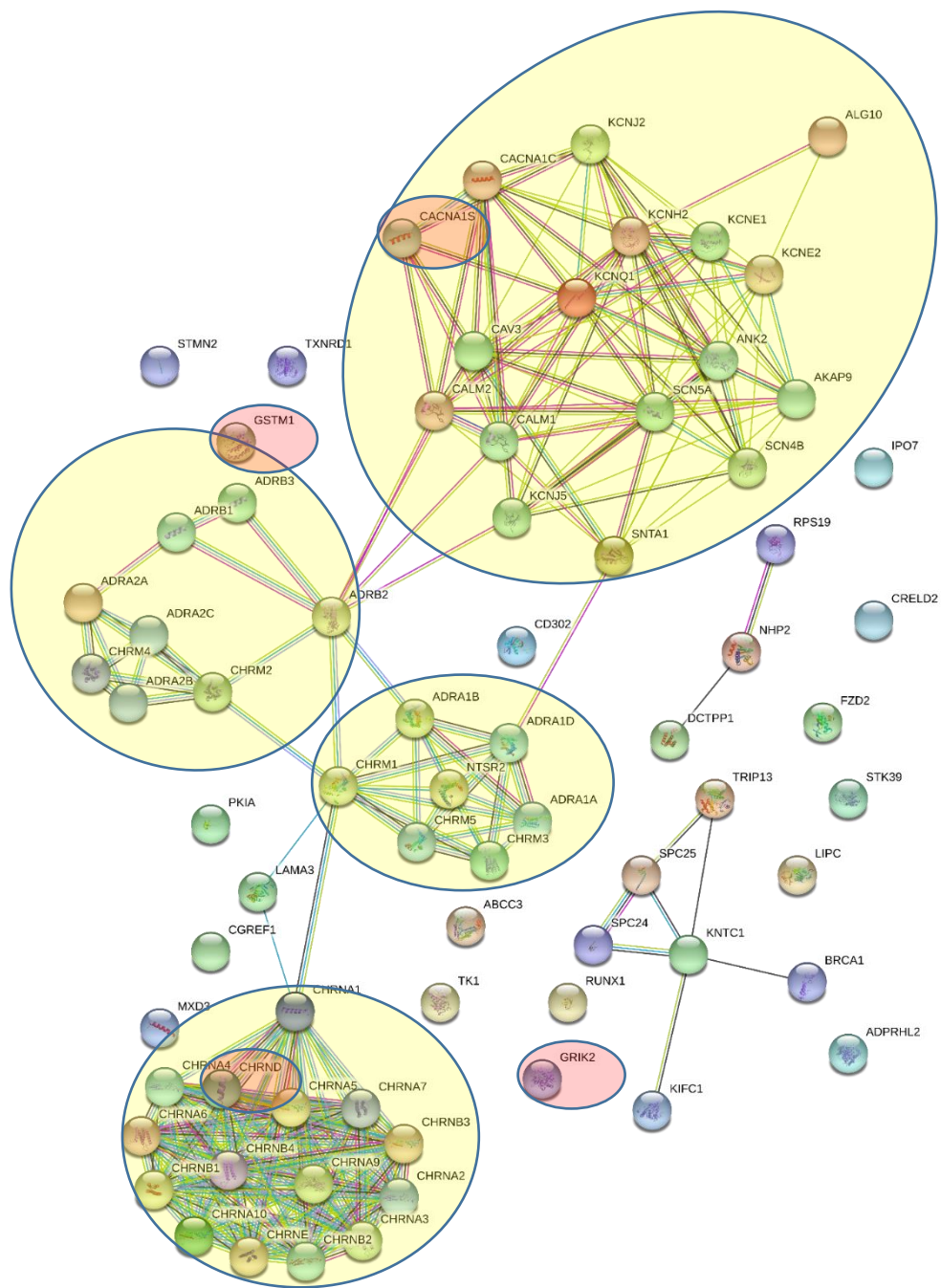
Permanent Link: http://bit.ly/2xnEr2k

Section 3.3.12.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cardiovascular Agents

In Figure 24, genes associated with cLQTS are highlighted in yellow in the two groups on the top. Genes associated with the ANS are highlighted yellow in the bottom three sections.

GSTM1 is associated with glutathione. Mean expression of GTSM1 was lower in the QT group compared to the NQT group.

CACNA1S is a calcium channel involved with excitation-contraction coupling which was differentially expressed in this group suggesting a possible influence of cytoplasmic calcium concentrations. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

GIRK2 is a G protein linked potassium channel which may also play a role in insulin regulation. Mean expression of GIRK2 was lower in the QT group compared to the NQT group.

CHRND is a chonliergic receptor which was also differentially expressed in this group, suggesting potential modifications of ANS activity. Mean expression of CHRND was lower in the QT group compared to the NQT group.

Section 3.3.13: Cardiovascular System

Table XX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cardiovascular System

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36
AA848834_PROBE1	DHDDS	Dehydrodolichyl diphosphate synthase subunit
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
M30596_PROBE1	ME1	Malic enzyme 1
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
NM_012600_PROBE1	ME1	Malic enzyme 1
AW915009_PROBE1	DHDDS	Dehydrodolichyl diphosphate synthase subunit
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
BE116152_PROBE1	ELOVL6	ELOVL fatty acid elongase 6
NM_012497_PROBE1	ALDOC	Aldolase, fructose-bisphosphate C
NM_017025_PROBE1	LDHA	Lactate dehydrogenase A
AB004329_PROBE1	ACACB	Acetyl-CoA carboxylase beta
NM_017177_PROBE1	CHKB	Choline kinase beta
AF254802_PROBE1	SLC4A4	Solute carrier family 4 member 4
L20900_PROBE1	ICA1	Islet cell autoantigen 1
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
AI411194_PROBE1	PNPLA2	Patatin like phospholipase domain containing 2
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
AW916819_PROBE1	NCKIPSD	NCK interacting protein with SH3 domain
NM_017083_PROBE1	MYO5B	Myosin VB
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
BE108830_PROBE1	SMOX	Spermine oxidase
AW919036_PROBE1	MGLL	Monoglyceride lipase
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3

Figure 25: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cardiovascular System

Permanent Link: http://bit.ly/2xngGas
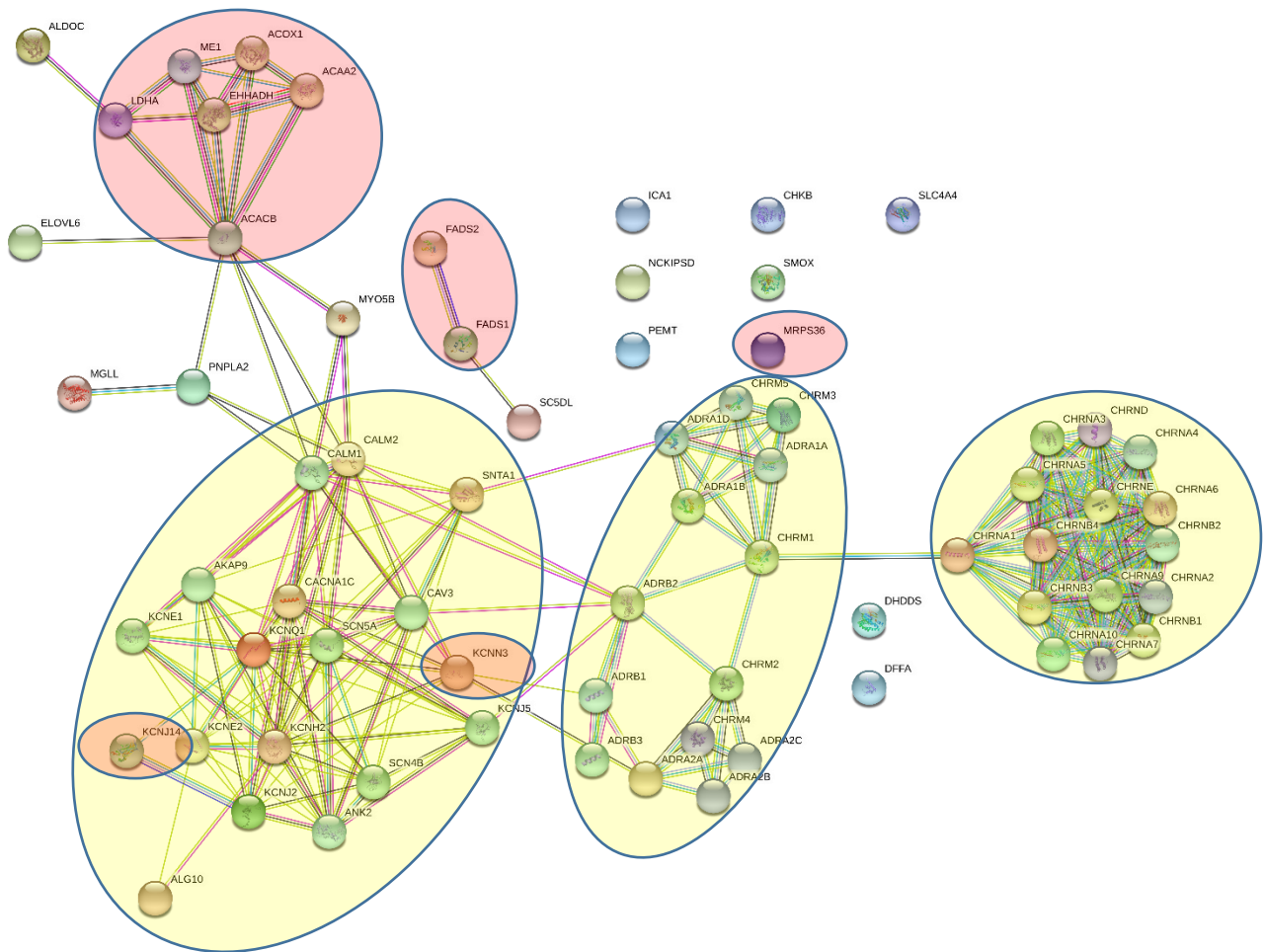
Section 3.3.13.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cardiovascular System

In Figure 25, genes associated with cLQTS are highlighted in yellow on the left. Genes associated with the ANS are highlighted yellow in the center and right sections.

FADS1, **FADS2**, **ME1**, **ELOVL6**, **ACACB**, **ACAA2**, and **ACOX1** are all associated with fatty acid metabolism. Mean expression levels for all of these proteins were lower in the QT group compared to the same probes in the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was lower in the QT group compared to the NQT group.

KCNJ14 and **KCNN3** are both potassium channels which were differentially expressed in this group. Mean expression of both KCNJ14 and KCNN3 was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.14: Central Nervous System Agents

Table XXI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Central Nervous System Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
U42976_PROBE1	CHRNB4	Cholinergic receptor nicotinic beta 4 subunit
BE109152_PROBE1	IK	IK cytokine, down-regulator of HLA II
D28508_PROBE1	JAK3	Janus kinase 3
U63111_PROBE1	DSPP	Dentin sialophosphoprotein
X97121_PROBE1	NTSR2	Neurotensin receptor 2
X98490_PROBE1	RPA2	Replication protein A2
BE108272_PROBE1	SLC7A6	Solute carrier family 7 member 6
AW144233_PROBE1	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
BE103518_PROBE1	PLXNA3	Plexin A3
AJ242554_PROBE1	ASIC4	Acid sensing ion channel subunit family member 4
NM_017208_PROBE1	LBP	Lipopolysaccharide binding protein
U52948_PROBE1	C9	Complement C9
AF034218_PROBE1	HYAL2	Hyaluronoglucosaminidase 2
AA859768_PROBE1	MCM5	Minichromosome maintenance complex component 5
AA891902_PROBE1	ANKFY1	Ankyrin repeat and FYVE domain containing 1
L20900_PROBE1	ICA1	Islet cell autoantigen 1
NM_019157_PROBE1	AQP7	Aquaporin 7
X13295_PROBE1	LCN2	Lipocalin 2
L11002_PROBE1	NFASC	Neurofascin
J00696_PROBE1	ORM1	Orosomucoid 1
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
J03960_PROBE1	ALOX5	Arachidonate 5-lipoxygenase
NM_012938_PROBE1	CTSE	Cathepsin E
AI180420_PROBE1	TUBGCP3	Tubulin gamma complex associated protein 3
BE109057_PROBE1	DCX	Doublecortin
BF406752_PROBE1	UPP1	Uridine phosphorylase 1
Z22812_PROBE1	IL1R2	Interleukin 1 receptor type 2
AA891839_PROBE1	MRPL50	Mitochondrial ribosomal protein L50
NM_019237_PROBE1	PCOLCE	Procollagen C-endopeptidase enhancer
L18948_PROBE1	S100A9	S100 calcium binding protein A9
AF036760_PROBE1	BRCA1	BRCA1, DNA repair associated
AW915685_PROBE1	FKBP11	FK506 binding protein 11
M69246_PROBE1	SERPINH1	Serpin family H member 1
AA875261_PROBE1	FBLIM1	Filamin binding LIM protein 1

Figure 26: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Central Nervous System Agents
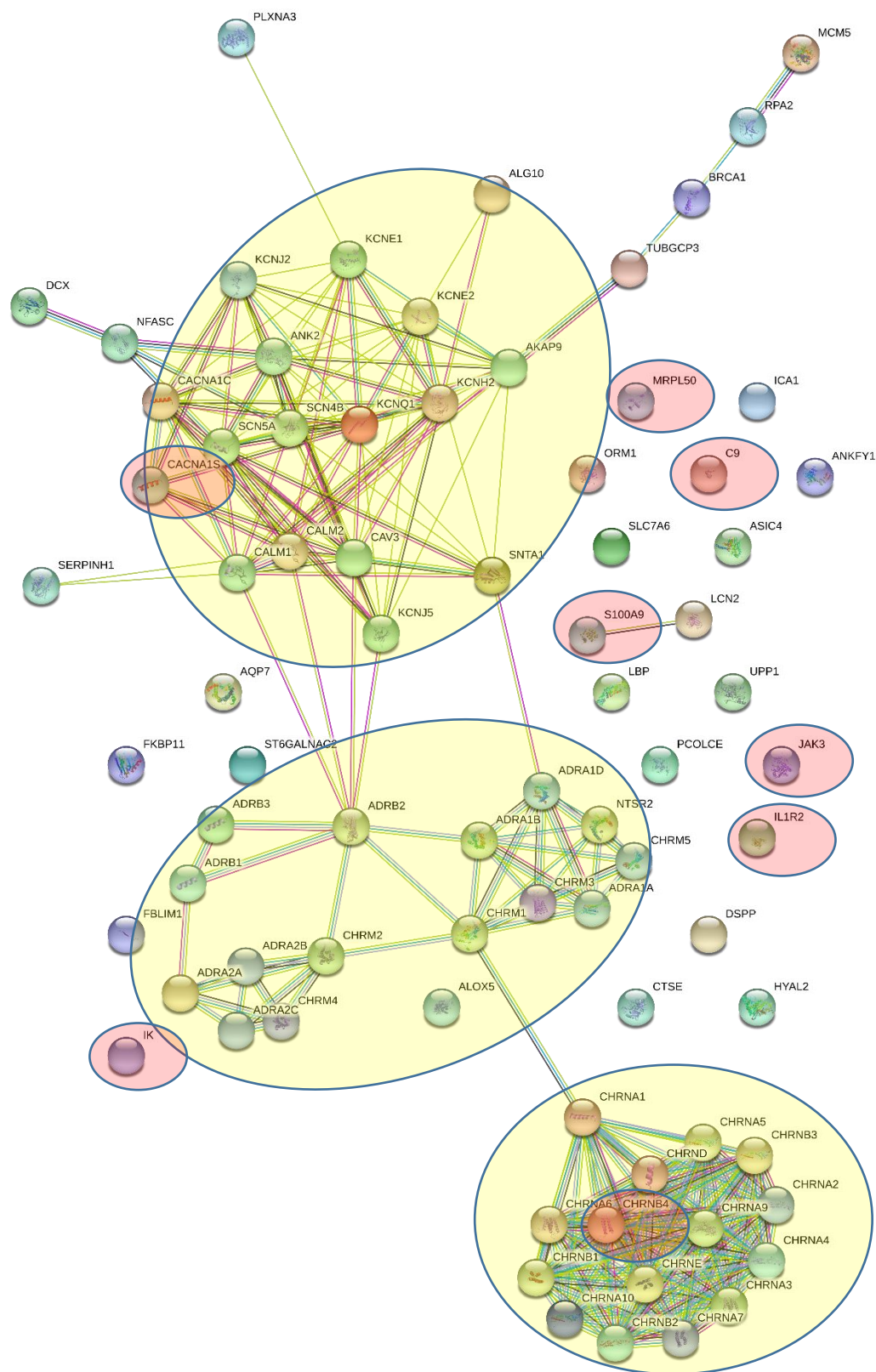
Permanent Link:

Section 3.3.14.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Central Nervous System Agents

In Figure 26, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

MLPR50 is a mitochondrial ribosomal protein. Mean expression of MLPR50 was lower in the QT group compared to the NQT group.

CACNA1S is a calcium ion channel which was differentially expressed. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

IK is a cytokine and **IL1R2** is an interleukin suggesting an association with immune components. Mean expression of both IK and IL1R2 were lower in the QT group compared to the same probes in the NQT group.

JAK3, **C9** and **S1009A** are all associated with immune responses. Mean expression for all three were lower in the QT group compared to the same probes in the NQT group.

CHRNB4 is a cholinergic receptor which was differentially expressed in this group which may directly impact ANS activity. Mean expression of CHRNB4 was lower in the QT group compared to the NQT group.

ASIC4 is an acid sensing ion channel. Mean expression of ASIC4 was lower in the QT group compared to the NQT group.

Section 3.3.15: Central Nervous System Depressants

Table XXII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Central Nervous System Depressants

Probe ID	Gene Symbol	Human Equivalent Gene Name
AA859768_PROBE1	MCM5	Minichromosome maintenance complex component 5
NM_012964_PROBE1	HMMR	Hyaluronan mediated motility receptor
AW918650_PROBE1	CHCHD6	Coiled-coil-helix-coiled-coil-helix domain containing 6
AA851306_PROBE1	HMGN3	High mobility group nucleosomal binding domain 3
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
AI230228_PROBE1	PSAT1	Phosphoserine aminotransferase 1
U45986_PROBE1	MXD3	MAX dimerization protein 3
BE104266_PROBE1	KNTC1	Kinetochore associated 1
NM_017353_PROBE1	SLC7A5	Solute carrier family 7 member 5
AI103327_PROBE1	TCF19	Transcription factor 19
AA858930_PROBE1	PDE4B	Phosphodiesterase 4B
NM_019157_PROBE1	AQP7	Aquaporin 7
AI412015_PROBE1	RRM1	Ribonucleotide reductase catalytic subunit M1
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
AW251612_PROBE1	TARS2	Threonyl-tRNA synthetase 2, mitochondrial (putative)
NM_017166_PROBE1	STMN1	Stathmin 1
U93851_PROBE1	CNGA1	Cyclic nucleotide gated channel alpha 1
AI598486_PROBE1	DPYSL3	Dihydropyrimidinase like 3
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
AA963234_PROBE1	TUBE1	Tubulin epsilon 1
BF285164_PROBE1	POPDC2	Popeye domain containing 2
X97831_PROBE1	SLC25A20	Solute carrier family 25 member 20
AF030253_PROBE1	SLC32A1	Solute carrier family 32 member 1
AF235993_PROBE1	BAX	BCL2 associated X, apoptosis regulator
AW252871_PROBE1	MKI67	Marker of proliferation Ki-67
AJ223083_PROBE1	RXRG	Retinoid X receptor gamma
AJ293948_PROBE1	KLHL41	Kelch like family member 41
AW915563_PROBE1	SPC25	SPC25, NDC80 kinetochore complex component
AY004290_PROBE1	STMN3	Stathmin 3
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
AJ245648_PROBE1	POLA2	DNA polymerase alpha 2, accessory subunit
L26009_PROBE1	FUT1	Fucosyltransferase 1 (H blood group)
NM_013076_PROBE1	LEP	Leptin
M61142_PROBE1	THOP1	Thimet oligopeptidase 1
X63854_PROBE1	TAP2	Transporter 2, ATP binding cassette subfamily B member
AI599126_PROBE1	INCENP	Inner centromere protein

Figure 27: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Central Nervous System Depressants
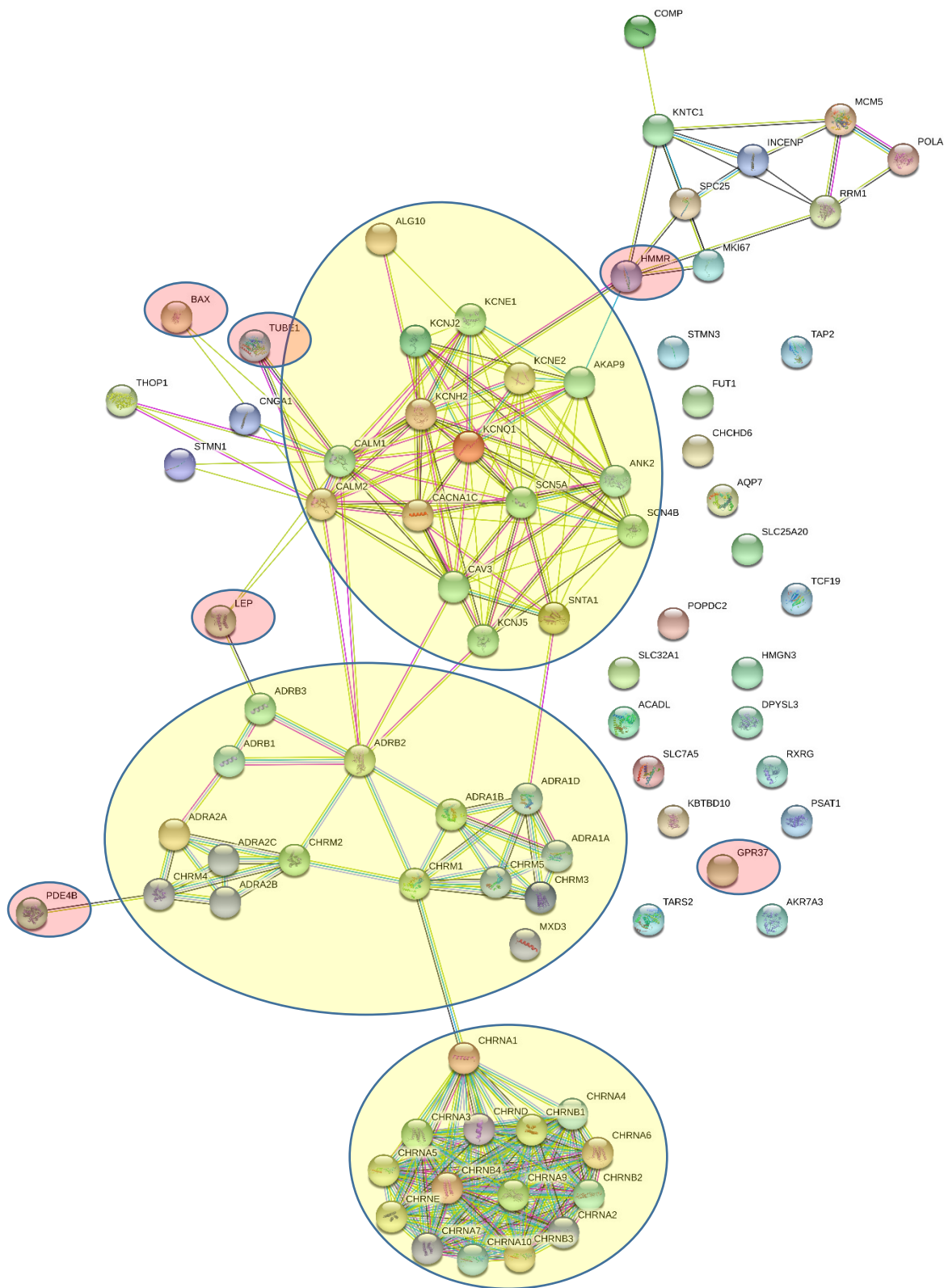
Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000341267%250D9606.ENSP00000217420%250D9606.ENSP00000222271%250D9606.ENSP00000258385%250D96
06.ENSP00000233710%250D9606.ENSP00000261622%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D960
6.ENSP00000378295%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000401867%250D9606.
ENSP00000312663%250D9606.ENSP00000304290%250D9606.ENSP00000250699%250D9606.ENSP00000155840%250D9606.E
NSP00000289957%250D9606.ENSP00000297988%250D9606.ENSP00000282074%250D9606.ENSP00000355377%250D9606.EN
SP00000264231%250D9606.ENSP00000358060%250D9606.ENSP00000357651%250D9606.ENSP00000306490%250D9606.ENS
P00000266376%250D9606.ENSP00000300738%250D9606.ENSP00000384264%250D9606.ENSP00000293288%250D9606.ENSP
00000328968%250D9606.ENSP00000276410%250D9606.ENSP00000385026%250D9606.ENSP00000357643%250D9606.ENSP0
0000359285%250D9606.ENSP00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000352900%250D9606.ENSP00
000386069%250D9606.ENSP00000377492%250D9606.ENSP00000359070%250D9606.ENSP00000319984%250D9606.ENSP000
00261751%250D9606.ENSP00000265465%250D9606.ENSP00000349588%250D9606.ENSP00000304467%250D9606.ENSP0000
0312021%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000
357461%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP000003
72750%250D9606.ENSP00000410452%250D9606.ENSP00000407546%250D9606.ENSP00000343690%250D9606.ENSP0000036
9960%250D9606.ENSP00000306449%250D9606.ENSP00000272298%250D9606.ENSP00000358301%250D9606.ENSP00000322
460%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000326305%250D9606.ENSP000003657
73%250D9606.ENSP00000337255%250D9606.ENSP00000332116%250D9606.ENSP00000365431%250D9606.ENSP0000026218
6%250D9606.ENSP00000255380%250D9606.ENSP00000328236%250D9606.ENSP00000280155%250D9606.ENSP00000216122
%250D9606.ENSP00000299565%250D9606.ENSP00000364034%250D9606.ENSP00000312652%250D9606.ENSP00000293780%
250D9606.ENSP00000284669%250D9606.ENSP00000306662%250D9606.ENSP00000290913%250D9606.ENSP00000348573

Section 3.3.15.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Central Nervous System Depressants

In Figure 27, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

HMMR and **LEP** are involved with ERK/MAPK activity. Mean expression of both HMMR and LEP was lower in the QT group compared to the same probes in the NQT group.

BAX is associated with apoptosis. Mean expression of BAX was lower in the QT group compared to the NQT group.

GPR37 and **TUBE1** are associated with G proteins. Mean expression of both GPR37 and TUBE 1 was lower in the QT group compared to the NQT group.

PDE4B is asscociated with cAMP regulation. cAMP is a second messenger associated with G proteins. Mean expression of PDE4B was higher in the QT group compared to the NQT group.

Section 3.3.16: Chemically-Induced Disorders

Table XXIII: Differentially Expressed Genes Used as Input using Drugs Classified in DrugBank as Chemically-Induced Disorders

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012545_PROBE1	DDC	Dopa decarboxylase
J04112_PROBE1	FBP1	Fructose-bisphosphatase 1
AW533663_PROBE1	PRODH	Proline dehydrogenase 1
AI410802_PROBE1	SLC22A18	Solute carrier family 22 member 18
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
AW523642_PROBE1	KMT5B	Lysine methyltransferase 5B
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
AW862653_PROBE1	NUDT4	Nudix hydrolase 4
BE116918_PROBE1	SF3A1	Splicing factor 3a subunit 1
AI406275_PROBE1	CBX7	Chromobox 7
AJ293617_PROBE1	MAGED2	MAGE family member D2
AA963282_PROBE1	NMNAT3	Nicotinamide nucleotide adenylyltransferase 3
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
AI169375_PROBE1	NUP93	Nucleoporin 93
D87212_PROBE1	CNTN5	Contactin 5
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
BF556833_PROBE1	RNF2	Ring finger protein 2
AI412180_PROBE1	GSR	Glutathione-disulfide reductase
AW918255_PROBE1	DGAT2	Diacylglycerol O-acyltransferase 2
NM_017084_PROBE1	GNMT	Glycine N-methyltransferase
U77697_PROBE1	PECAM1	Platelet and endothelial cell adhesion molecule 1
AI598402_PROBE1	COL6A1	Collagen type VI alpha 1 chain
AW917211_PROBE1	QPRT	Quinolinate phosphoribosyltransferase
AA892567_PROBE1	ARCN1	Archain 1
AI548694_PROBE1	COMTD1	Catechol-O-methyltransferase domain containing 1
AW142847_PROBE1	HSF2	Heat shock transcription factor 2
BF281319_PROBE1	TBCE	Tubulin folding cofactor E
NM_012844_PROBE1	EPHX1	Epoxide hydrolase 1
NM_017264_PROBE1	PSME1	Proteasome activator subunit 1
NM_017305_PROBE1	GCLM	Glutamate-cysteine ligase modifier subunit
AI172272_PROBE1	TCEA3	Transcription elongation factor A3

Figure 28: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Chemically-Induced Disorders

Permanent Link: http://bit.ly/2xnGe7y
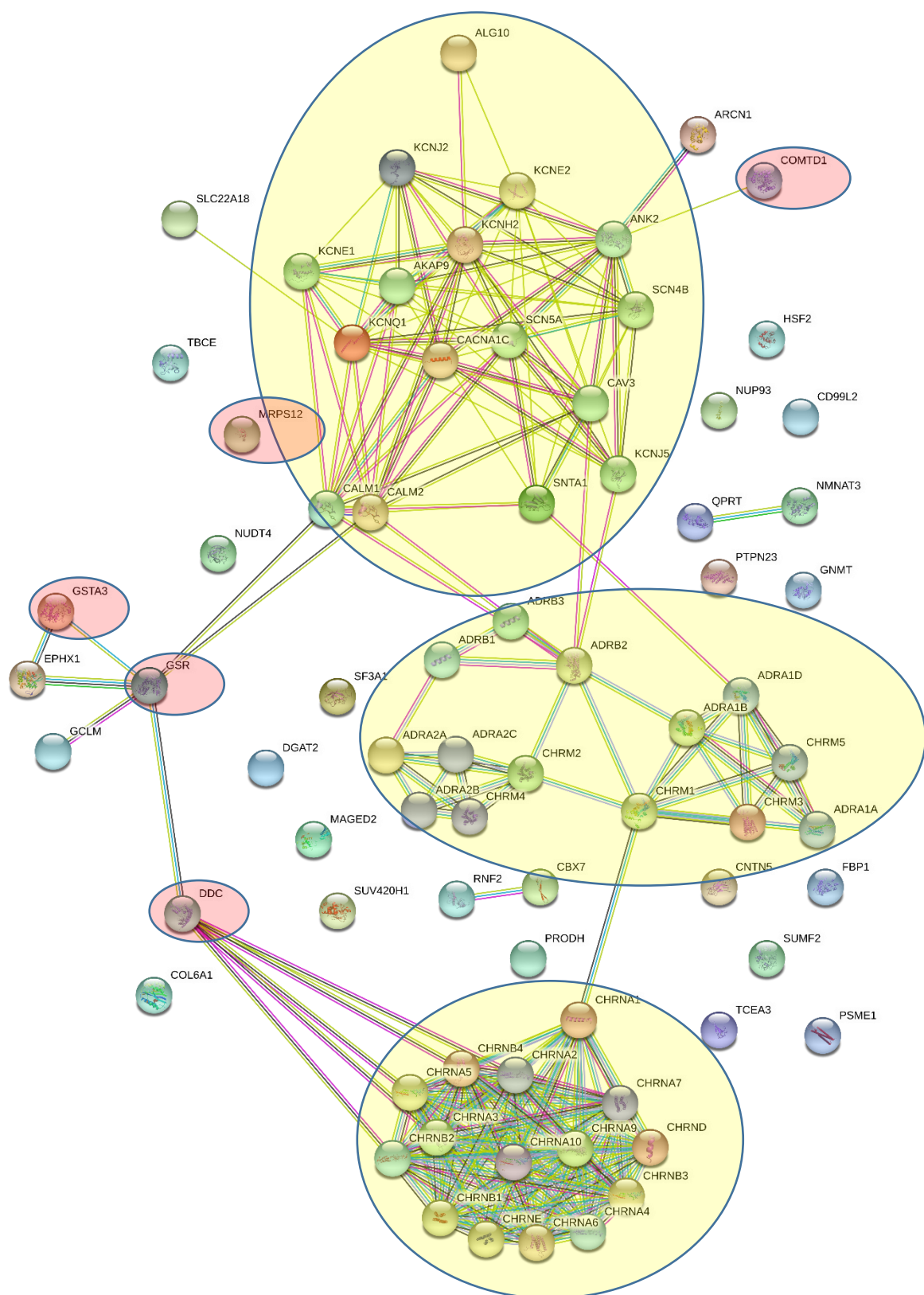
Section 3.3.16.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Chemically-Induced Disorders

In Figure 28, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

GSTA3 and **GSR** are associated with glutathione, and by extension, electron transport. Mean expression of both GSTA3 and GSR was lower in the QT group compared to the NQT group.

DDC and **COMTD1** are related to catecholamine metabolism. Mean expression of both DDC and COMTD1 was lower in the QT group compared to the NQT group.

Section 3.3.17: Combined Inducers of CYP3A4 and P-Glycoprotein

Table XXIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Combined Inducers of CYP3A4 and P-Glycoprotein

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB001321_PROBE1	SLC13A2	Solute carrier family 13 member 2
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36
NM_017129_PROBE1	CTF1	Cardiotrophin 1
BF407531_PROBE1	RASL10B	RAS like family 10 member B
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3
AI236640_PROBE1	SMS	Spermine synthase
AB037934_PROBE1	RGN	Regucalcin
AF067728_PROBE1	PSMD9	Proteasome 26S subunit, non-ATPase 9
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
L20900_PROBE1	ICA1	Islet cell autoantigen 1
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
M84488_PROBE1	VCAM1	Vascular cell adhesion molecule 1
BE113016_PROBE1	RDX	Radixin
U13253_PROBE1	COL4A1	Collagen type IV alpha 1 chain
NM_021654_PROBE1	GJA4	Gap junction protein alpha 4
AB000215_PROBE1	SMPD3	Sphingomyelin phosphodiesterase 3
D13374_PROBE1	NME1	NME/NM23 nucleoside diphosphate kinase 1
AF078798_PROBE1	MAPK15	Mitogen-activated protein kinase 15
NM_012545_PROBE1	DDC	Dopa decarboxylase
AF013241_PROBE1	P2RX2	Purinergic receptor P2X 2
AI556941_PROBE1	SLC39A4	Solute carrier family 39 member 4
AF272158_PROBE1	CXXC4	CXXC finger protein 4
M55601_PROBE1	PTN	Pleiotrophin
AF081582_PROBE1	PLEKHB1	Pleckstrin homology domain containing B1
M35106_PROBE1	ROS1	ROS proto-oncogene 1, receptor tyrosine kinase
AF242391_PROBE1	ARL6IP5	ADP ribosylation factor like GTPase 6 interacting protein 5

Figure 29: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Combined Inducers of CYP3A4 and P-Glycoprotein
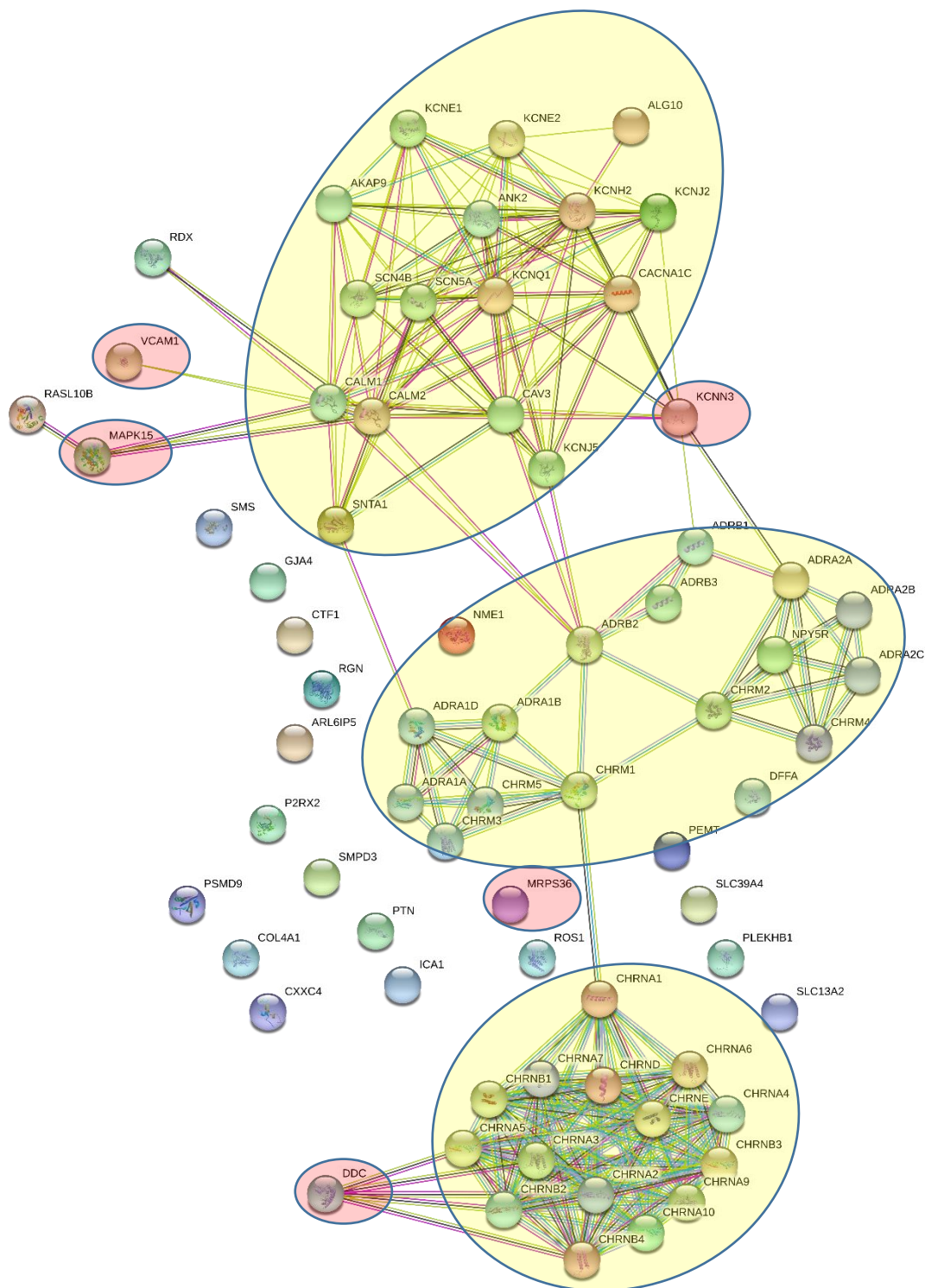
Section 3.3.17.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Combined Inducers of CYP3A4 and P-Glycoprotein

In Figure 29, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

VCAM1 is associated with immune responses and inflammation. Mean expression of VCAM1 was lower in the QT group compared to the NQT group.

MAPK15 is a member of the MAPK family. Mean expression of MAPK15 was lower in the QT group compared to the NQT group.

DDC is involved with catecholamine synthesis. Mean expression of DDC was lower in the QT group compared to the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was lower in the QT group compared to the NQT group.

KCNN3 is a potassium ion channel which was differentially expressed. Mean expression of KCNN3 was lower in the QT group compared to the NQT group.

Section 3.3.18: Combined Inhibitors of CYP3A4 and P-Glycoprotein

Table XXV: Differentially Expressed Genes Used as Input using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein

Probe ID	Gene Symbol	Human Equivalent Gene Name
D87839_PROBE1	ABAT	4-aminobutyrate aminotransferase
BF282594_PROBE1	NUDT16	Nudix hydrolase 16
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
AI408929_PROBE1	HINT2	Histidine triad nucleotide binding protein 2
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
AI169375_PROBE1	NUP93	Nucleoporin 93
BE113170_PROBE1	ANKRD24	Ankyrin repeat domain 24
NM_012600_PROBE1	ME1	Malic enzyme 1
NM_012682_PROBE1	UCP1	Uncoupling protein 1
BF282437_PROBE1	TBC1D10A	TBC1 domain family member 10A
AI104251_PROBE1	ABHD14A	Abhydrolase domain containing 14A
AI406275_PROBE1	CBX7	Chromobox 7
AW915264_PROBE1	IGSF11	Immunoglobulin superfamily member 11
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
AA850288_PROBE1	GNPTG	N-acetylglucosamine-1-phosphate transferase gamma subunit
AI045074_PROBE1	GLB1	Galactosidase beta 1
AW913929_PROBE1	IMP3	IMP3, U3 small nucleolar ribonucleoprotein
D85760_PROBE1	GNA12	G protein subunit alpha 12
NM_012842_PROBE1	EGF	Epidermal growth factor
NM_019376_PROBE1	YWHAG	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
AW532870_PROBE1	POLR2I	RNA polymerase II subunit I
BF419241_PROBE1	MOCS1	Molybdenum cofactor synthesis 1
M30596_PROBE1	ME1	Malic enzyme 1
NM_012941_PROBE1	CYP51A1	Cytochrome P450 family 51 subfamily A member 1
BF405883_PROBE1	DHX16	DEAH-box helicase 16

Figure 30: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein

Permanent Link: http://bit.ly/2xmYnCz
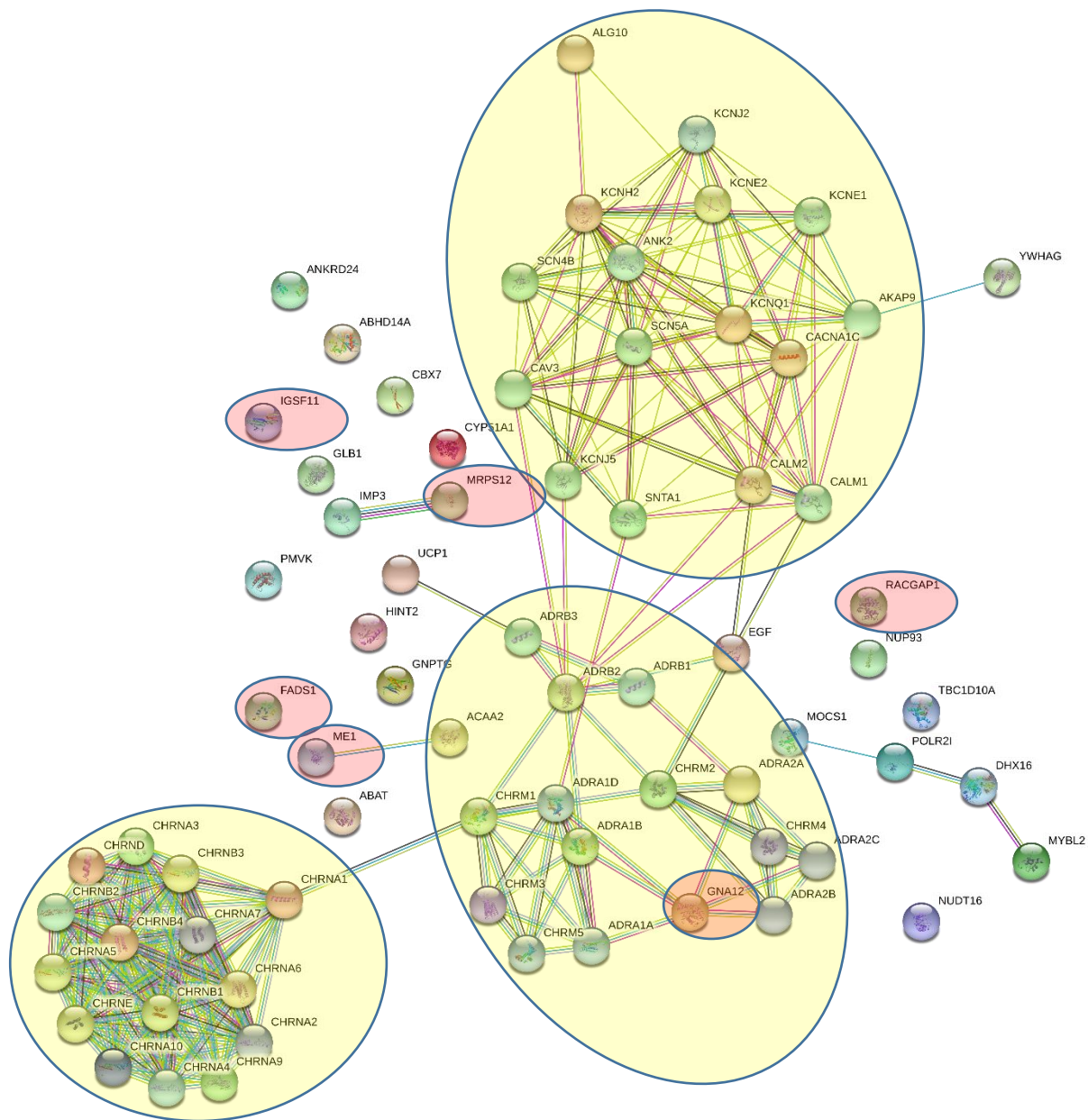
Section 3.3.18.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein

In Figure 30, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

FADS1 and **ME1** are involved with fatty acid metabolism. Mean expression of both FADS2 and ME1 was lower in the QT group compared to the same probes in the NQT group.

RACGAP1 and **GNA12** are involved with the activity of G proteins. Mean expression of RACGAP1 was lower in the QT group compared to the NQT group. Mean expression of GNA12 was higher in the QT group compared to the NQT group.

IGSF11 suggests an immune component through immunoglobulins. Mean expression of IGSF11 was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

Section 3.3.19: CYP2D6 Inhibitors (Weak)

Table XXVI: Differentially Expressed Genes Used as Input using Drugs Classified in DrugBank as CYP2D6 Inhibitors (Weak)

Probe ID	Gene Symbol	Human Equivalent Gene Name
AA848534_PROBE1	MRPS5	Mitochondrial ribosomal protein S5
AW253690_PROBE1	DEPDC1	DEP domain containing 1
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
BE111659_PROBE1	CKAP5	Cytoskeleton associated protein 5
AA799676_PROBE1	LACTB2	Lactamase beta 2
AF072439_PROBE1	ZFP37	ZFP37 zinc finger protein
AA892918_PROBE1	TJP1	Tight junction protein 1
NM_019257_PROBE1	SRSF5	Serine and arginine rich splicing factor 5
AB003726_PROBE1	HOMER1	Homer scaffolding protein 1
BE113146_PROBE1	FARSB	phenylalanyl-tRNA synthetase beta subunit
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2 sapiens
U53512_PROBE1	MRPL17	Mitochondrial ribosomal protein L17
AI102978_PROBE1	ACTL6A	Actin like 6A
U24175_PROBE1	STAT5A	Signal transducer and activator of transcription 5A
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
AI177845_PROBE1	TRIP12	Thyroid hormone receptor interactor 12
AI408929_PROBE1	HINT2	Histidine triad nucleotide binding protein 2
AB002086_PROBE1	SEC23IP	SEC23 interacting protein
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
AW251335_PROBE1	SPC24	SPC24, NDC80 kinetochore complex component
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
BF397719_PROBE1	PLEKHG2	Pleckstrin homology and RhoGEF domain containing G2
L24051_PROBE1	EBF1	Early B-cell factor 1
J04791_PROBE1	ODC1	Ornithine decarboxylase 1
AF031880_PROBE1	NEFL	Neurofilament light
AW917543_PROBE1	SSH3	Slingshot protein phosphatase 3
Y00047_PROBE1	PCNA	Proliferating cell nuclear antigen
D50695_PROBE1	PSMC4	Proteasome 26S subunit, ATPase 4

Figure 31: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as CYP2D6 Inhibitors (Weak)

Permanent Link: http://bit.ly/2xngurX
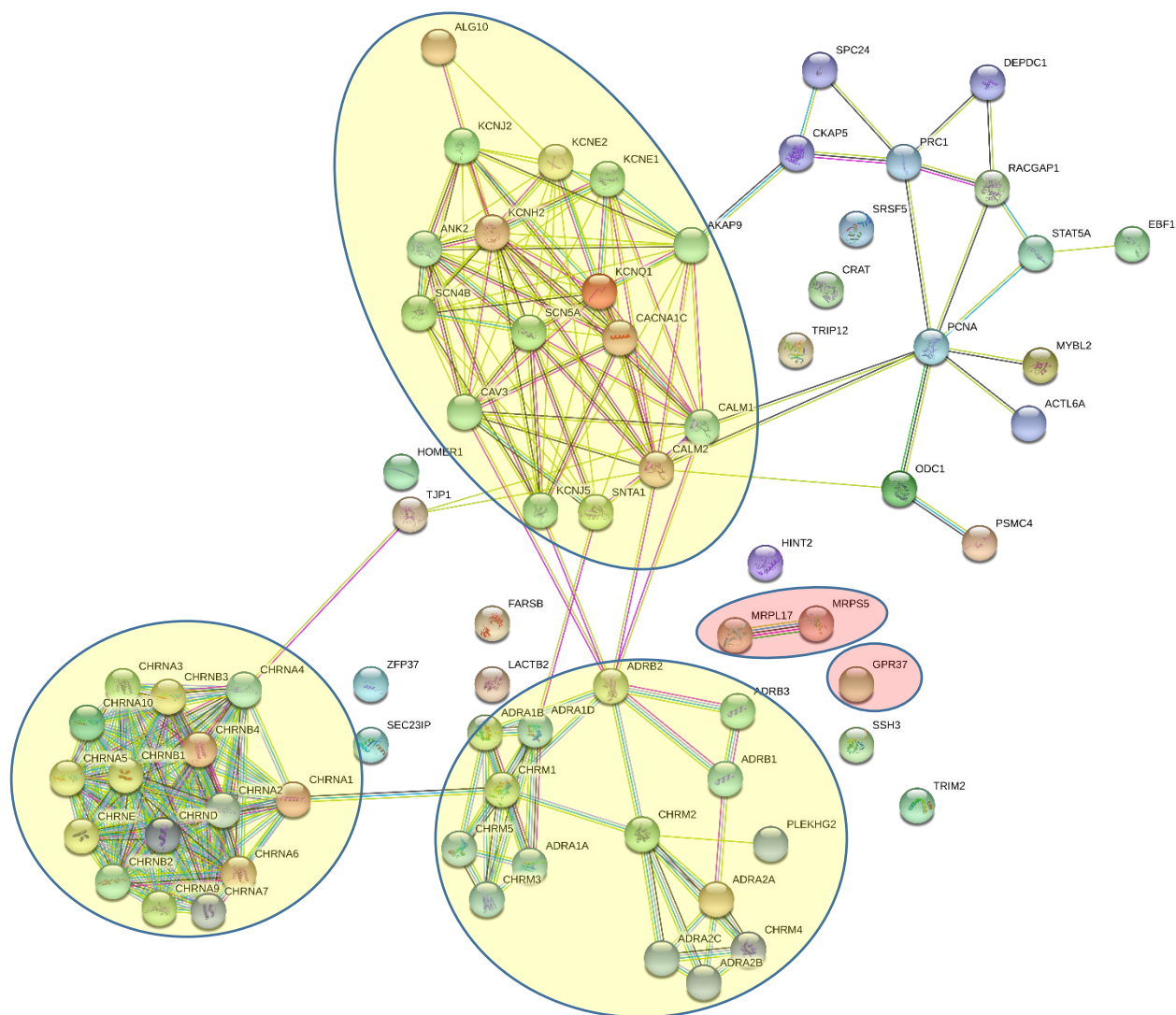
Section 3.3.19.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as CYP2D6 Inhibitors (Weak)

In Figure 31enes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

MRPS5 and **MRPL17** are mitochondrial ribosomal proteins. Mean expression for both MRPS5 and MRPL17 was lower in the QT group compared to the same probes in the NQT group.

GPR37 is a subunit associated with G proteins. Mean expression of GPR37 was lower in the QT group compared to the NQT group.

Section 3.3.20: CYP3A4 Inhibitors (Weak)

Table XXVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as CYP3A4 Inhibitors (Weak)

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_021858_PROBE1	GNB3	G protein subunit beta 3
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
AF139055_PROBE1	MYH10	Myosin heavy chain 10
L04535_PROBE1	SSTR5	Somatostatin receptor 5
NM_020073_PROBE1	PTH1R	Parathyroid hormone 1 receptor
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
BF283407_PROBE1	XPO4	Exportin 4
AF074952_PROBE1	EREG	Epiregulin
L27058_PROBE1	PDE4B	Phosphodiesterase 4B
NM_021654_PROBE1	GJA4	Gap junction protein alpha 4
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
NM_012699_PROBE1	DNAJB9	DnaJ heat shock protein family (Hsp40) member B9
AA944451_PROBE1	OTUB1	OTU deubiquitinase, ubiquitin aldehyde binding 1
X59601_PROBE1	PLEC	Plectin
AA946035_PROBE1	MYO5C	Myosin VC
AI103106_PROBE1	LMNB1	Lamin B1
AA850771_PROBE1	VPS37C	VPS37C, ESCRT-I subunit
AA925353_PROBE1	LAPTM5	Lysosomal protein transmembrane 5
NM_017062_PROBE1	PDLIM4	PDZ and LIM domain 4
NM_019368_PROBE1	BET1L	Bet1 Golgi vesicular membrane trafficking protein like
NM_012747_PROBE1	STAT3	Signal transducer and activator of transcription 3
AF061442_PROBE1	CYP2E1	Cytochrome P450 family 2 subfamily E member 1
AF070065_PROBE1	CIT	Citron rho-interacting serine/threonine kinase
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
AF155196_PROBE1	SPON2	Spondin 2
D83231_PROBE1	TFF1	Trefoil factor 1

Figure 32: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as CYP3A4 Inhibitors (Weak)

Permanent Link: http://bit.ly/2xnbC65
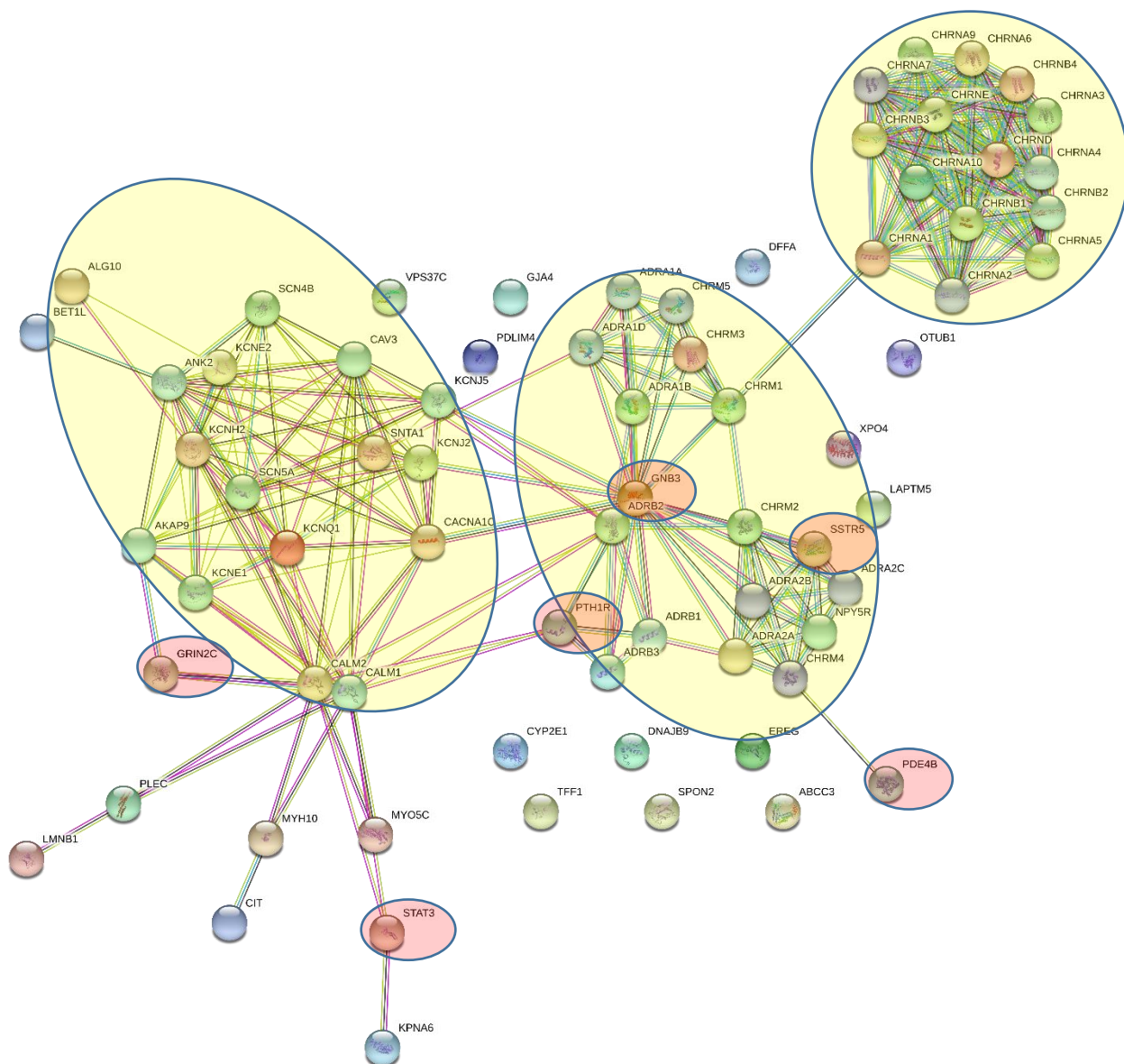
Section 3.3.20.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as CYP3A4 Inhibitors (Weak)

In Figure 32, genes associated with cLQTS are highlighted in yellow on the left. Genes associated with the ANS are highlighted yellow in the center and right.

GNB3, **PTH1R**, and **SSTR5** are associated with G protein activity, and PTH1R specifically has Ca^{2+} as a second messenger. Mean expression for GNB3 and PTH1R was higher in the QT group compared to the NQT group for the same probes. Mean expression of SSTR5 was lower in the QT group compared to the same probes in the NQT group.

PDE4B is involved with second messenger systems using cAMP, which is associated with G protein-mediated signal transduction. Mean expression of PDE4B was lower in the QT group compared to the NQT group.

GRIN2C is a receptor protein which is part of an ion channel with high Ca^{2+} permeability. Mean expression of GRIN2C was lower in the QT group compared to the NQT group.

STAT3 is associated with immune activity and is important in insulin secretion. Mean expression of STAT3 was lower in the QT group compared to the NQT group.

Section 3.3.21: Cytochrome P-450 CYP1A2 Inhibitors

Table XXVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
NM_012600_PROBE1	ME1	Malic enzyme 1
NM_017000_PROBE1	NQO1	NAD(P)H quinone dehydrogenase 1
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
NM_019157_PROBE1	AQP7	Aquaporin 7
AW143008_PROBE1	SLC16A6	Solute carrier family 16 member 6
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
X71429_PROBE1	PDCD2	Programmed cell death 2
AI412180_PROBE1	GSR	Glutathione-disulfide reductase
BF564217_PROBE1	ANGPT1	Angiopoietin 1
AI409182_PROBE1	ARL6	ADP ribosylation factor like GTPase 6
AF061442_PROBE1	CYP2E1	Cytochrome P450 family 2 subfamily E member 1
AI172302_PROBE1	SRXN1	Sulfiredoxin 1
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
AW918650_PROBE1	CHCHD6	Coiled-coil-helix-coiled-coil-helix domain containing 6
AI169375_PROBE1	NUP93	Nucleoporin 93
BF281319_PROBE1	TBCE	Tubulin folding cofactor E
AB013732_PROBE1	UGDH	UDP-glucose 6-dehydrogenase
AW141985_PROBE1	ABCC4	ATP binding cassette subfamily C member 4
BF402596_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
NM_021754_PROBE1	NOP56	NOP56 ribonucleoprotein
M30596_PROBE1	ME1	Malic enzyme 1
U94340_PROBE1	PARP1	Poly(ADP-ribose) polymerase 1
U72353_PROBE1	LMNB1	Lamin B1
AI171798_PROBE1	L3MBTL2	L3MBTL2, polycomb repressive complex 1 subunit
AF059530_PROBE1	PRMT3	Protein arginine methyltransferase 3

Figure 33: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors
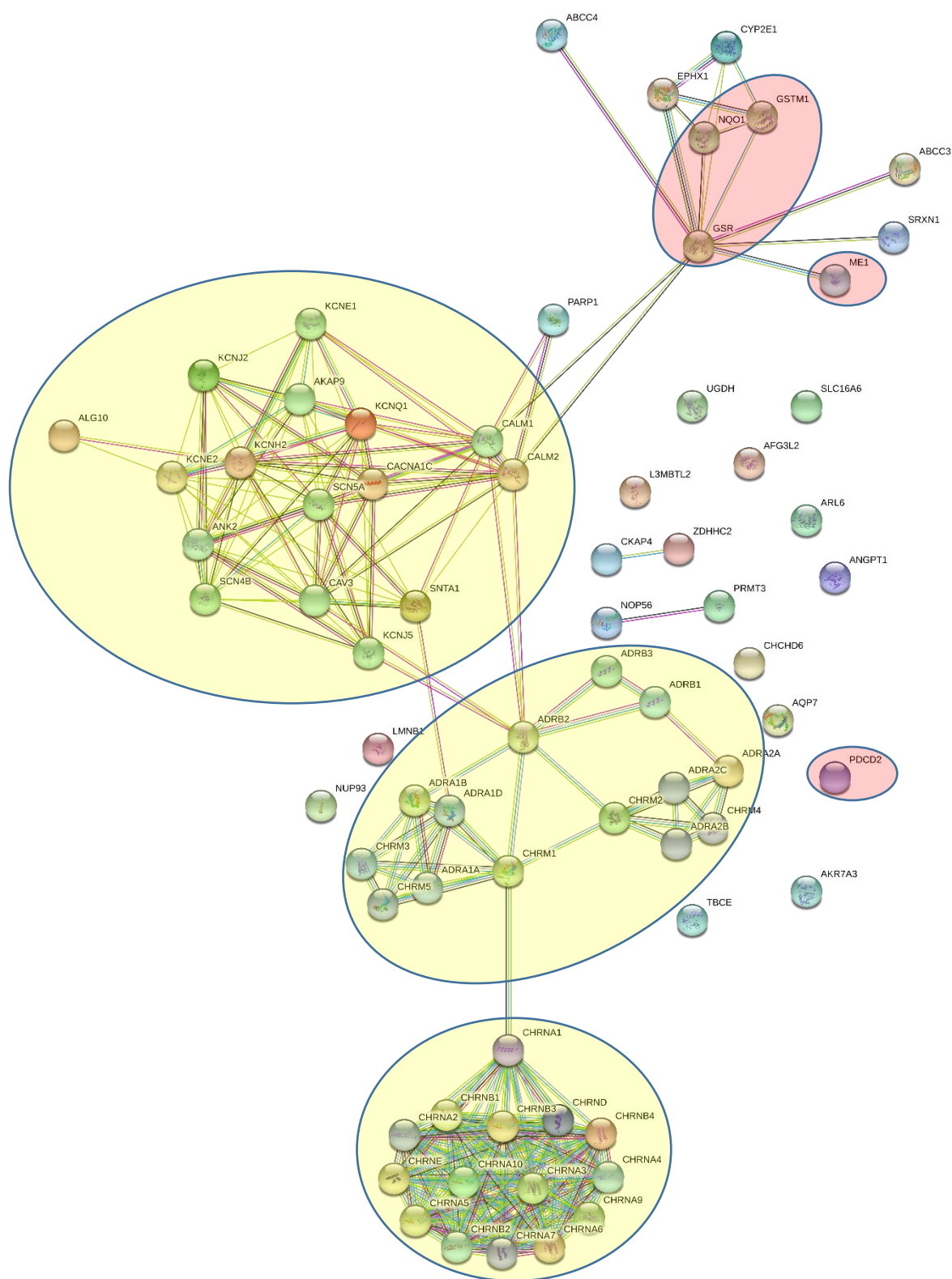
Permanent Link:

Section 3.3.21.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors

In Figure 33, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

ME1 is associated with fatty acid metabolism. Mean expression of ME1 was lower in the QT group compared to the NQT group.

GSTM1, **NQO1**, and **GSR** are associated with glutathione and electron transport proteins. Mean expression of all three of these was lower in the QT group compared to the same probes in the NQT group.

PDCD2 is associated with apoptosis. Mean expression of PDCD2 was lower in the QT group compared to the NQT group.

Section 3.3.22: Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

Table XXIX: Differentially Expressed Genes Used as Input using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
AW915662_PROBE1	RCE1	Ras converting CAAX endopeptidase 1
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
AF271156_PROBE1	CAMK2N1	Calcium/calmodulin dependent protein kinase II inhibitor 1
AI231601_PROBE1	ZWINT	ZW10 interacting kinetochore protein
NM_012844_PROBE1	EPHX1	Epoxide hydrolase 1
U33847_PROBE1	GUCY2GP	Guanylate cyclase 2G, pseudogene
AB017188_PROBE1	PSMD4	Proteasome 26S subunit, non-ATPase 4
AI172269_PROBE1	NPLOC4	NPL4 homolog, ubiquitin recognition factor
AI412180_PROBE1	GSR	Glutathione-disulfide reductase
AI175044_PROBE1	CRELD1	Cysteine rich with EGF like domains 1
AI177058_PROBE1	SNAPC2	Small nuclear RNA activating complex polypeptide 2
AI233729_PROBE1	PSMD5	Proteasome 26S subunit, non-ATPase 5
AI410456_PROBE1	PFDN1	Prefoldin subunit 1
AW914085_PROBE1	RPS19	Ribosomal protein S19
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
AI233262_PROBE1	IPO4	Importin 4
AI411422_PROBE1	PPCDC	Phosphopantothenoylcysteine decarboxylase
AW919474_PROBE1	MRPS18A	Mitochondrial ribosomal protein S18A
BF284899_PROBE1	CIDEA	Cell death-inducing DFFA-like effector a
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
NM_012833_PROBE1	ABCC2	ATP binding cassette subfamily C member 2
BF412111_PROBE1	GDPD2	Glycerophosphodiester phosphodiesterase domain containing 2
D38072_PROBE1	PTPN12	Protein tyrosine phosphatase, non-receptor type 12
AF228917_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
AA894030_PROBE1	TDP1	Tyrosyl-DNA phosphodiesterase 1
AF067728_PROBE1	PSMD9	Proteasome 26S subunit, non-ATPase 9
AI233266_PROBE1	PRODH2	Proline dehydrogenase 2
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
NM_012588_PROBE1	IGFBP3	Insulin like growth factor binding protein 3

Figure 34: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Moderate)
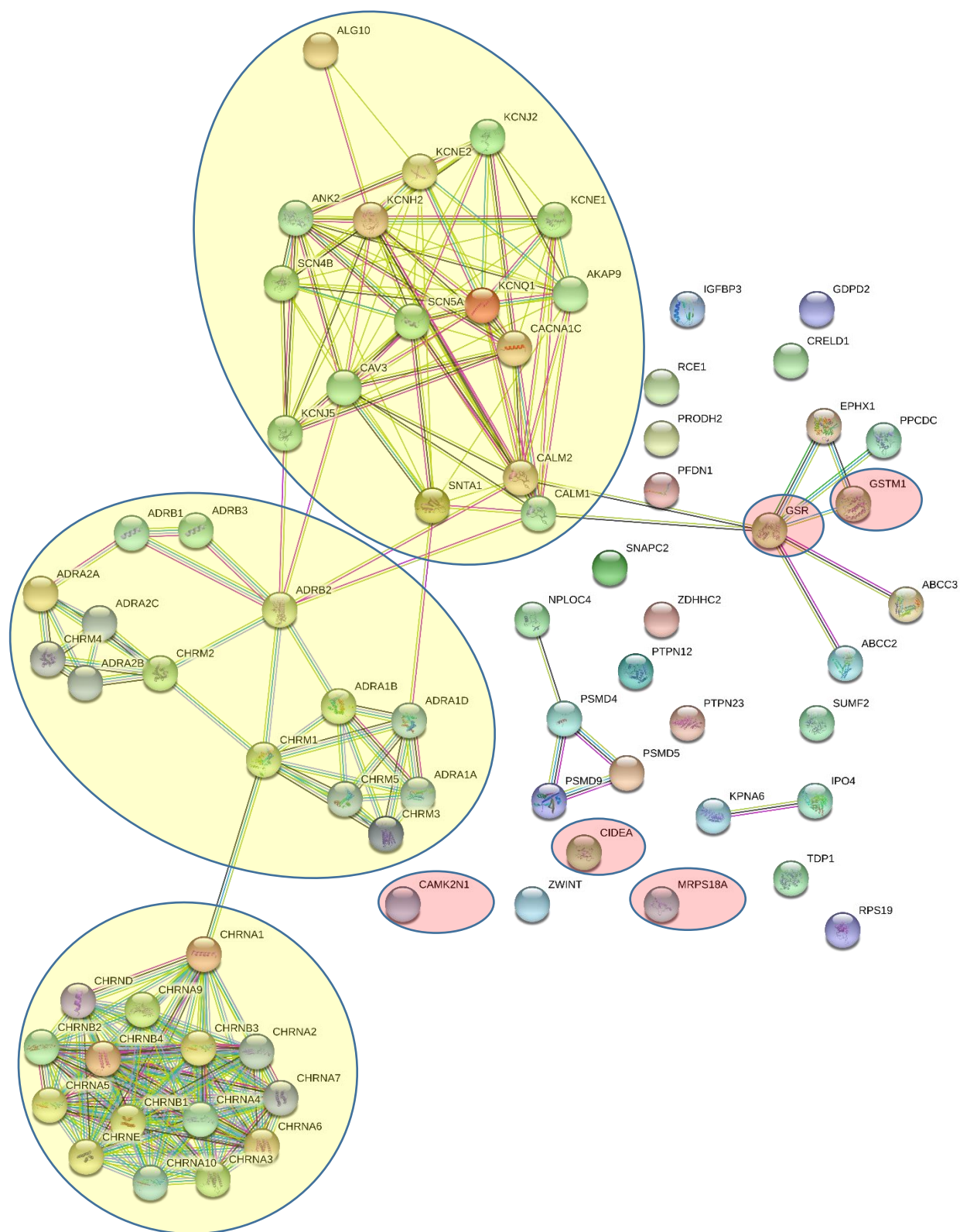
Section 3.3.22.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

In Figure 34, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are highlighted yellow in the center and bottom.

GSTM1 and **GSR** are associated with glutathione. Mean expression of both GSTM1 and GSR was lower in the QT group compared to the same probes in the NQT group.

CAMK2N1 is associated with calcium regulation. Mean expression of CAMK2N1 was lower in the QT group compared to the NQT group.

MRPS18A mitochondrial ribosomal protein. Mean expression of MRPS18A was lower in the QT group compared to the NQT group.

CIDEA is associated with apoptosis. Mean expression of CIDEA was lower in the QT group compared to the NQT group.

Section 3.3.23: Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Table XXX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
AB013732_PROBE1	UGDH	UDP-glucose 6-dehydrogenase
AB032178_PROBE1	COX17	COX17, cytochrome c oxidase copper chaperone
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
BF281319_PROBE1	TBCE	Tubulin folding cofactor E
AA926279_PROBE1	BIN3	Bridging integrator 3
AF117330_PROBE1	CLCC1	Chloride channel CLIC like 1
AF290194_PROBE1	COMMD5	COMM domain containing 5
AI716240_PROBE1	SSX2IP	SSX family member 2 interacting protein
BF282437_PROBE1	TBC1D10A	TBC1 domain family member 10A
BF282594_PROBE1	NUDT16	Nudix hydrolase 16
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
AA848420_PROBE1	UNG	Uracil DNA glycosylase
BF557396_PROBE1	FUT8	Fucosyltransferase 8
AI406275_PROBE1	CBX7	Chromobox 7
BF398680_PROBE1	MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4
AF017637_PROBE1	CPZ	Carboxypeptidase Z
AI102009_PROBE1	PRKRA	Protein activator of interferon induced protein kinase EIF2AK2
AJ293697_PROBE1	NSMF	NMDA receptor synaptonuclear signaling and neuronal migration factor
BE107136_PROBE1	CHD4	Chromodomain helicase DNA binding protein 4
BF415017_PROBE1	BET1L	Bet1 Golgi vesicular membrane trafficking protein like
BF564217_PROBE1	ANGPT1	Angiopoietin 1
U61729_PROBE1	PNRC1	Proline rich nuclear receptor coactivator 1
BF393911_PROBE1	HNRNPUL1	Heterogeneous nuclear ribonucleoprotein U like 1
BF394166_PROBE1	GPM6A	Glycoprotein M6A
AA891834_PROBE1	COL4A5	Collagen type IV alpha 5 chain
AI104251_PROBE1	ABHD14A	Abhydrolase domain containing 14A
AI171632_PROBE1	TRIM11	Tripartite motif containing 11

Figure 35: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Permanent Link: http://bit.ly/2xnuUbo
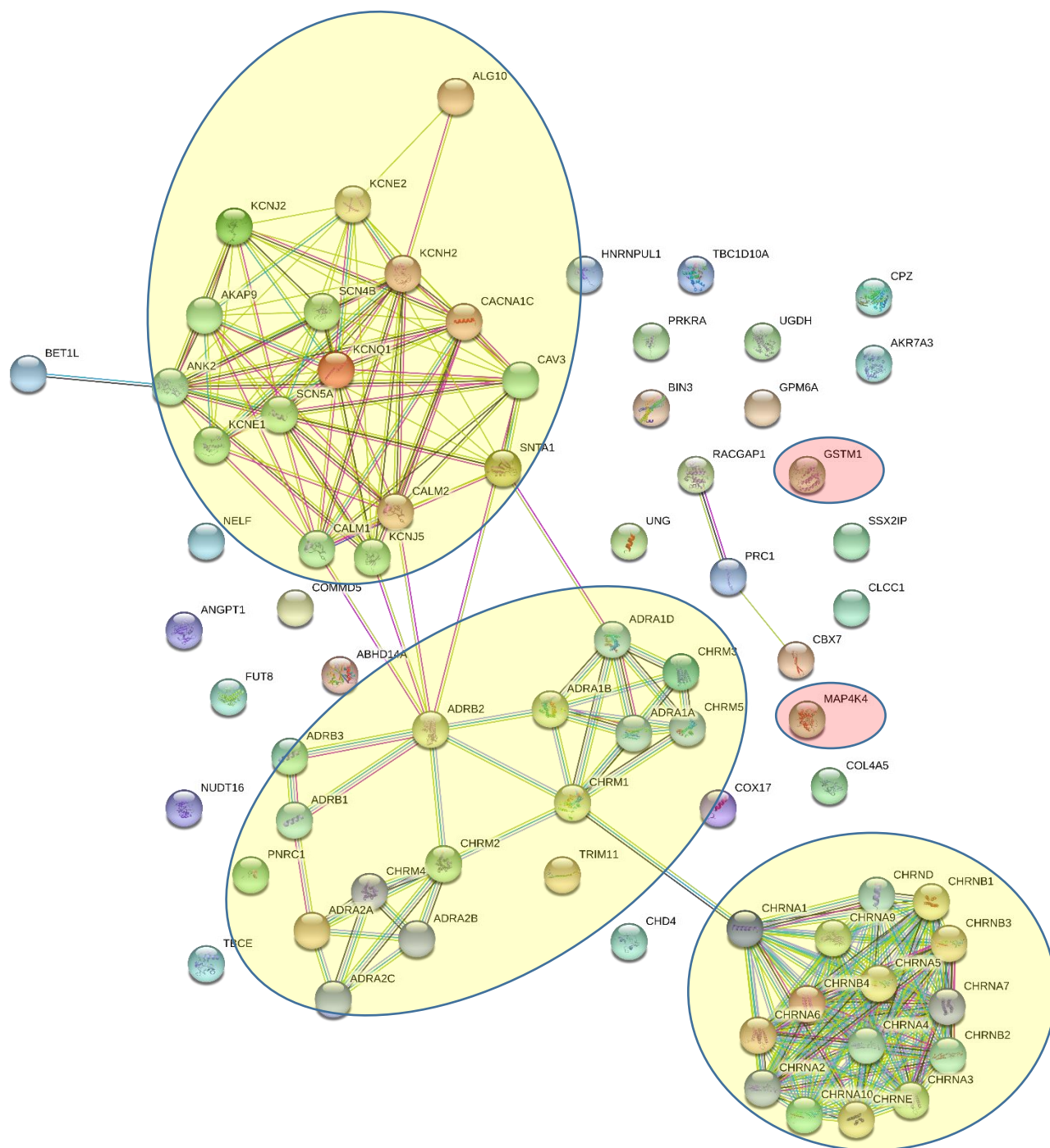
Section 3.3.23.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak)

In Figure 35, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow in the center and bottom right.

GSTM1 is associated with glutathione. Mean expression of GSTM1 was lower in the QT group compared to the NQT group.

MAPK4 is a member of the MAPK family. Mean expression of MAPK4 was lower in the QT group compared to the NQT group.

Section 3.3.24: Cytochrome P-450 CYP1A2 Substrates

Table XXXI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW533292_PROBE1	FNDC3B	Fibronectin type III domain containing 3B
X97121_PROBE1	NTSR2	Neurotensin receptor 2
D00833_PROBE1	GLRA1	Glycine receptor alpha 1
U63111_PROBE1	DSPP	Dentin sialophosphoprotein
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
AW531368_PROBE1	KIF21A	Kinesin family member 21A
U02315_PROBE1	NRG1	Neuregulin 1
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
U20796_PROBE1	NR1D2	Nuclear receptor subfamily 1 group D member 2
AF115508_PROBE1	ADORA2A	Adenosine A2a receptor
AI102065_PROBE1	HEBP1	Heme binding protein 1
L13722_PROBE1	CHM	CHM, Rab escort protein 1
BE115600_PROBE1	XPO5	Exportin 5
AF197561_PROBE1	PHKA1	Phosphorylase kinase regulatory subunit alpha 1
AJ245619_PROBE1	SLC44A1	Solute carrier family 44 member 1
D37920_PROBE1	SQLE	Squalene epoxidase
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
NM_019380_PROBE1	NPTN	Neuroplastin
U26397_PROBE1	INPP4A	Inositol polyphosphate-4-phosphatase type I A
BF555949_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
AJ132846_PROBE1	SLC1A5	Solute carrier family 1 member 5
AF116344_PROBE1	DNMT1	DNA methyltransferase 1
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
X81395_PROBE1	CES1	Carboxylesterase 1
AA944278_PROBE1	IARS	Isoleucyl-tRNA synthetase
AI229939_PROBE1	DPP8	Dipeptidyl peptidase 8
BF553500_PROBE1	CITED4	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4
X65227_PROBE1	GRIN1	(glutamate ionotropic receptor NMDA type subunit 1) Homo sapiens

Figure 36: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Substrates

Permanent Link: http://bit.ly/2xnlnRC
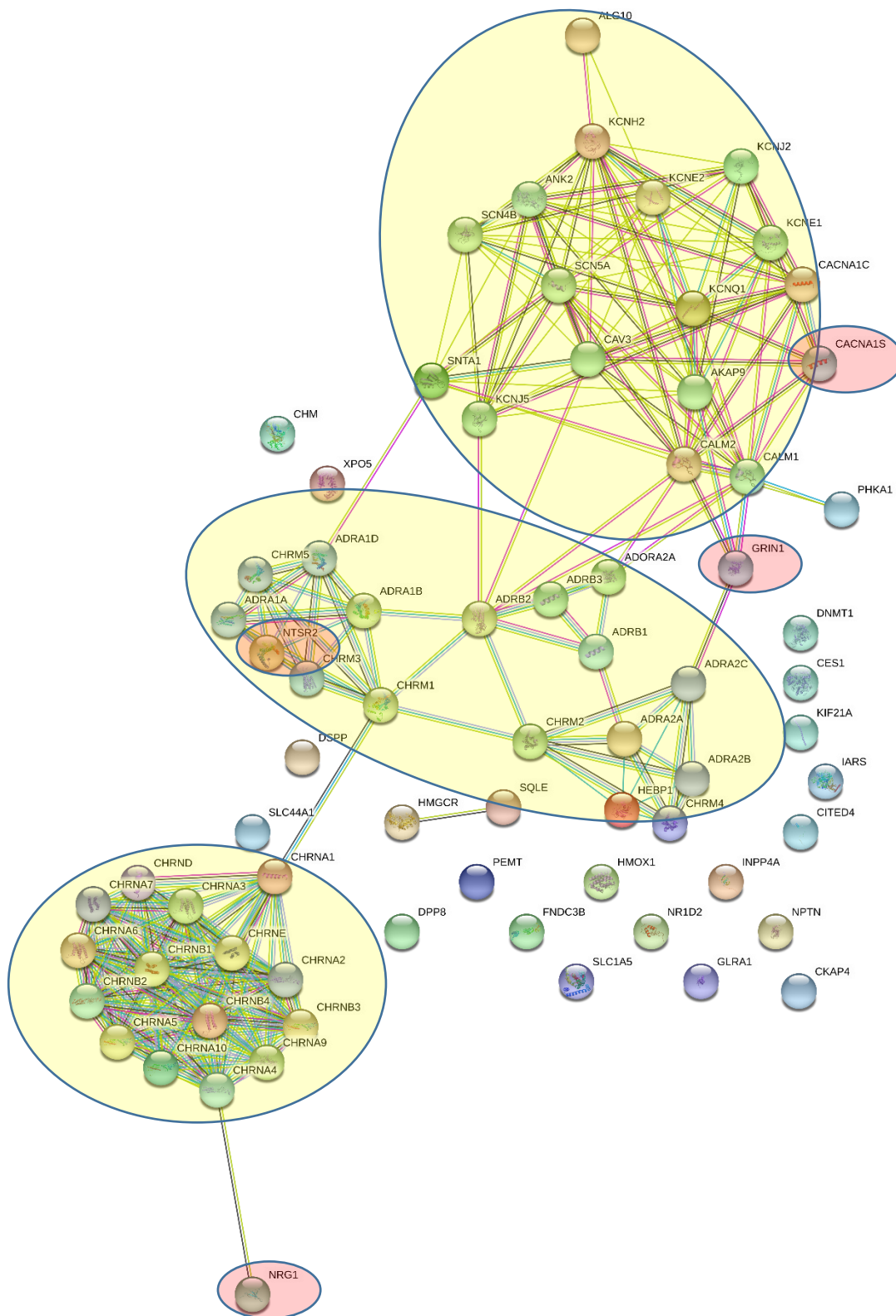
Section 3.3.24.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Substrates

In Figure 36, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow in the center and bottom left.

CACNA1S calcium ion channel expression. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

GRIN1 is a glutamate receptor which may have direct or indirect links to glutathione metabolism or activity. Mean expression of GRIN1 was lower in the QT group compared to the NQT group.

NTSR2 is associate with G proteins which use Ca^{2+} as a second messenger. Mean expression of NTSR2 was lower in the QT group compared to the NQT group.

NRG1 is an activator of multiple MAPKs. Mean expression of NRG1 was lower in the QT group compared to the NQT group.

Section 3.3.25: Cytochrome P-450 CYP2A6 Inhibitors

Table XXXII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
BF402596_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
AW441131_PROBE1	PLEKHB1	Pleckstrin homology domain containing B1
BE118720_PROBE1	KDM6B	Lysine demethylase 6B
AI171798_PROBE1	L3MBTL2	L3MBTL2, polycomb repressive complex 1 subunit
X07648_PROBE1	APP	Amyloid beta precursor protein
AI138048_PROBE1	RCAN2	Regulator of calcineurin 2
L17127_PROBE1	PSMB4	Proteasome subunit beta 4
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
BE107247_PROBE1	TNRC6A	Trinucleotide repeat containing 6A
D37979_PROBE1	PAICS	Phosphoribosylaminoimidazole carboxylase and phosphoribosylaminoimidazolesuccinocarboxamide synthase
U60882_PROBE1	PRMT1	Protein arginine methyltransferase 1
AA946485_PROBE1	IL10	Interleukin 10
AB017188_PROBE1	PSMD4	Proteasome 26S subunit, non-ATPase 4
AF220455_PROBE1	DDX20	DEAD-box helicase 20
AF228917_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
AI103616_PROBE1	RAC1	Rac family small GTPase 1
AI412298_PROBE1	DNPEP	Aspartyl aminopeptidase
AW919320_PROBE1	CHST2	Carbohydrate sulfotransferase 2
D30035_PROBE1	PRDX1	Peroxiredoxin 1
D85035_PROBE1	DPYD	Dihydropyrimidine dehydrogenase
NM_017022_PROBE1	ITGB1	Integrin subunit beta 1
X53585_PROBE1	HSPD1	Heat shock protein family D (Hsp60) member 1
X68282_PROBE1	RPL13A	Ribosomal protein L13a
BF396180_PROBE1	EIF3A	Eukaryotic translation initiation factor 3 subunit A
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
NM_017153_PROBE1	RPS3A	Ribosomal protein S3A
M25157_PROBE1	SOD1	Superoxide dismutase 1
NM_012783_PROBE1	BSG	Basigin (Ok blood group)
NM_019281_PROBE1	GJA9	Gap junction protein alpha 9
U62316_PROBE1	SLC16A7	Solute carrier family 16 member 7
L19931_PROBE1	SLC20A2	Solute carrier family 20 member 2
AW253398_PROBE1	GATAD2A	GATA zinc finger domain containing 2A

Figure 37: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Inhibitors

Permanent Link: http://bit.ly/2xnvzJQ
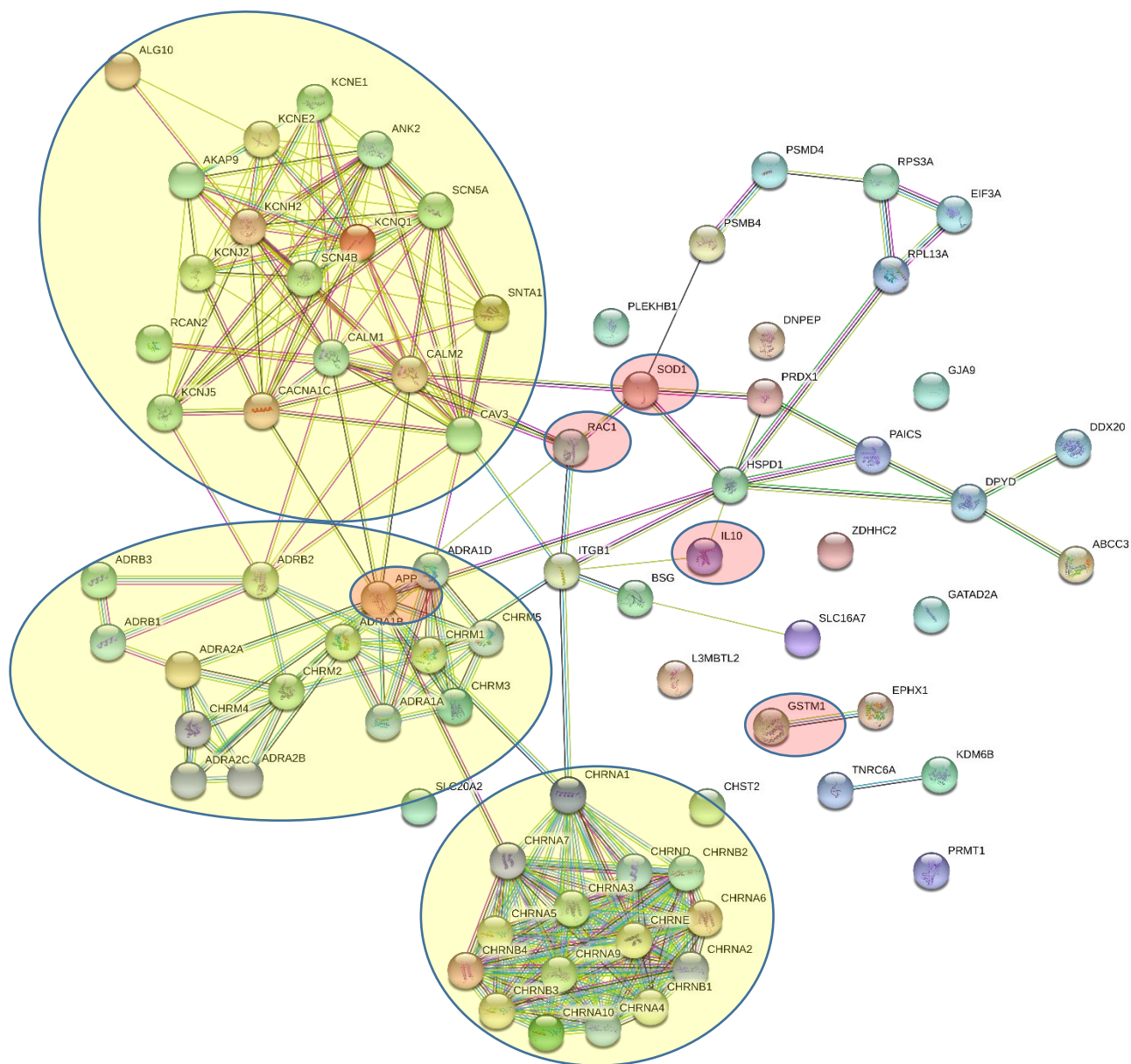
Section 3.3.25.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Inhibitors

In Figure 37, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow in the center left and bottom center.

GTSM1 is associated with glutathione. Mean expression of GTSM1 was lower in the QT group compared to the NQT group.

IL10 is involved with immune responses. Mean expression of IL10 was lower in the QT group compared to the NQT group.

SOD1 detoxifies oxygen free radicals. Mean expression of SOD1 was lower in the QT group compared to the NQT group.

RAC1 is associated with G proteins. Mean expression of RAC1 was lower in the QT group compared to the NQT group.

APP is involved with a pathway that activates MAPKs. Mean expression of APP was lower in the QT group compared to the NQT group.

Section 3.3.26: Cytochrome P-450 CYP2A6 Substrates

Table XXXIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
NM_012545_PROBE1	DDC	Dopa decarboxylase
M34643_PROBE1	NTF3	Neurotrophin 3
M22631_PROBE1	PCCA	Propionyl-CoA carboxylase alpha subunit
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36
M55601_PROBE1	PTN	Pleiotrophin
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3
X53003_PROBE1	ACACA	Acetyl-CoA carboxylase alpha
AF062402_PROBE1	VCAN	Versican
M22899_PROBE1	IL2	Interleukin 2
AW523755_PROBE1	PPP1R1A	Protein phosphatase 1 regulatory inhibitor subunit 1A
AB000215_PROBE1	SMPD3	Sphingomyelin phosphodiesterase 3
AI412626_PROBE1	CLYBL	Citrate lyase beta like
BF550568_PROBE1	UBA5	Ubiquitin like modifier activating enzyme 5
X97121_PROBE1	NTSR2	Neurotensin receptor 2
AI058901_PROBE1	CCL27	C-C motif chemokine ligand 27
AI412473_PROBE1	DISP2	Dispatched RND transporter family member 2
U04738_PROBE1	SSTR4	Somatostatin receptor 4
AF087454_PROBE1	KCNQ3	Potassium voltage-gated channel subfamily Q member 3
D28773_PROBE1	TBXAS1	Thromboxane A synthase 1

Figure 38: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Substrates

Permanent Link:

Section 3.3.26.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Substrates

In Figure 38, genes associated with cLQTS are highlighted in yellow at the bottom left. Genes associated with the ANS are connected and highlighted yellow at the top center and left.

DDC is associated with catecholamine biosynthesis. Mean expression of DDC was lower in the QT group compared to the NQT group.

KCNQ3 and **KCNN3** are both potassium ion channels which were differentially expressed. Mean expression for both of these was lower in the QT group compared to the same probes in the NQT group.

IL2 is an interleukins asaociated with inflammatory responses. Mean expression of IL2 was lower in the QT group compared to the NQT group.

ACACA is associated with fatty acid metabolism. Mean expression of ACACA was lower in the QT group compared to the NQT group.

NPY5R and **NTSR2** are associated with G proteins and calcium second messengers. Mean expression for both of these was lower in the QT group compared to the same probes in the NQT group.

SSTR4 is involved with MAPKs. Mean expression of SSTR4 was lower in the QT group compared to the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was lower in the QT group compared to the NQT group.

Section 3.3.27: Cytochrome P-450 CYP2B6 Substrates

Table XXXIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2B6 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_019246_PROBE1	PCSK7	Proprotein convertase subtilisin/kexin type 7
AW143206_PROBE1	DHRS1	Dehydrogenase/reductase 1
AA800232_PROBE1	NRBP1	Nuclear receptor binding protein 1
AI059234_PROBE1	LRBA	LPS responsive beige-like anchor protein
NM_012775_PROBE1	TGFBR1	Transforming growth factor beta receptor 1
Z11994_PROBE1	LRPAP1	LDL receptor related protein associated protein 1
AB016160_PROBE1	GABBR1	Gamma-aminobutyric acid type B receptor subunit 1
AI228548_PROBE1	S100A1	S100 calcium binding protein A1
BE113264_PROBE1	OSBPL9	Oxysterol binding protein like 9
U67138_PROBE1	DLGAP2	DLG associated protein 2
X07365_PROBE1	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1
AA851239_PROBE1	EXTL2	Exostosin like glycosyltransferase 2
U51013_PROBE1	ADAP1	ArfGAP with dual PH domains 1
BF407819_PROBE1	CBX5	Chromobox 5
U04738_PROBE1	SSTR4	Somatostatin receptor 4
AA892504_PROBE1	LRCH4	Leucine rich repeats and calponin homology domain containing 4
AI409748_PROBE1	ERCC3	ERCC excision repair 3, TFIIH core complex helicase subunit
NM_012613_PROBE1	NPR1	Natriuretic peptide receptor 1
AF230367_PROBE1	GAB2	GRB2 associated binding protein 2
AI104326_PROBE1	TMEM38A	Transmembrane protein 38A
AI012476_PROBE1	NANS	N-acetylneuraminate synthase
AW917684_PROBE1	TMEM106B	Transmembrane protein 106B
BF420163_PROBE1	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1
NM_017290_PROBE1	ATP2A2	ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2
AA858677_PROBE1	IGSF8	Immunoglobulin superfamily member 8
AI235431_PROBE1	TNPO2	Transportin 2
AI412393_PROBE1	HSPA12A	Heat shock protein family A (Hsp70) member 12A
AI136709_PROBE1	RND2	Rho family GTPase 2
AF007549_PROBE1	GOSR2	Golgi SNAP receptor complex member 2

Figure 39: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2B6 Substrates
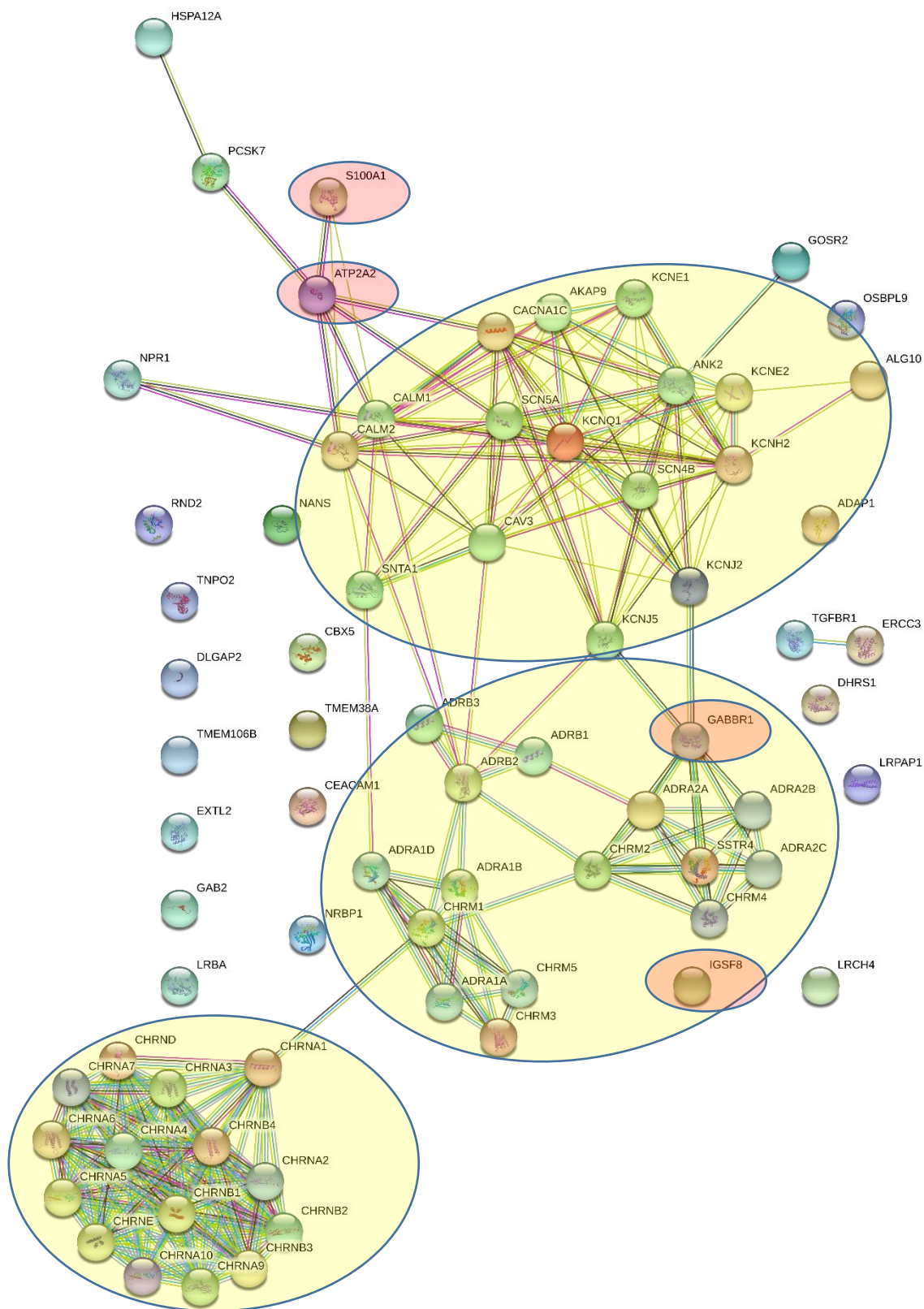
Section 3.3.27.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2B6 Substrates

In Figure 39, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

IGSF8 is associated with immune responses. Mean expression of IGSF8 was lower in the QT group compared to the NQT group.

S100A1 is a calcium binding protein which is part of a second messenger system. Mean expression of S100A1 was lower in the QT group compared to the NQT group.

GABBR1 is assocated with G proteins which use calcium as a second messenger. Mean expression of GABBR1 was lower in the QT group compared to the NQT group.

ATP2A2 is involved with the myocardial contraction and relaxation cycle and interacts with calcium-induced conformational changes to generate mitochondrial reactive oxygen species. Mean expression of ATP2A2 was higher in the QT group compared to the NQT group.

Section 3.3.28: Cytochrome P-450 CYP2C8 Inhibitors

Table XXXV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2
NM_012600_PROBE1	ME1	Malic enzyme 1
BE108949_PROBE1	TMEM30B	Transmembrane protein 30B
AF111268_PROBE1	CD36	CD36 molecule
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
AW141928_PROBE1	VNN1	Vanin 1
BF408216_PROBE1	ACBD6	Acyl-CoA binding domain containing 6
D00913_PROBE1	ICAM1	Intercellular adhesion molecule 1
D85189_PROBE1	ACSL4	Acyl-CoA synthetase long chain family member 4
J02752_PROBE1	ACOX1	Acyl-CoA oxidase 1
AA899304_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
AW507123_PROBE1	CYB561	Cytochrome b561
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
NM_017075_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1
AF044058_PROBE1	PIAS2	Protein inhibitor of activated STAT 2
BF415760_PROBE1	PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2
NM_012556_PROBE1	FABP1	Fatty acid binding protein 1
AA800303_PROBE1	PLSCR3	Phospholipid scramblase 3
BE113101_PROBE1	ATG4B	Autophagy related 4B cysteine peptidase
AI598399_PROBE1	RBM3	RNA binding motif (RNP1, RRM) protein 3
NM_017135_PROBE1	AK3	Adenylate kinase 3)
AW918222_PROBE1	TOR3A	Torsin family 3 member A
X65083_PROBE1	EPHX2	Epoxide hydrolase 2
AW918650_PROBE1	CHCHD6	Coiled-coil-helix-coiled-coil-helix domain containing 6
AW919036_PROBE1	MGLL	Monoglyceride lipase
NM_017083_PROBE1	MYO5B	Myosin VB
NM_019157_PROBE1	AQP7	Aquaporin 7
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
NM_012679_PROBE1	CLU	Clusterin
AA944380_PROBE1	NUDT7	Nudix hydrolase 7

Figure 40: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors

Permanent Link: http://bit.ly/2w8BrrV
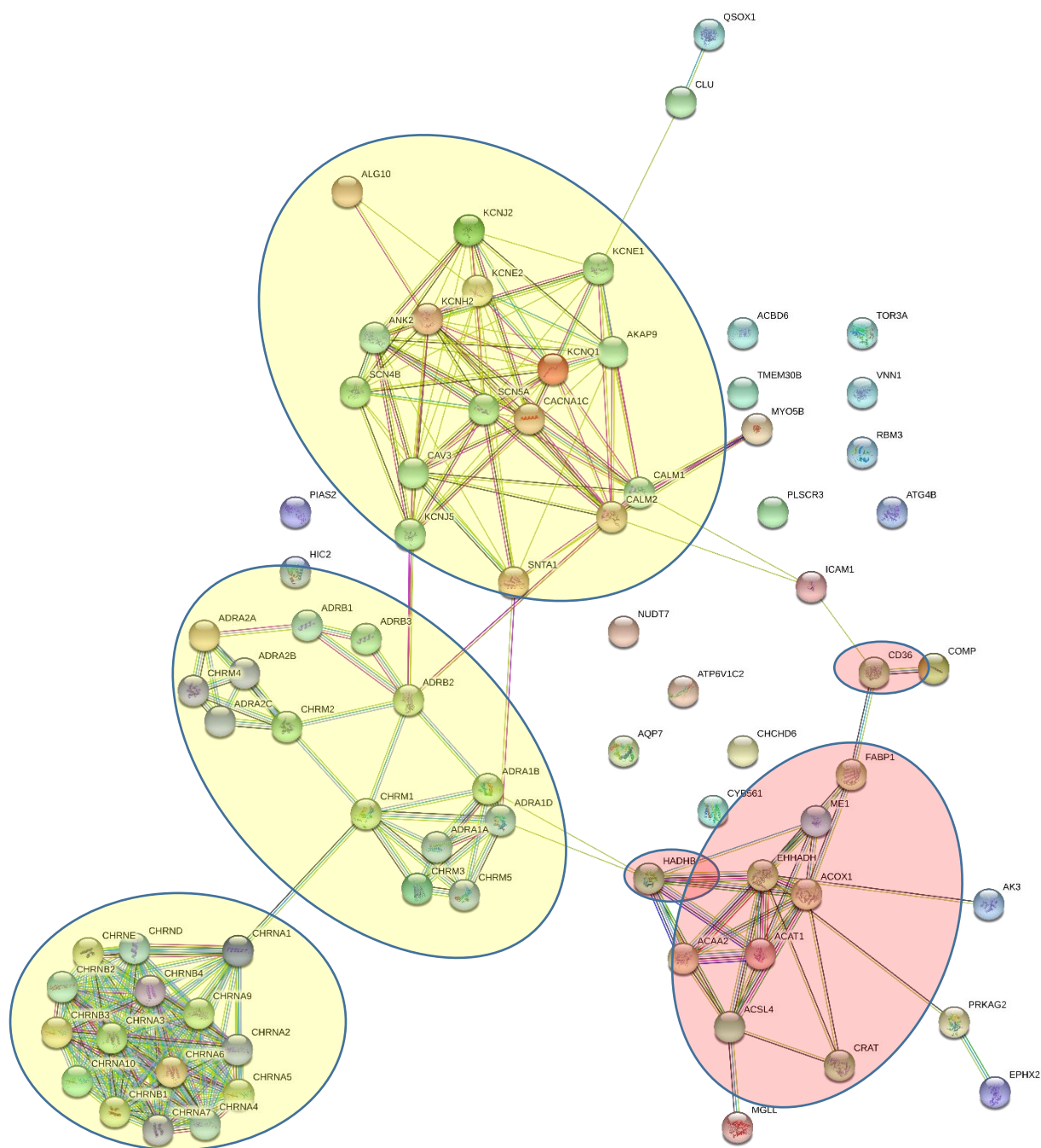
Section 3.3.28.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors

In Figure 40, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

ME1, **HADHB**, **FABP1** and **ACOX1** are genes associated with fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.29: Cytochrome P-450 CYP2C8 Substrates

Table XXXVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB006137_PROBE1	FUT1	Fucosyltransferase 1 (H blood group)
BE110722_PROBE1	GTF2H3	General transcription factor IIH subunit 3
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
U72353_PROBE1	LMNB1	Lamin B1
AF139055_PROBE1	MYH10	Myosin heavy chain 10
NM_019157_PROBE1	AQP7	Aquaporin 7
NM_012550_PROBE1	EDNRA	Endothelin receptor type A
M22642_PROBE1	TK1	Thymidine kinase 1
AW251213_PROBE1	IPO7	Importin 7
NM_017116_PROBE1	CAPN2	Calpain 2
BF398009_PROBE1	PMM2	Phosphomannomutase 2
D44481_PROBE1	CRK	CRK proto-oncogene, adaptor protein
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
M22323_PROBE1	ACTA2	Actin, alpha 2, smooth muscle, aorta
M30596_PROBE1	ME1	Malic enzyme 1
AB010467_PROBE1	ABCC3	ATP binding cassette subfamily C member 3
J00696_PROBE1	ORM1	Orosomucoid 1
NM_017223_PROBE1	SLC20A2	Solute carrier family 20 member 2
NM_021763_PROBE1	ARFIP1	ADP ribosylation factor interacting protein 1
AW141939_PROBE1	RHOA	Ras homolog family member A
NM_019192_PROBE1	SELENOP	Selenoprotein P
AF187065_PROBE1	BEX3	Brain expressed X-linked 3
AF240784_PROBE1	SCAMP5	Secretory carrier membrane protein 5
BE099950_PROBE1	ADPRHL2	ADP-ribosylhydrolase like 2
BE109057_PROBE1	DCX	Doublecortin
L02615_PROBE1	PKIA	cAMP-dependent protein kinase inhibitor alpha
NM_012715_PROBE1	ADM	Adrenomedullin
NM_017010_PROBE1	GRIN1	Glutamate ionotropic receptor NMDA type subunit 1
NM_017180_PROBE1	PHLDA1	Pleckstrin homology like domain family A member 1
AW144233_PROBE1	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
AA819103_PROBE1	PFKL	Phosphofructokinase, liver type
NM_017331_PROBE1	TPM1	Tropomyosin 1
AI599376_PROBE1	SEC22B	SEC22 homolog B, vesicle trafficking protein (gene/pseudogene)

Figure 41: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Substrates

Permanent Link: http://bit.ly/2w9CBnj
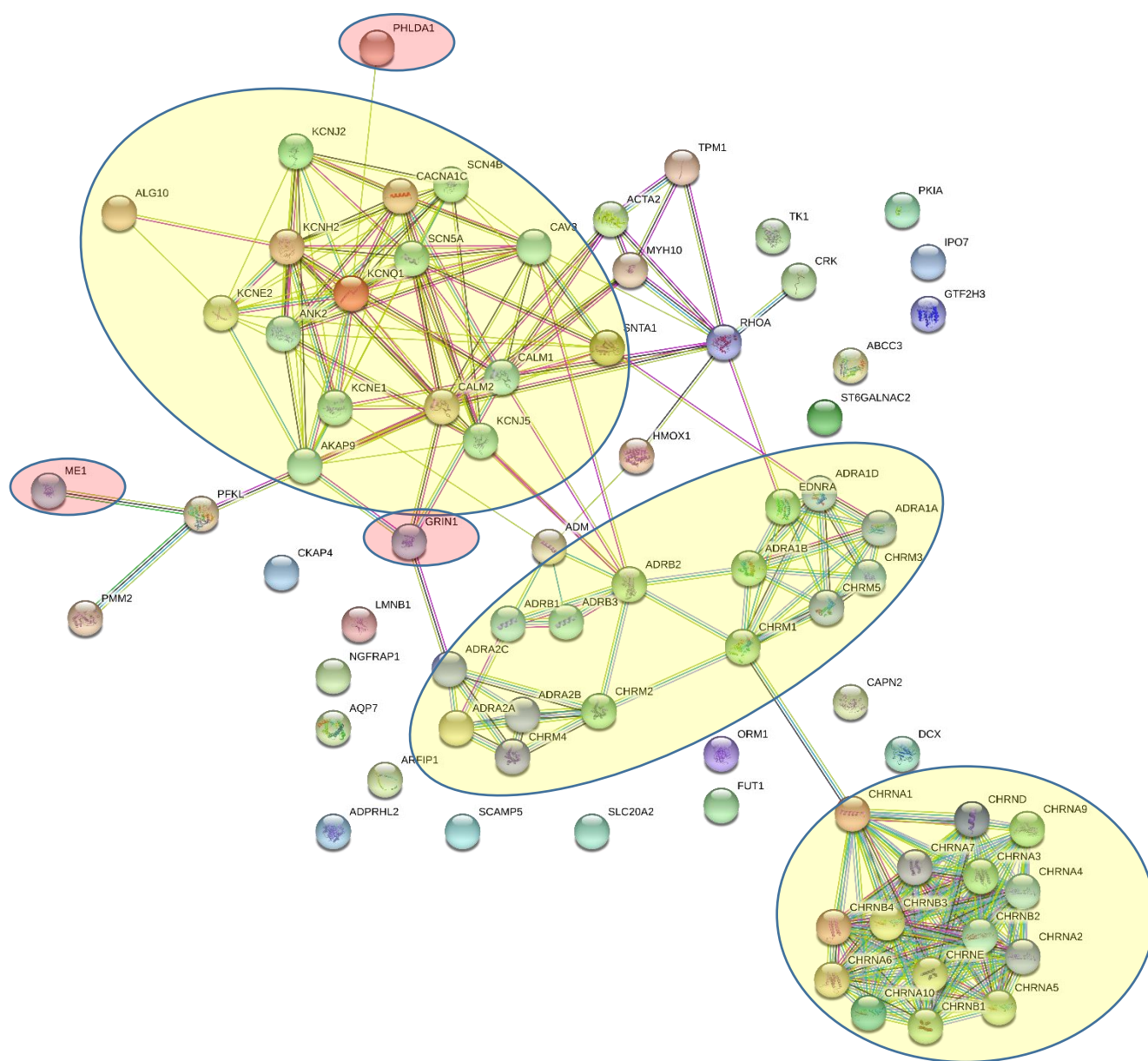
Section 3.3.29.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Substrates

In Figure 41, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the center and bottom right.

ME1 is associated width fatty acid metabolism. Mean expression of ME1 was lower in the QT group compared to the NQT group.

GRIN1 suggests a link to glutamate and glutathione activity. Mean expression of GRIN1 was lower in the QT group compared to the NQT group.

PHLDA1 is associated with regulation of apoptosis. Mean expression of PHLDA1 was lower in the QT group compared to the NQT group.

Section 3.3.30: Cytochrome P-450 CYP2C9 Inhibitors

Table XXXVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
AF034577_PROBE1	PDK4	Pyruvate dehydrogenase kinase 4
M30596_PROBE1	ME1	Malic enzyme 1
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
J02752_PROBE1	ACOX1	Acyl-CoA oxidase 1
U46149_PROBE1	COQ7	Coenzyme Q7, hydroxylase
NM_019157_PROBE1	AQP7	Aquaporin 7
AA850909_PROBE1	NECTIN2	Nectin cell adhesion molecule 2
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
AI137488_PROBE1	PGRMC2	Progesterone receptor membrane component 2
BF548116_PROBE1	ELMO2	Engulfment and cell motility 2
NM_012600_PROBE1	ME1	Malic enzyme 1
AW144226_PROBE1	ABHD6	Abhydrolase domain containing 6
AI172579_PROBE1	PGGHG	Protein-glucosylgalactosylhydroxylysine glucosidase
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
AF061947_PROBE1	CABIN1	Calcineurin binding protein 1
BE113210_PROBE1	CREBL2	cAMP responsive element binding protein like 2
AA799707_PROBE1	NDUFB5	NADH:ubiquinone oxidoreductase subunit B5
AI012951_PROBE1	PEX13	Peroxisomal biogenesis factor 13
BE116152_PROBE1	ELOVL6	ELOVL fatty acid elongase 6
BF561196_PROBE1	RDH11	Retinol dehydrogenase 11 (all-trans/9-cis/11-cis)
AI144583_PROBE1	PPP2R5E	Protein phosphatase 2 regulatory subunit B'epsilon
AA891834_PROBE1	COL4A5	Collagen type IV alpha 5 chain
NM_017294_PROBE1	PACSIN1	Protein kinase C and casein kinase substrate in neurons 1
AW253928_PROBE1	ETV4	ETS variant 4
M55601_PROBE1	PTN	Pleiotrophin
AW918222_PROBE1	TOR3A	Torsin family 3 member A
M15327_PROBE1	ADH1A	Alcohol dehydrogenase 1A (class I), alpha polypeptide
U69485_PROBE1	FKBP1A	FK506 binding protein 1A

Figure 42: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors

Permanent Link: http://bit.ly/2w9l5PO
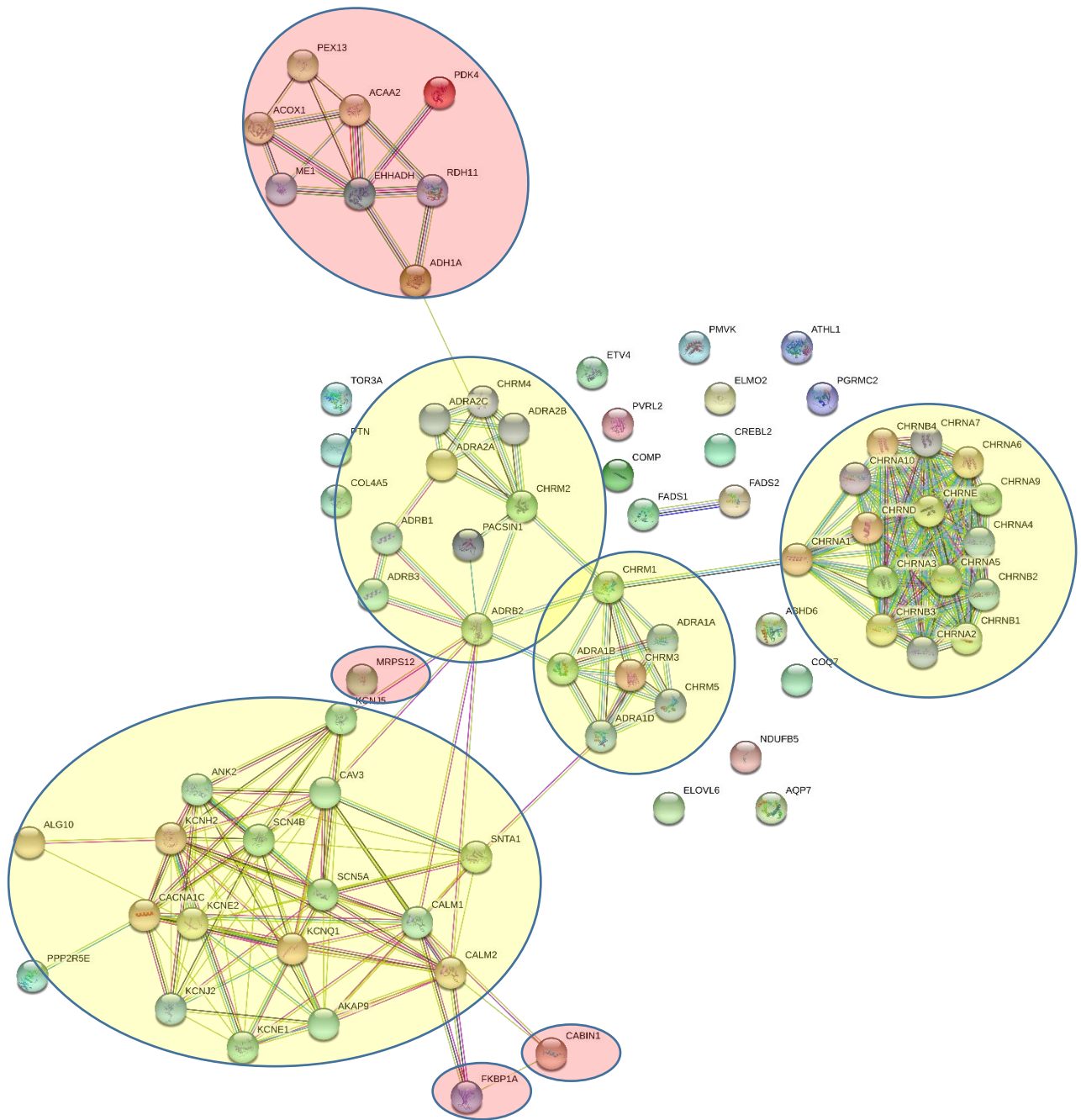
Section 3.3.30.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors

In Figure 42, genes associated with cLQTS are highlighted in yellow at the bottom left. Genes associated with the ANS are highlighted yellow at the center and the two groups left of center. The genes highlighted in red are summarized below.

FADS1, **EHHADH**, **ACAA2**, **FADS2**, and **ACOX1** are all genes associated with fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

CABIN1 may have immune function by regulation of T cell receptors based on calcium and protein kinase C levels. Mean expression of CABIN1 was lower in the QT group compared to the NQT group.

Section 3.3.31: Cytochrome P-450 CYP2C9 Substrates

Table XXXVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW915795_PROBE1	PQLC3	PQ loop repeat containing 3
AF081582_PROBE1	PLEKHB1	Pleckstrin homology domain containing B1
AW525211_PROBE1	PYCR2	Pyrroline-5-carboxylate reductase 2
BE096098_PROBE1	AMIGO3	Adhesion molecule with Ig like domain 3
AF112184_PROBE1	CDKL3	Cyclin dependent kinase like 3
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
L20900_PROBE1	ICA1	Islet cell autoantigen 1
AI454418_PROBE1	IGSF1	Immunoglobulin superfamily member 1
X97121_PROBE1	NTSR2	Neurotensin receptor 2
AF187065_PROBE1	BEX3	Brain expressed X-linked 3
BF409371_PROBE1	EIF2AK4	Eukaryotic translation initiation factor 2 alpha kinase 4
U46149_PROBE1	COQ7	Coenzyme Q7, hydroxylase
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AA800587_PROBE1	GPX2	Glutathione peroxidase 2
AI058276_PROBE1	COQ8B	Coenzyme Q8B
L33413_PROBE1	AGER	Advanced glycosylation end-product specific receptor
U02315_PROBE1	NRG1	Neuregulin 1
BE104266_PROBE1	KNTC1	Kinetochore associated 1
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
M30596_PROBE1	ME1	Malic enzyme 1
D28508_PROBE1	JAK3	Janus kinase 3
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
J03960_PROBE1	ALOX5	Arachidonate 5-lipoxygenase
U67136_PROBE1	AKAP5	A-kinase anchoring protein 5
X13295_PROBE1	LCN2	Lipocalin 2
U66470_PROBE1	CGREF1	Cell growth regulator with EF-hand domain 1
BE099603_PROBE1	PRR3	Proline rich 3
L18948_PROBE1	S100A9	S100 calcium binding protein A9
AI012951_PROBE1	PEX13	Peroxisomal biogenesis factor 13
AW142717_PROBE1	COPA	Coatomer protein complex subunit alpha
M15327_PROBE1	ADH1A	Alcohol dehydrogenase 1A (class I), alpha polypeptide
AF240784_PROBE1	SCAMP5	Secretory carrier membrane protein 5
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
L36388_PROBE1	FOXJ1	Forkhead box J1
AW915121_PROBE1	BRD9	Bromodomain containing 9
AI227742_PROBE1	BOK	BOK, BCL2 family apoptosis regulator

Figure 43: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates
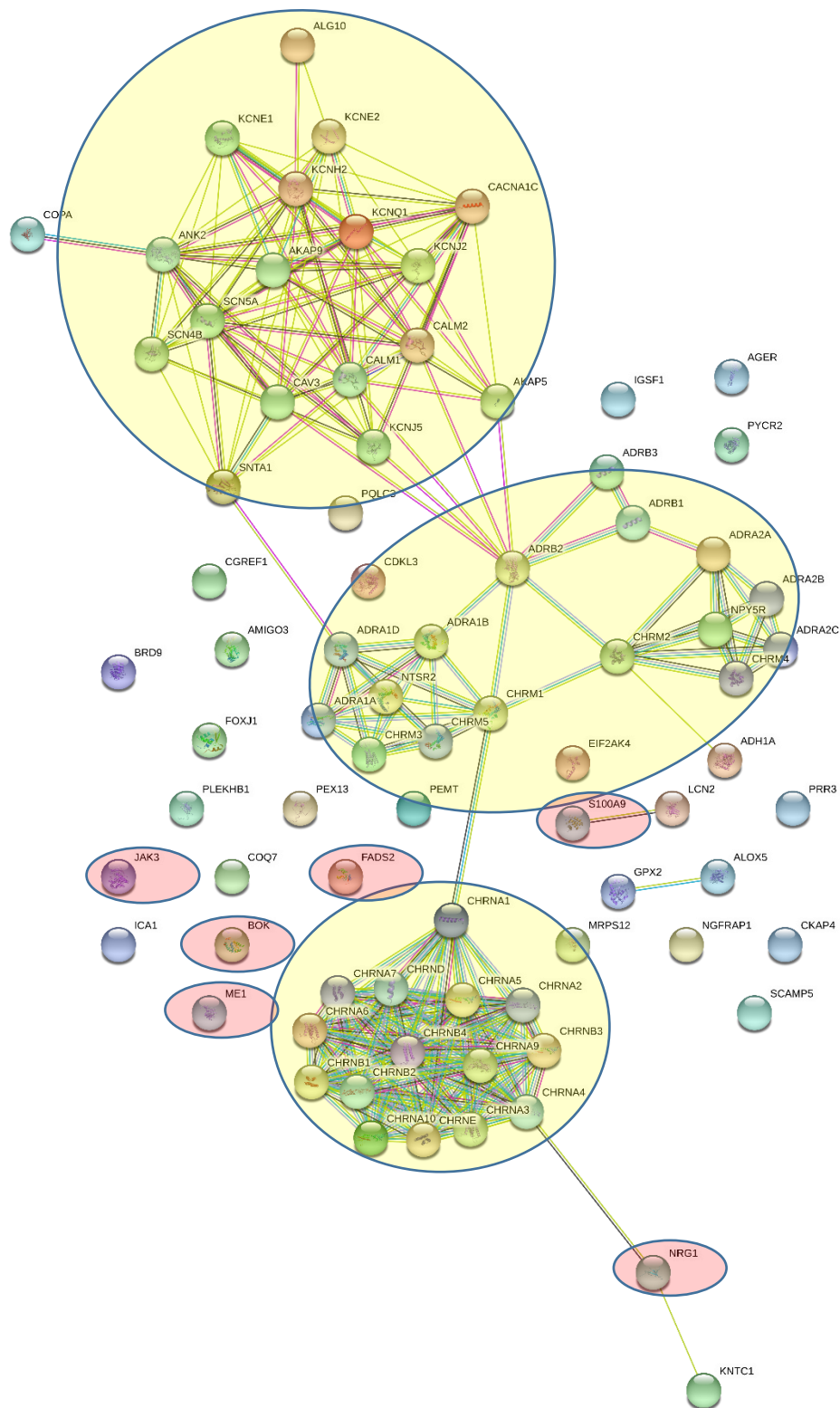
Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000322316%250D9606.ENSP00000295030%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D96
06.ENSP00000349467%250D9606.ENSP00000209668%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D960
6.ENSP00000303686%250D9606.ENSP00000364217%250D9606.ENSP00000339377%250D9606.ENSP00000419765%250D9606.
ENSP00000312663%250D9606.ENSP00000304290%250D9606.ENSP00000278840%250D9606.ENSP00000250699%250D9606.E
NSP00000346127%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000349275%250D9606.EN
SP00000265334%250D9606.ENSP00000363512%250D9606.ENSP00000306490%250D9606.ENSP00000266376%250D9606.ENS
P00000328968%250D9606.ENSP00000276410%250D9606.ENSP00000385026%250D9606.ENSP00000324025%250D9606.ENSP
00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000263791%250D9606.ENSP00000266483%250D9606.ENSP0
0000359940%250D9606.ENSP00000314132%250D9606.ENSP00000386069%250D9606.ENSP00000357727%250D9606.ENSP00
000319984%250D9606.ENSP00002255389%250D9606.ENSP00000308845%250D9606.ENSP00002261751%250D9606.ENSP000
00367265%250D9606.ENSP00000357048%250D9606.ENSP00000365744%250D9606.ENSP00000349588%250D9606.ENSP0000
0368766%250D9606.ENSP00000323096%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000
391676%250D9606.ENSP00000357461%250D9606.ENSP00000387281%250D9606.ENSP00000295083%250D9606.ENSP000003
39960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP0000036
9960%250D9606.ENSP00000355387%250D9606.ENSP00000342502%250D9606.ENSP00000272298%250D9606.ENSP00000358
301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000299872%250D9606.ENSP000003156
15%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000374265%250D9606.ENSP0000026218
6%250D9606.ENSP00000255380%250D9606.ENSP00000328236%250D9606.ENSP00000280155%250D9606.ENSP00000358719
%250D9606.ENSP00000379908%250D9606.ENSP00000299565%250D9606.ENSP00000323880%250D9606.ENSP00000277480%
250D9606.ENSP00000293780%250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.31.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates

In Figure 43, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the center and bottom right.

ME1 and **FADS2** are associated with fatty acid metabolism. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

IGSF1 and **JAK3** are associated with immune responses. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

S100A9 is associated with an immune response and it binds Ca^{2+}. Mean expression of S100A9 was lower in the QT group compared to the NQT group.

NRG1 is associated with MAPK activities. Mean expression of NRG1 was lower in the QT group compared to the NQT group.

BOK is associated with apoptosis regulation. Mean expression of BOK was lower in the QT group compared to the NQT group.

Section 3.3.32: Cytochrome P-450 CYP2C19 Inhibitors

Table XXXIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
L19658_PROBE1	CD36	CD36 molecule
AF111268_PROBE1	CD36	CD36 molecule
NM_012708_PROBE1	PSMB9	Proteasome subunit beta 9
D90109_PROBE1	ACSL1	Acyl-CoA synthetase long chain family member 1
Y13413_PROBE1	APBB3	Amyloid beta precursor protein binding family B member 3
U73142_PROBE1	MAPK14	Mitogen-activated protein kinase 14
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
AI144583_PROBE1	PPP2R5E	Protein phosphatase 2 regulatory subunit B'epsilon
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
AW918222_PROBE1	TOR3A	Torsin family 3 member A
AW254166_PROBE1	STAG1	Stromal antigen 1
BE116569_PROBE1	ZC3H7A	Zinc finger CCCH-type containing 7A
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
AI104251_PROBE1	ABHD14A	Abhydrolase domain containing 14A
X97831_PROBE1	SLC25A20	Solute carrier family 25 member 20
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
J02752_PROBE1	ACOX1	Acyl-CoA oxidase 1
BF408022_PROBE1	MYH9	Myosin heavy chain 9
M30596_PROBE1	ME1	Malic enzyme 1
AA850909_PROBE1	NECTIN2	Nectin cell adhesion molecule 2
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1
X62528_PROBE1	RNH1	Ribonuclease/angiogenin inhibitor 1
BF561196_PROBE1	RDH11	Retinol dehydrogenase 11 (all-trans/9-cis/11-cis)
AF034577_PROBE1	PDK4	Pyruvate dehydrogenase kinase 4
BE113101_PROBE1	ATG4B	Autophagy related 4B cysteine peptidase
NM_017268_PROBE1	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
NM_021670_PROBE1	BMP15	Bone morphogenetic protein 15
BF555949_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
U53706_PROBE1	MVD	Mevalonate diphosphate decarboxylase
AF189019_PROBE1	NSF	N-ethylmaleimide sensitive factor, vesicle fusing ATPase
AA946474_PROBE1	CAST	Calpastatin
NM_019157_PROBE1	AQP7	Aquaporin 7
NM_013134_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
BF397726_PROBE1	NFE2	Nuclear factor, erythroid 2
M29472_PROBE1	MVK	Mevalonate kinase

Figure 44: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors

Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000281455%250D9606.ENSP00000293217%250D9606.ENSP00000222271%250D9606.ENSP00000322706%250D9606.ENSP00000312436%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000228510%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000301012%250D9606.ENSP00000312663%250D9606.ENSP00000304290%250D9606.ENSP00000250699%250D9606.ENSP00000363993%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000297988%250D9606.ENSP00000306490%250D9606.ENSP00000231887%250D9606.ENSP00000252677%250D9606.ENSP00000005178%250D9606.ENSP00000266376%250D9606.ENSP00000252483%250D9606.ENSP00003328968%250D9606.ENSP00000276410%250D9606.ENSP00000385026%250D9606.ENSP00000273596%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000287936%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000346378%250D9606.ENSP00000319984%250D9606.ENSP00000229794%250D9606.ENSP00000346402%250D9606.ENSP00000308845%250D9606.ENSP00000216181%250D9606.ENSP00000261751%250D9606.ENSP00000349588%250D9606.ENSP00000372689%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000357461%250D9606.ENSP00000370750%250D9606.ENSP00000347999%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000269143%250D9606.ENSP00003372750%250D9606.ENSP00004407546%250D9606.ENSP00003357452%250D9606.ENSP00000369960%250D9606.ENSP00000272298%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000326305%250D9606.ENSP00000337255%250D9606.ENSP00000381293%250D9606.ENSP00000384259%250D9606.ENSP00000337641%250D9606.ENSP00000356599%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000358719%250D9606.ENSP00000299565%250D9606.ENSP00000379157%250D9606.ENSP00000308165%250D9606.ENSP00000293780%250D9606.ENSP00000356574%250D9606.ENSP00000306662%250D9606.ENSP00000311095%250D9606.ENSP00000348573

Section 3.3.32.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors

In Table 44, genes associated with cLQTS are highlighted in yellow in the center. Genes associated with the ANS are highlighted yellow in the two clusters to the left.

CD36, **EHHADH**, **ACOX1**, and **ME1** are examples of proteins associated with lipid and fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

MAPK14 is part of the MAPK family, specifically involved with proinflammatory responses. Mean expression of MAPK14 was lower in the QT group compared to the NQT group.

**MRPS12** is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

Section 3.3.33: Cytochrome P-450 CYP2C19 Substrates

Table XL: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
AF081582_PROBE1	PLEKHB1	Pleckstrin homology domain containing B1
AF187065_PROBE1	BEX3	Brain expressed X-linked 3
AW520767_PROBE1	FBXO7	F-box protein 7
BE113306_PROBE1	MSH5	MutS homolog 5
NM_021657_PROBE1	PHLPP1	PH domain and leucine rich repeat protein phosphatase 1
AW525211_PROBE1	PYCR2	Pyrroline-5-carboxylate reductase 2
BF403319_PROBE1	LENG8	Leukocyte receptor cluster member 8
AW252096_PROBE1	FGF12	Fibroblast growth factor 12
D28508_PROBE1	JAK3	Janus kinase 3
AI030203_PROBE1	IRX3	Iroquois homeobox 3
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
L20900_PROBE1	ICA1	Islet cell autoantigen 1
M85299_PROBE1	SLC9A1	Solute carrier family 9 member A1
U26595_PROBE1	PTGFRN	Prostaglandin F2 receptor inhibitor
U90888_PROBE1	AMPD3	Adenosine monophosphate deaminase 3
AF254800_PROBE1	RAB31	RAB31, member RAS oncogene family
AI171088_PROBE1	SRM	Spermidine synthase
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
BE103518_PROBE1	PLXNA3	Plexin A3
BF408022_PROBE1	MYH9	Myosin heavy chain 9
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
BE113101_PROBE1	ATG4B	Autophagy related 4B cysteine peptidase
NM_012675_PROBE1	TNF	Tumor necrosis factor
AF070065_PROBE1	CIT	Citron rho-interacting serine/threonine kinase
AA800303_PROBE1	PLSCR3	Phospholipid scramblase 3
AW915661_PROBE1	PERP	PERP, TP53 apoptosis effector
BE109033_PROBE1	AGO1	Argonaute 1, RISC catalytic component
BF564263_PROBE1	IFT81	Intraflagellar transport 81

Figure 45: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates

Permanent Link: http://bit.ly/2w9CeZA
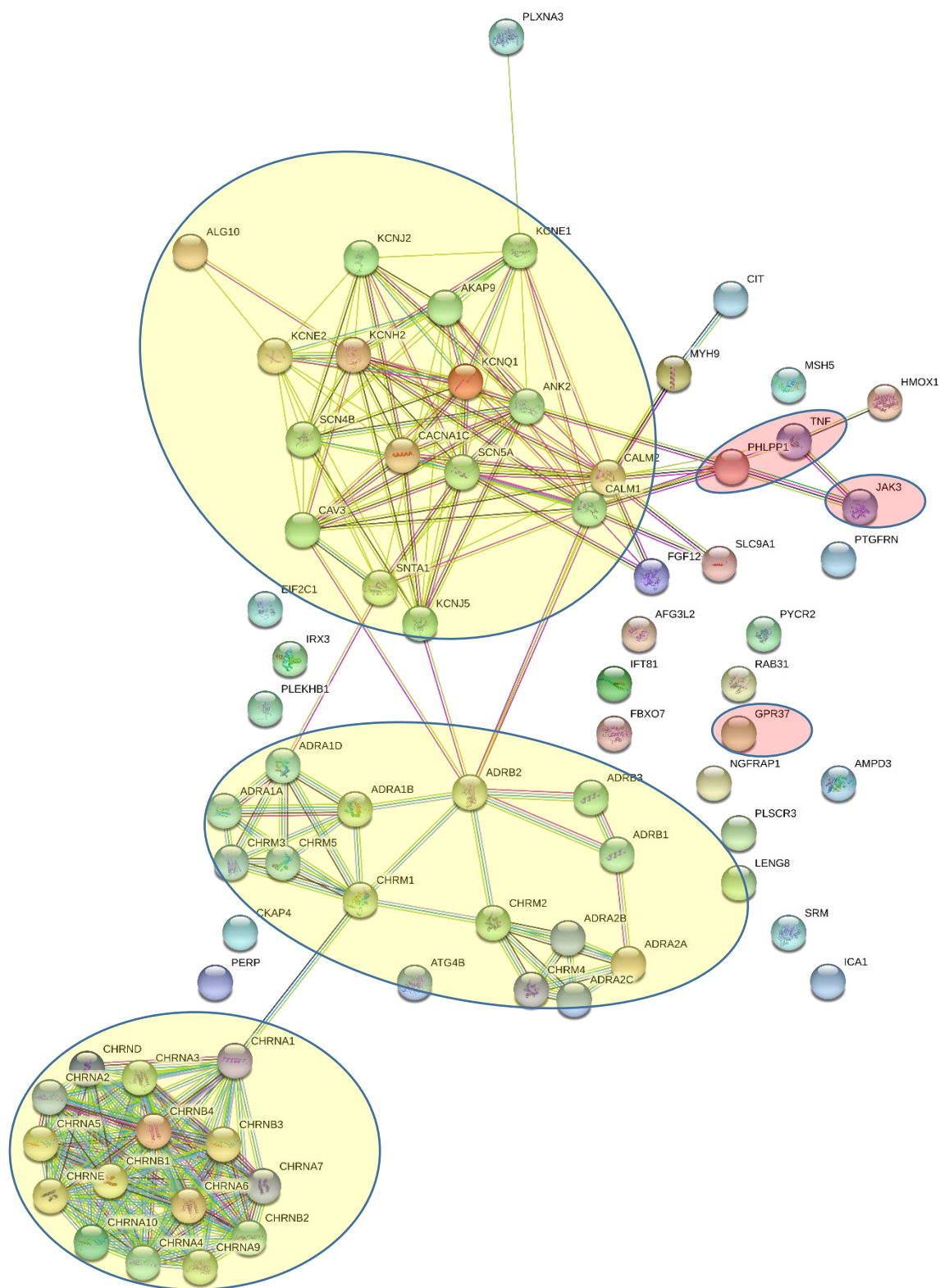
Section 3.3.33.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates

In Figure 45, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the center and bottom right.

JAK3 is associated with immune responses. Mean expression of JAK3 was lower in the QT group compared to the NQT group.

TNF and **PHLPP1** are associated with immune responses and apoptosis. Mean expression of TNF was lower in the QT group compared to the NQT group. Mean expression of PHLPP1 was higher in the QT group compared to the NQT group.

GPR37 is associated with G proteins. Mean expression of GPR37 was lower in the QT group compared to the NQT group.

Section 3.3.34: Cytochrome P-450 CYP2D6 Inhibitors

Table XLI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW918650_PROBE1	CHCHD6	Coiled-coil-helix-coiled-coil-helix domain containing 6
AJ001044_PROBE1	EPCAM	Epithelial cell adhesion molecule
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
AA850909_PROBE1	NECTIN2	Nectin cell adhesion molecule 2
NM_012600_PROBE1	ME1	Malic enzyme 1
AW252110_PROBE1	REXO2	RNA exonuclease 2
AI176781_PROBE1	FDFT1	Farnesyl-diphosphate farnesyltransferase 1
BF555949_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
M29472_PROBE1	MVK	Mevalonate kinase
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
AI411530_PROBE1	ACY1	Aminoacylase 1
NM_012941_PROBE1	CYP51A1	Cytochrome P450 family 51 subfamily A member 1
AA891902_PROBE1	ANKFY1	Ankyrin repeat and FYVE domain containing 1
M30596_PROBE1	ME1	Malic enzyme 1
BF392344_PROBE1	MTMR7	Myotubularin related protein 7
AI177016_PROBE1	LSM8	LSM8 homolog, U6 small nuclear RNA associated
BF550292_PROBE1	MCM4	Minichromosome maintenance complex component 4
U53706_PROBE1	MVD	Mevalonate diphosphate decarboxylase
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
D37920_PROBE1	SQLE	Squalene epoxidase
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
U02096_PROBE1	FABP7	Fatty acid binding protein 7
BE108886_PROBE1	MSL2	MSL complex subunit 2
BE116569_PROBE1	ZC3H7A	Zinc finger CCCH-type containing 7A
AI169353_PROBE1	DCXR	Dicarbonyl and L-xylulose reductase
BF397726_PROBE1	NFE2	Nuclear factor, erythroid 2
NM_019157_PROBE1	AQP7	Aquaporin 7
U53512_PROBE1	MRPL17	Mitochondrial ribosomal protein L17

Figure 46: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors

Permanent Link: http://bit.ly/2w9jUzT
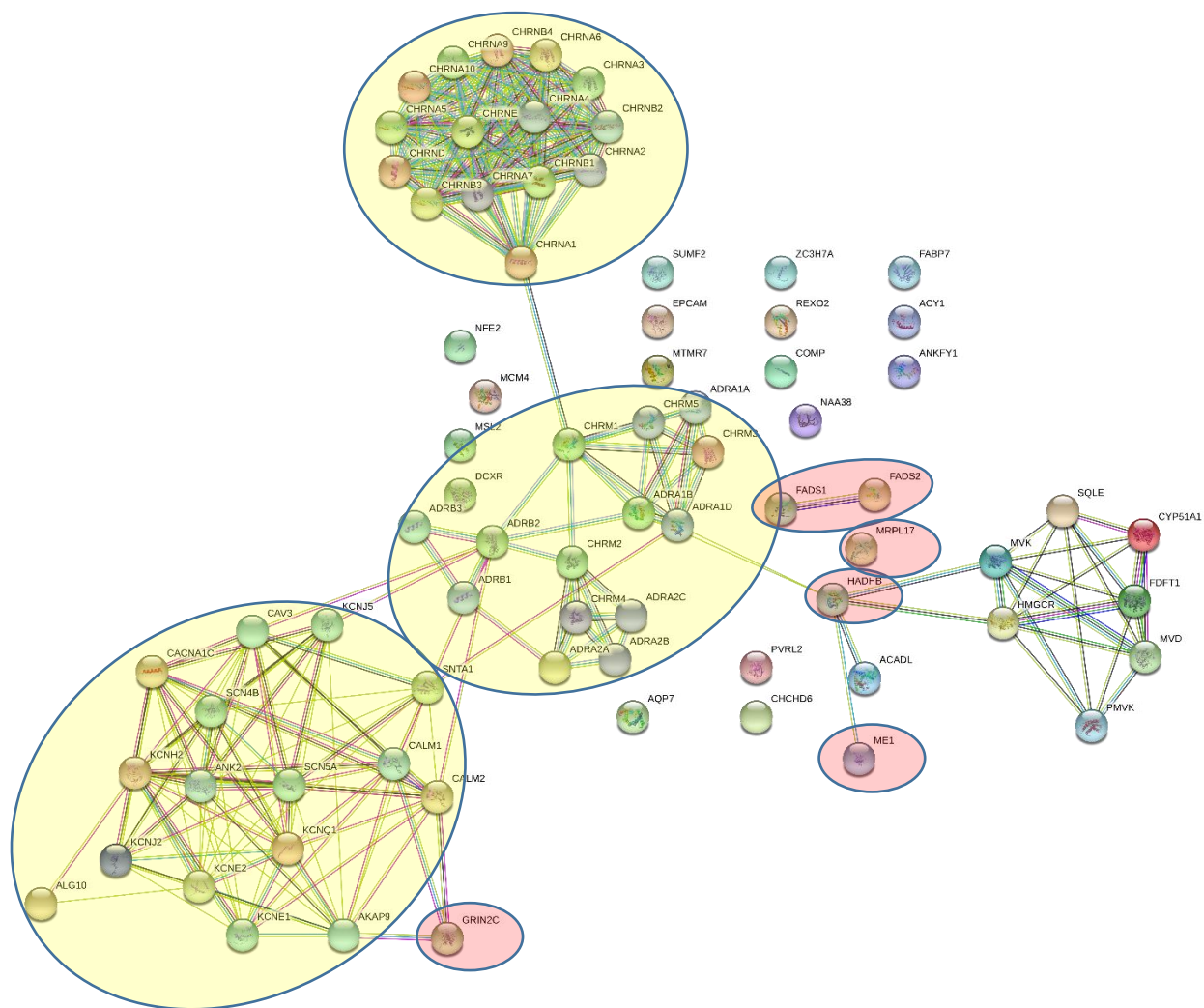
Section 3.3.34.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors

In Figure 46, genes associated with cLQTS are highlighted in yellow at the bottom left. Genes associated with the ANS are connected and highlighted yellow at the center and top. The gene highlighted in red is summarized below.

FABP7, **FADS1**, **FADS2**, **HADHB**, and **ME1** are examples of genes associated with fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

GRIN2C associated with glutamate and by extension may be associated with glutathione. Mean expression of GRIN2C was lower in the QT group compared to the NQT group.

MRPL17 is a mitochondrial ribosomal protein. Mean expression of MRPL17 was lower in the QT group compared to the NQT group.

Section 3.3.35: Cytochrome P-450 CYP2D6 Substrates

Table XLII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB014722_PROBE1	SART1	SART1, U4/U6.U5 tri-snRNP-associated protein 1
AF276774_PROBE1	LIG1	DNA ligase 1
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
M61142_PROBE1	THOP1	Thimet oligopeptidase 1
NM_019157_PROBE1	AQP7	Aquaporin 7
AA851306_PROBE1	HMGN3	High mobility group nucleosomal binding domain 3
AF182946_PROBE1	BARD1	BRCA1 associated RING domain 1
AA859768_PROBE1	MCM5	Minichromosome maintenance complex component 5
AW253880_PROBE1	KIFC1	Kinesin family member C1
L16922_PROBE1	PGR	Progesterone receptor
AA891902_PROBE1	ANKFY1	Ankyrin repeat and FYVE domain containing 1
NM_017288_PROBE1	SCN1B	Sodium voltage-gated channel beta subunit 1
AF032666_PROBE1	EXOC2	Exocyst complex component 2
AF151373_PROBE1	RAI14	Retinoic acid induced 14
AI412015_PROBE1	RRM1	Ribonucleotide reductase catalytic subunit M1
M76734_PROBE1	OBP2B	Odorant binding protein 2B
U63111_PROBE1	DSPP	Dentin sialophosphoprotein
Z11994_PROBE1	LRPAP1	LDL receptor related protein associated protein 1
AF031880_PROBE1	NEFL	Neurofilament light
BF398378_PROBE1	PHF3	PHD finger protein 3
X07365_PROBE1	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1
BE104266_PROBE1	KNTC1	Kinetochore associated 1
U45986_PROBE1	MXD3	MAX dimerization protein 3
NM_012514_PROBE1	BRCA1	BRCA1, DNA repair associated
AW253928_PROBE1	ETV4	ETS variant 4
AB003726_PROBE1	HOMER1	Homer scaffolding protein 1
U18650_PROBE1	FUBP1	Far upstream element binding protein 1
AF048687_PROBE1	B4GALT6	Beta-1,4-galactosyltransferase 6
AJ293948_PROBE1	KLHL41	Kelch like family member 41
U04319_PROBE1	IL1RL1	Interleukin 1 receptor like 1
AW915563_PROBE1	SPC25	SPC25, NDC80 kinetochore complex component
NM_021670_PROBE1	BMP15	Bone morphogenetic protein 15
BF566580_PROBE1	FANCD2	Fanconi anemia complementation group D2
AA851296_PROBE1	BYSL	Bystin like
NM_017331_PROBE1	TPM1	Tropomyosin 1
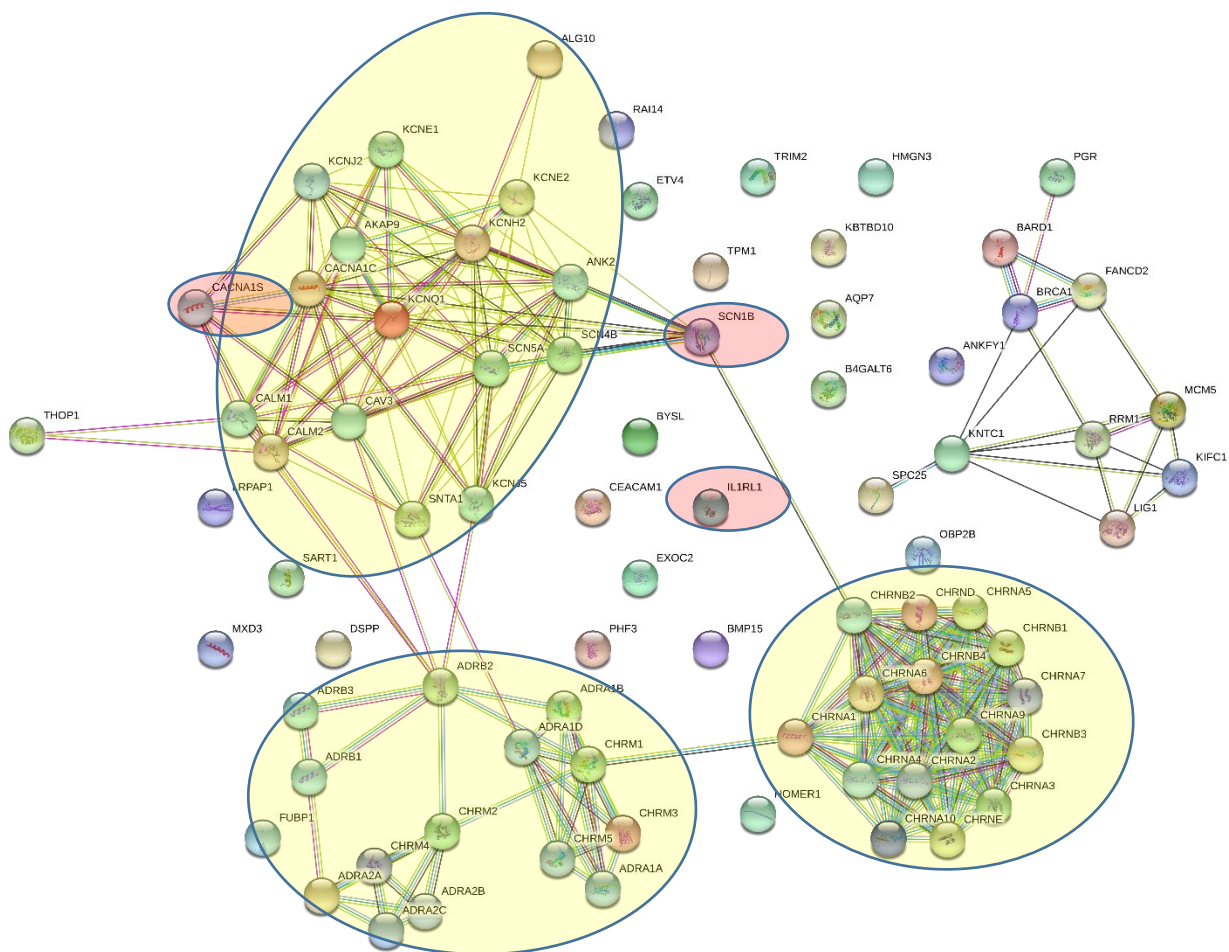
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000341267%250D9606.ENSP00000359804%250D9606.ENSP00000258385%250D9606.ENSP00000306459%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000418960%250D9606.ENSP00000261007%250D9606.ENSP00000401867%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000396915%250D9606.ENSP00000355192%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000297988%250D9606.ENSP00000282074%250D9606.ENSP00000287647%250D9606.ENSP00000230449%250D9606.ENSP00000393963%250D9606.ENSP00000306490%250D9606.ENSP00000252677%250D9606.ENSP00000266376%250D9606.ENSP00000300738%250D9606.ENSP00000276410%250D9606.ENSP00000262043%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000263274%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000267996%250D9606.ENSP00000319984%250D9606.ENSP00000321835%250D9606.ENSP00000261751%250D9606.ENSP00000339659%250D9606.ENSP00000349588%250D9606.ENSP00000304467%250D9606.ENSP00000233954%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000325120%250D9606.ENSP00000357461%250D9606.ENSP00000260947%250D9606.ENSP00000459775%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP00000310448%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000361104%250D9606.ENSP00000337255%250D9606.ENSP00000282478%250D9606.ENSP00000421922%250D9606.ENSP00000427123%250D9606.ENSP00000334382%250D9606.ENSP00000262186%250D9606.ENSP00000230340%250D9606.ENSP00000161559%250D9606.ENSP00000255380%250D9606.ENSP00000328236%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000216122%250D9606.ENSP00000293780%250D9606.ENSP00000284669%250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.35.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Substrates

In Figure 47, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the bottom center and bottom right.

CACNA1S is a Ca^{2+} channel which was differentially expressed. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

SCN1B was a Na^+ channel that was differentially expressed. Mean expression of SCN1B was higher in the QT group compared to the NQT group.

IL1RL1 is an interleukin-like immune response protein. Mean expression of IL1RL1 was lower in the QT group compared to the NQT group.

Section 3.3.36: Cytochrome P-450 CYP2E1 Inhibitors

Table XLIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012844_PROBE1	EPHX1	Epoxide hydrolase 1
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
AI599126_PROBE1	INCENP	Inner centromere protein
AI598467_PROBE1	CDCA8	Cell division cycle associated 8
D89731_PROBE1	AURKB	Aurora kinase B
NM_012964_PROBE1	HMMR	Hyaluronan mediated motility receptor
AI103327_PROBE1	TCF19	Transcription factor 19
NM_017166_PROBE1	STMN1	Stathmin 1
AI603128_PROBE1	CCNA2	Cyclin A2
AW141928_PROBE1	VNN1	Vanin 1
BE104266_PROBE1	KNTC1	Kinetochore associated 1
AW915563_PROBE1	SPC25	SPC25, NDC80 kinetochore complex component
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
U45986_PROBE1	MXD3	MAX dimerization protein 3
AW252871_PROBE1	MKI67	Marker of proliferation Ki-67
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
AW251335_PROBE1	SPC24	SPC24, NDC80 kinetochore complex component
AW253880_PROBE1	KIFC1	Kinesin family member C1
BF566580_PROBE1	FANCD2	Fanconi anemia complementation group D2
AA850509_PROBE1	TRIP13	Thyroid hormone receptor interactor 13
NM_017353_PROBE1	SLC7A5	Solute carrier family 7 member 5
M63991_PROBE1	SERPINA7	Serpin family A member 7
AF133037_PROBE1	HMMR	Hyaluronan mediated motility receptor
NM_013069_PROBE1	CD74	CD74 molecule
U71294_PROBE1	SYT12	Synaptotagmin 12
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
NM_017187_PROBE1	HMGB2	High mobility group box 2
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
NM_012492_PROBE1	ADRB2	Adrenoceptor beta 2
U73174_PROBE1	GSR	Glutathione-disulfide reductase
J03863_PROBE1	SDS	Serine dehydratase
NM_013076_PROBE1	LEP	Leptin

Figure 48: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Inhibitors

Permanent Link: http://bit.ly/2w8YfHZ
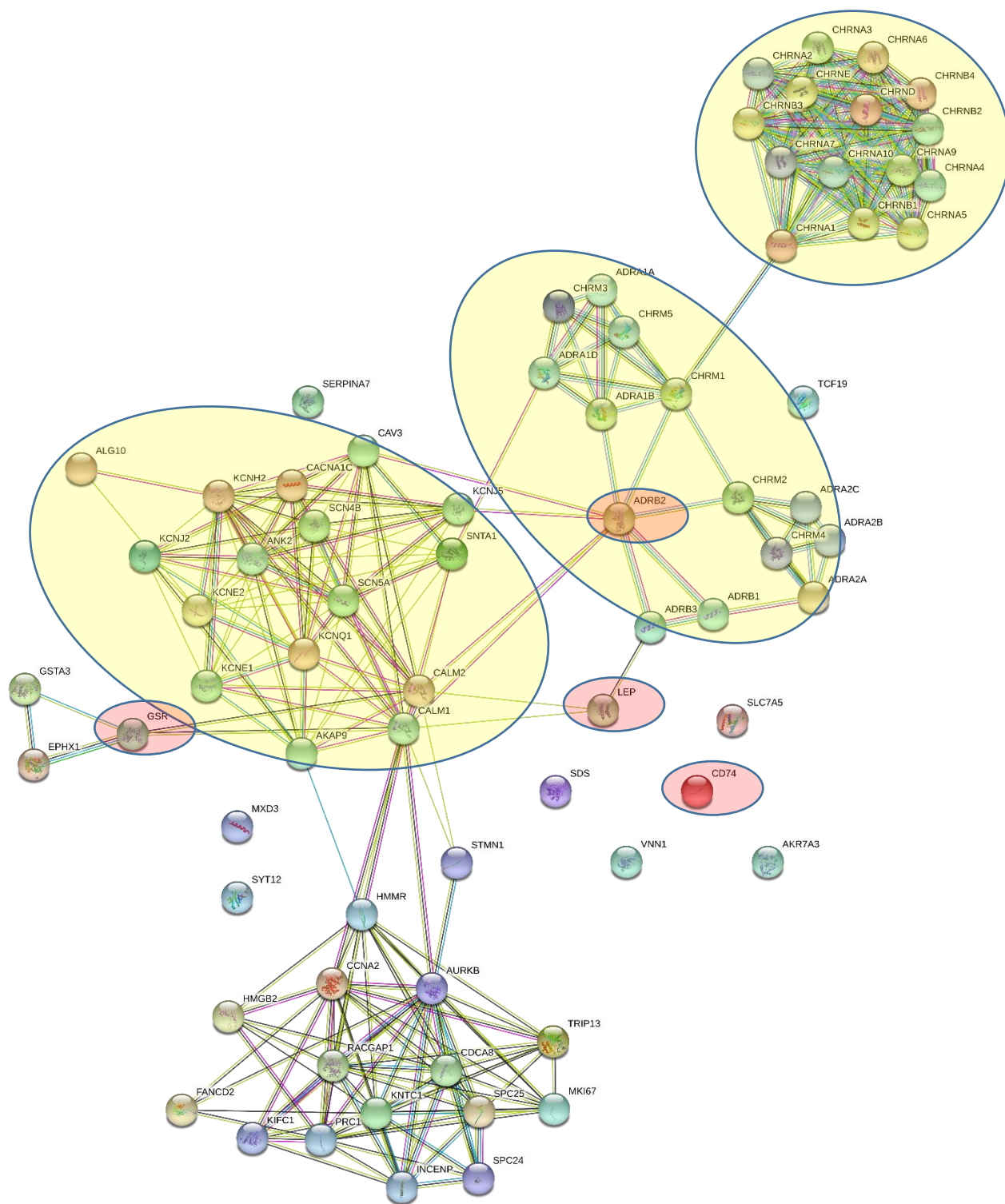
Section 3.3.36.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Inhibitors

In Figure 48, genes associated with cLQTS are highlighted in yellow at the center left. Genes associated with the ANS are connected and highlighted yellow at the center right and top right.

CD74 is a histocompatibility protein associated with the immune system. Mean expression of CD74 was lower in the QT group compared to the NQT group.

LEP is associated with MAPKs and glucose metabolism. Mean expression of LEP was lower in the QT group compared to the NQT group.

GSR is associated with glutathione activity and metabolism. Mean expression of GSR was lower in the QT group compared to the NQT group.

ADRAB2 is an adrenergic receptor which can directly influence both the autonomic nervous system and the heart. Mean expression of ADRAB2 was lower in the QT group compared to the NQT group.

Section 3.3.37: Cytochrome P-450 CYP2E1 Substrates

Table XLIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF087454_PROBE1	KCNQ3	Potassium voltage-gated channel subfamily Q member 3
AI030203_PROBE1	IRX3	Iroquois homeobox 3
J00750_PROBE1	EMC3	ER membrane protein complex subunit 3
U33847_PROBE1	GUCY2GP	Guanylate cyclase 2G, pseudogene
U06273_PROBE1	GUCY2GP	Guanylate cyclase 2G, pseudogene
M60655_PROBE1	ADRA1B	Adrenoceptor alpha 1B
AI454418_PROBE1	IGSF1	Immunoglobulin superfamily member 1
M99418_PROBE1	CCKBR	Cholecystokinin B receptor
X56661_PROBE1	GRPR	Gastrin releasing peptide receptor
AF007108_PROBE1	CYB5A	Cytochrome b5 type A
AI598486_PROBE1	DPYSL3	Dihydropyrimidinase like 3
NM_012707_PROBE1	GCG	Glucagon
X51992_PROBE1	GABRA5	Gamma-aminobutyric acid type A receptor alpha5 subunit
AA800298_PROBE1	COL15A1	Collagen type XV alpha 1 chain
AF005099_PROBE1	NPTXR	Neuronal pentraxin receptor
AI412625_PROBE1	ELMOD1	ELMO domain containing 1
AB023634_PROBE1	PPM1F	Protein phosphatase, Mg2+/Mn2+ dependent 1F
L24051_PROBE1	EBF1	Early B-cell factor 1
NM_012651_PROBE1	SLC4A1	Solute carrier family 4 member 1 (Diego blood group)
U69487_PROBE1	ABCB11	ATP binding cassette subfamily B member 11
AF143410_PROBE1	MEFV	MEFV, pyrin innate immunity regulator
BE111625_PROBE1	PKD2	Polycystin 2, transient receptor potential cation channel
AF219904_PROBE1	FOLR1	Folate receptor 1
NM_019353_PROBE1	TPO	Thyroid peroxidase
AA944415_PROBE1	RIPPLY3	Ripply transcriptional repressor 3
U67138_PROBE1	DLGAP2	DLG associated protein 2
NM_013080_PROBE1	PTPRZ1	Protein tyrosine phosphatase, receptor type Z1
BE113053_PROBE1	ST6GALNAC6	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 6
NM_012940_PROBE1	CYP1B1	Cytochrome P450 family 1 subfamily B member 1
AB004559_PROBE1	SLC22A6	Solute carrier family 22 member 6
AA996517_PROBE1	TCOF1	Treacle ribosome biogenesis factor 1
AF038043_PROBE1	TREH	Trehalase
D28498_PROBE1	FLT1	Fms related tyrosine kinase 1
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
D17447_PROBE1	YWHAG	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma

Figure 49: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Substrates
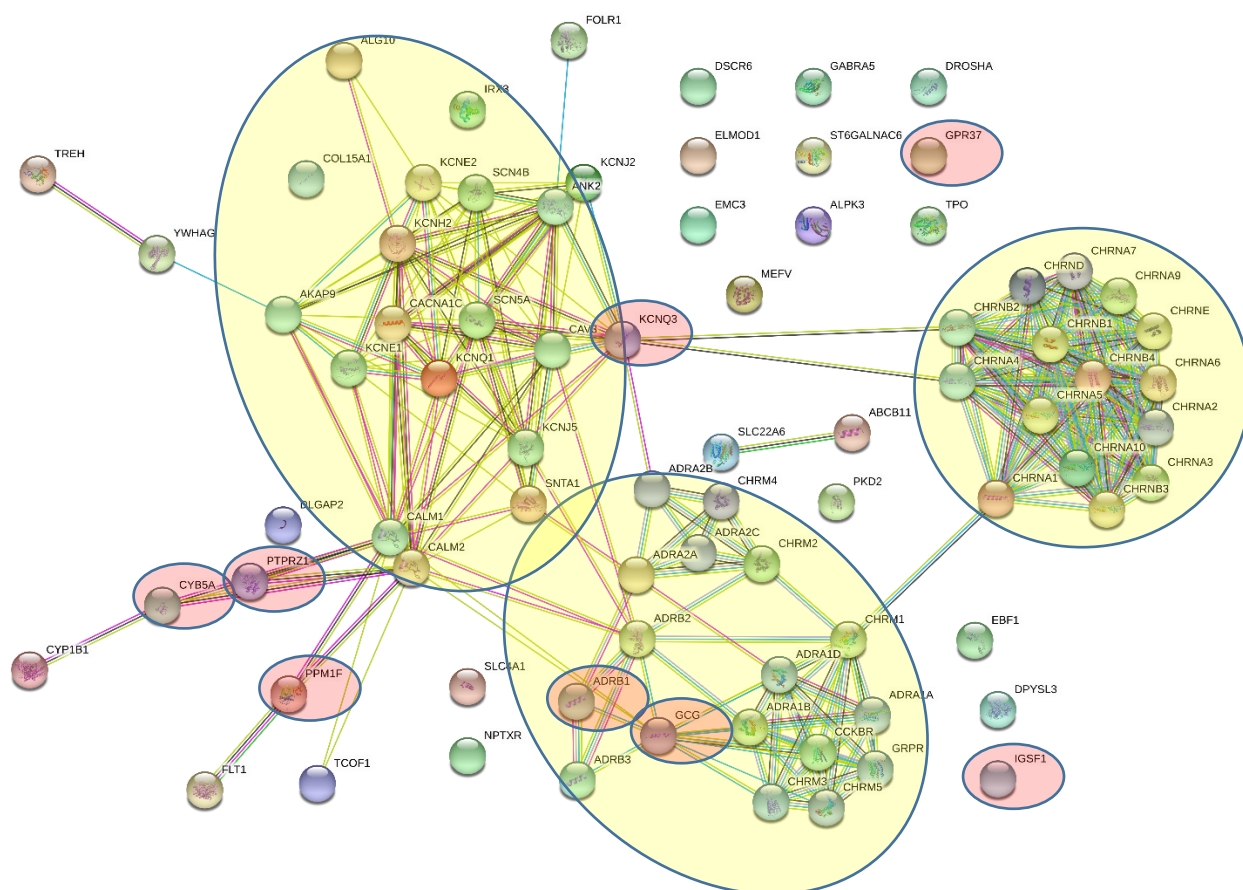
Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000282397%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D96
06.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000265840%250D9606.ENSP00000331734%250D960
6.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000155840%250D9606
.ENSP00000289957%250D9606.ENSP00000258888%250D9606.ENSP00000219596%250D9606.ENSP00000306330%250D9606.
ENSP00000263212%250D9606.ENSP00000306490%250D9606.ENSP00000266376%250D9606.ENSP00000262418%250D9606.E
NSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000359285%250D9606.EN
SP00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000359940%250D9606.ENSP00000364140%250D9606.ENS
P00000386069%250D9606.ENSP00000319984%250D9606.ENSP00000261751%250D9606.ENSP00000421655%250D9606.ENSP
00000349588%250D9606.ENSP00000387662%250D9606.ENSP00000367102%250D9606.ENSP00000264029%250D9606.ENSP0
0000368766%250D9606.ENSP00000331608%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00
000322898%250D9606.ENSP00000339845%250D9606.ENSP00000357461%250D9606.ENSP00000260630%250D9606.ENSP000
00335544%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP0000
0372750%250D9606.ENSP00000291839%250D9606.ENSP00000343690%250D9606.ENSP00000407546%250D9606.ENSP00000
306449%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP000003
22460%250D9606.ENSP00000243457%250D9606.ENSP00000245046%250D9606.ENSP00000263817%250D9606.ENSP0000034
1940%250D9606.ENSP00000337255%250D9606.ENSP00000318820%250D9606.ENSP00000373648%250D9606.ENSP00000400
258%250D9606.ENSP00000237596%250D9606.ENSP00000262186%250D9606.ENSP00000335592%250D9606.ENSP000002553
80%250D9606.ENSP00000308137%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP0000037704
7%250D9606.ENSP00000341625%250D9606.ENSP00000293780%250D9606.ENSP00000369643%250D9606.ENSP00000327545
%250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.37.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Substrates

In Figure 49, genes associated with cLQTS are highlighted in yellow at the top center left. Genes

associated with the ANS are connected and highlighted yellow at the bottom center right and top right.

KCNQ3 is a potassium ion channel that was differentially expressed in this class. Mean

expression of KCNQ3 was lower in the QT group compared to the NQT group.

ADRA1B is an adrenergic receptor which can influence the autonomic nervous system and the

heart, and activate RAS activity, which is also associated with QT prolongation. Mean expression of

ADRA1B was lower in the QT group compared to the NQT group.

IGSF1, **PPM1F** and **PTPRZ1** are associated with immune responses and apoptosis. Mean

expression of all three of these was lower in the QT group compared to the same probes in the NQT

group.

GCG is glucagon, which is associated with raising glucose and fat in the bloodstream and it may

impact the QT interval through fatty acid metabolism or through mechanisms associated with diabetes.

Mean expression of GCG was lower in the QT group compared to the NQT group.

GPR37 is associated with G protein activity. Mean expression of GPR37 was lower in the QT group compared to the NQT group.
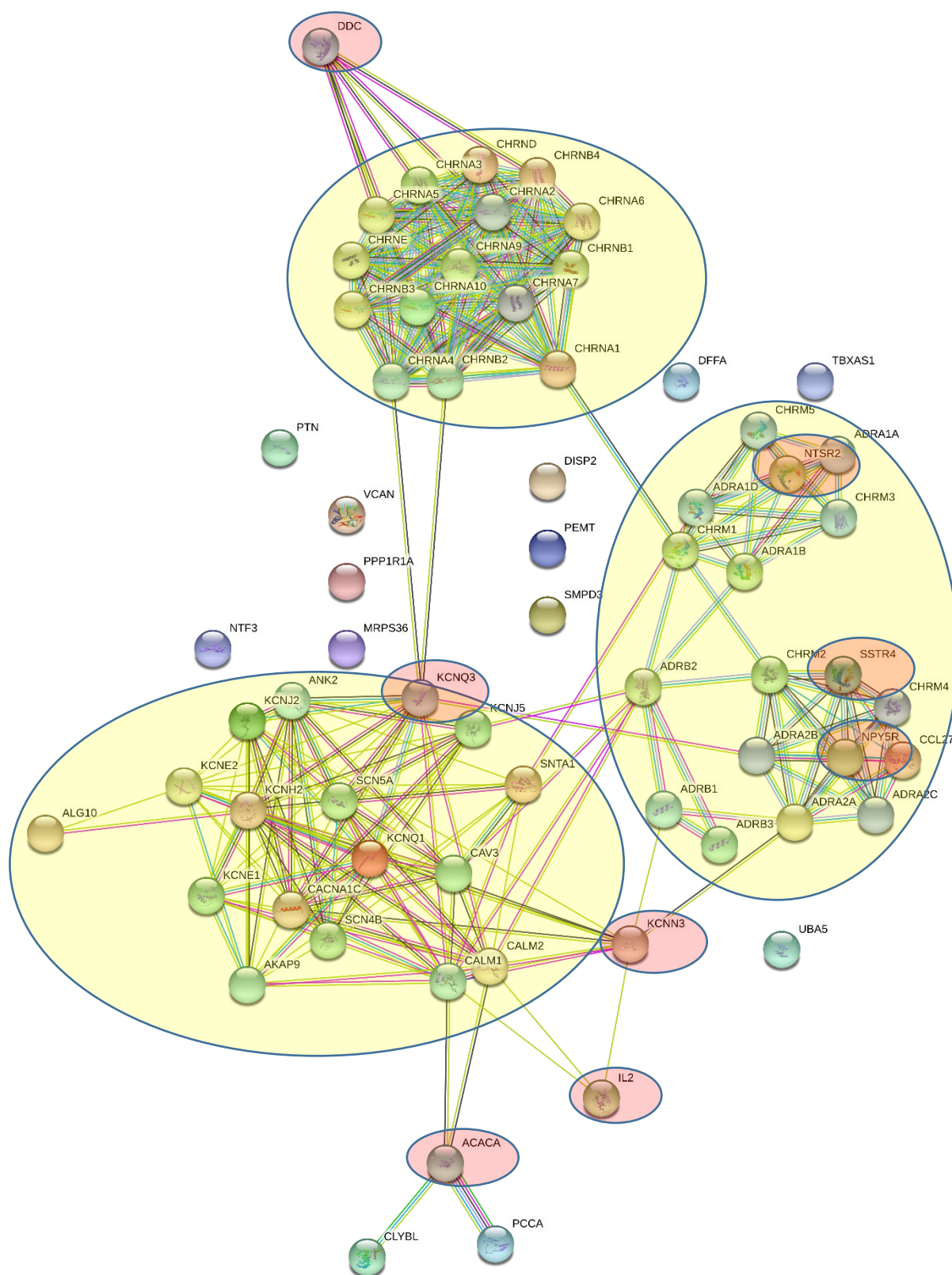
Section 3.3.38: Cytochrome P-450 CYP3A4 Substrates

Table XLV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
J02752_PROBE1	ACOX1	Acyl-CoA oxidase 1
M30596_PROBE1	ME1	Malic enzyme 1
NM_012600_PROBE1	ME1	Malic enzyme 1
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
AW918222_PROBE1	TOR3A	Torsin family 3 member A
AW918650_PROBE1	CHCHD6	Coiled-coil-helix-coiled-coil-helix domain containing 6
AW141928_PROBE1	VNN1	Vanin 1
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
D00569_PROBE1	DECR1	2,4-dienoyl-CoA reductase 1
AA944380_PROBE1	NUDT7	Nudix hydrolase 7
AW916833_PROBE1	RETSAT	Retinol saturase
NM_019157_PROBE1	AQP7	Aquaporin 7
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
AF034577_PROBE1	PDK4	Pyruvate dehydrogenase kinase 4
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
U02096_PROBE1	FABP7	Fatty acid binding protein 7
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
NM_017083_PROBE1	MYO5B	Myosin VB
D10926_PROBE1	TFPI	Tissue factor pathway inhibitor
AI137488_PROBE1	PGRMC2	Progesterone receptor membrane component 2
BF555949_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
D87839_PROBE1	ABAT	4-aminobutyrate aminotransferase
NM_017075_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AA899304_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
D30035_PROBE1	PRDX1	Peroxiredoxin 1
AW144226_PROBE1	ABHD6	Abhydrolase domain containing 6
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
AW915187_PROBE1	CKAP4	Cytoskeleton associated protein 4
AB001075_PROBE1	LGALS2	Galectin 2
AF111268_PROBE1	CD36	CD36 molecule
BF283382_PROBE1	PGRMC2	Progesterone receptor membrane component 2
NM_017268_PROBE1	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
D30666_PROBE1	ACSL3	Acyl-CoA synthetase long chain family member 3
AI231601_PROBE1	ZWINT	ZW10 interacting kinetochore protein
NM_012941_PROBE1	CYP51A1	Cytochrome P450 family 51 subfamily A member 1
AI410548_PROBE1	HIBCH	3-hydroxyisobutyryl-CoA hydrolase

Figure 50: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates
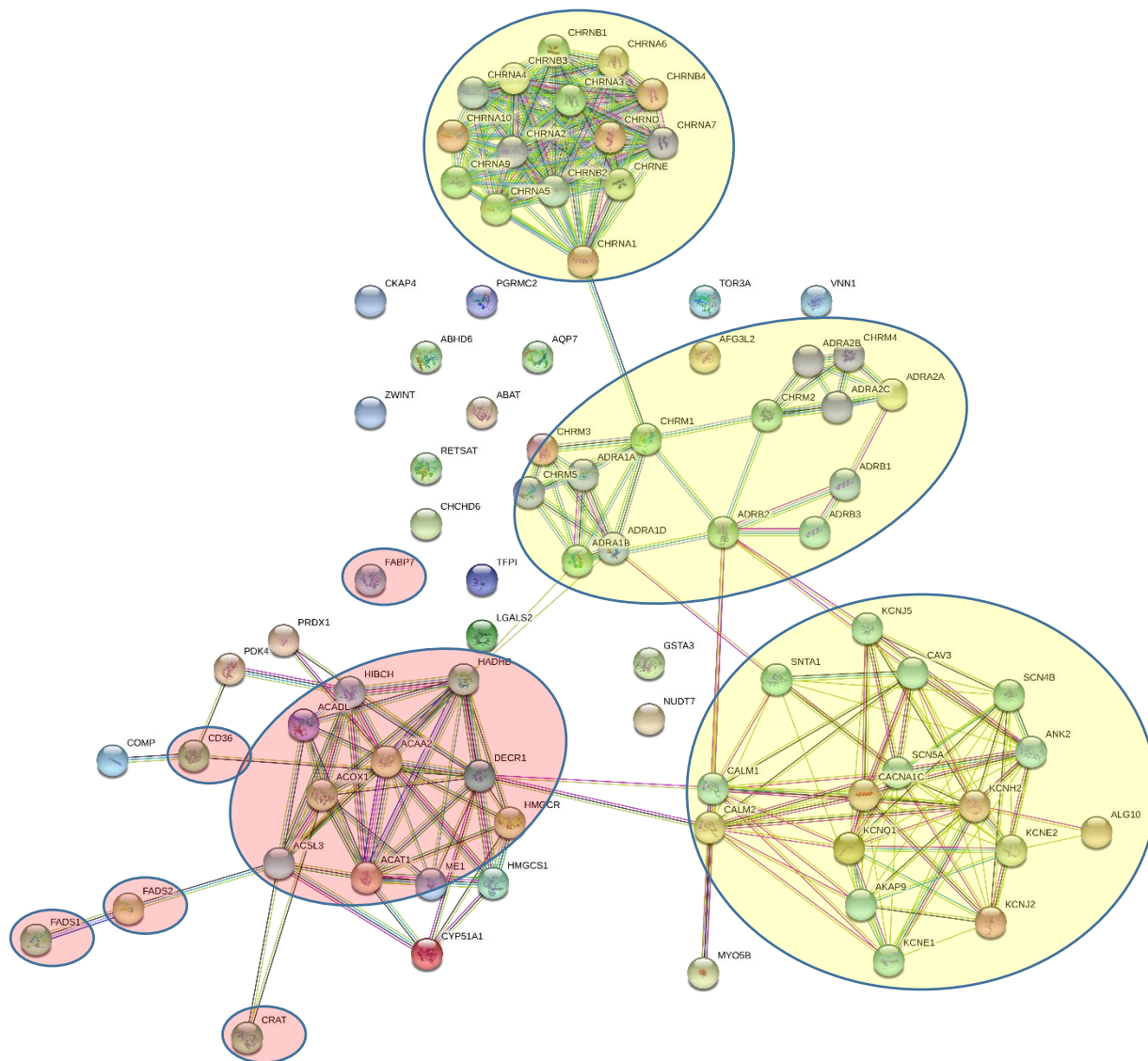
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000293217%250D9606.ENSP00000222271%250D9606.ENSP00000429301%250D9606.ENSP00000322706%250D9606.ENSP00000233710%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000265838%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000278840%250D9606.ENSP00000363055%250D9606.ENSP00000211122%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000297988%250D9606.ENSP00000268251%250D9606.ENSP00000352706%250D9606.ENSP00000306490%250D9606.ENSP00000005178%250D9606.ENSP00000266376%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000220764%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000287936%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000295962%250D9606.ENSP00000285093%250D9606.ENSP00000315013%250D9606.ENSP00000319984%250D9606.ENSP00000262746%250D9606.ENSP00000261751%250D9606.ENSP00000325136%250D9606.ENSP00000367265%250D9606.ENSP00000215886%250D9606.ENSP00000285039%250D9606.ENSP00000349588%250D9606.ENSP00000003100%250D9606.ENSP00000357429%250D9606.ENSP00000295802%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000268533%250D9606.ENSP00000409378%250D9606.ENSP00000357461%250D9606.ENSP00000387281%250D9606.ENSP00000350012%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000269143%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000233156%250D9606.ENSP00000369960%250D9606.ENSP00000322460%250D9606.ENSP00000358301%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000356905%250D9606.ENSP00000337255%250D9606.ENSP00000356599%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000358719%250D9606.ENSP00000299565%250D9606.ENSP00000308165%250D9606.ENSP00000322229%250D9606.ENSP00000293780%250D9606.ENSP00000306662%250D9606.ENSP00000348573%250D9606.ENSP00000290913

Section 3.3.38.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates

In Figure 50, genes associated with cLQTS are highlighted in yellow at the bottom left. Genes associated with the ANS are connected and highlighted yellow at the center and top.

ACADL, **ACAA2**, **ACOX1**, **ME1, FADS1**, **FADS2**, **FABP7**, **CRAT**, and **ACAT1** are examples from this group which are associated with fatty acid metabolism. Mean expression for all of these was lower in the QT group compared to the same probes in the NQT group.

DECR1 is a mitochondrial protein associated with beta oxidation. Mean expression of DECR1 was lower in the QT group compared to the NQT group.

CD36 is involved with immune responses and fatty acid metabolism. Mean expression of CD36 was lower in the QT group compared to the NQT group.

Section 3.3.39: Cytochrome P-450 CYP3A Inducers

Table XLVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inducers

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF136601_PROBE1	DFFA	DNA fragmentation factor subunit alpha
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3
AB000215_PROBE1	SMPD3	Sphingomyelin phosphodiesterase 3
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AI227832_PROBE1	MON1B	MON1 homolog B, secretory trafficking associated
AF062402_PROBE1	VCAN	Versican
U02315_PROBE1	NRG1	Neuregulin 1
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
AB046592_PROBE1	LAPTM5	Lysosomal protein transmembrane 5
AA997397_PROBE1	EFS	Embryonal Fyn-associated substrate
BE109861_PROBE1	SORCS3	Sortilin related VPS10 domain containing receptor 3
NM_017136_PROBE1	SQLE	Squalene epoxidase
M22899_PROBE1	IL2	Interleukin 2
AF016247_PROBE1	DDR2	Discoidin domain receptor tyrosine kinase 2
AI111840_PROBE1	PMVK	phosphomevalonate kinase
AI070394_PROBE1	BRINP2	BMP/retinoic acid inducible neural specific 2
BF408022_PROBE1	MYH9	Myosin heavy chain 9
NM_012719_PROBE1	SSTR1	Somatostatin receptor 1
L22558_PROBE1	HTR7	5-hydroxytryptamine receptor 7
M29472_PROBE1	MVK	Mevalonate kinase
AI137259_PROBE1	LSS	lanosterol synthase
AF119667_PROBE1	LSR	Lipolysis stimulated lipoprotein receptor
AF203906_PROBE1	SHARPIN	SHANK associated RH domain interactor
AI556941_PROBE1	SLC39A4	Solute carrier family 39 member 4
BF561196_PROBE1	RDH11	Retinol dehydrogenase 11 (all-trans/9-cis/11-cis)
AF110021_PROBE1	AQP2	Aquaporin 2
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
AF059530_PROBE1	PRMT3	Protein arginine methyltransferase 3

Figure 51: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inducers

Permanent Link: http://bit.ly/2w9mnKF
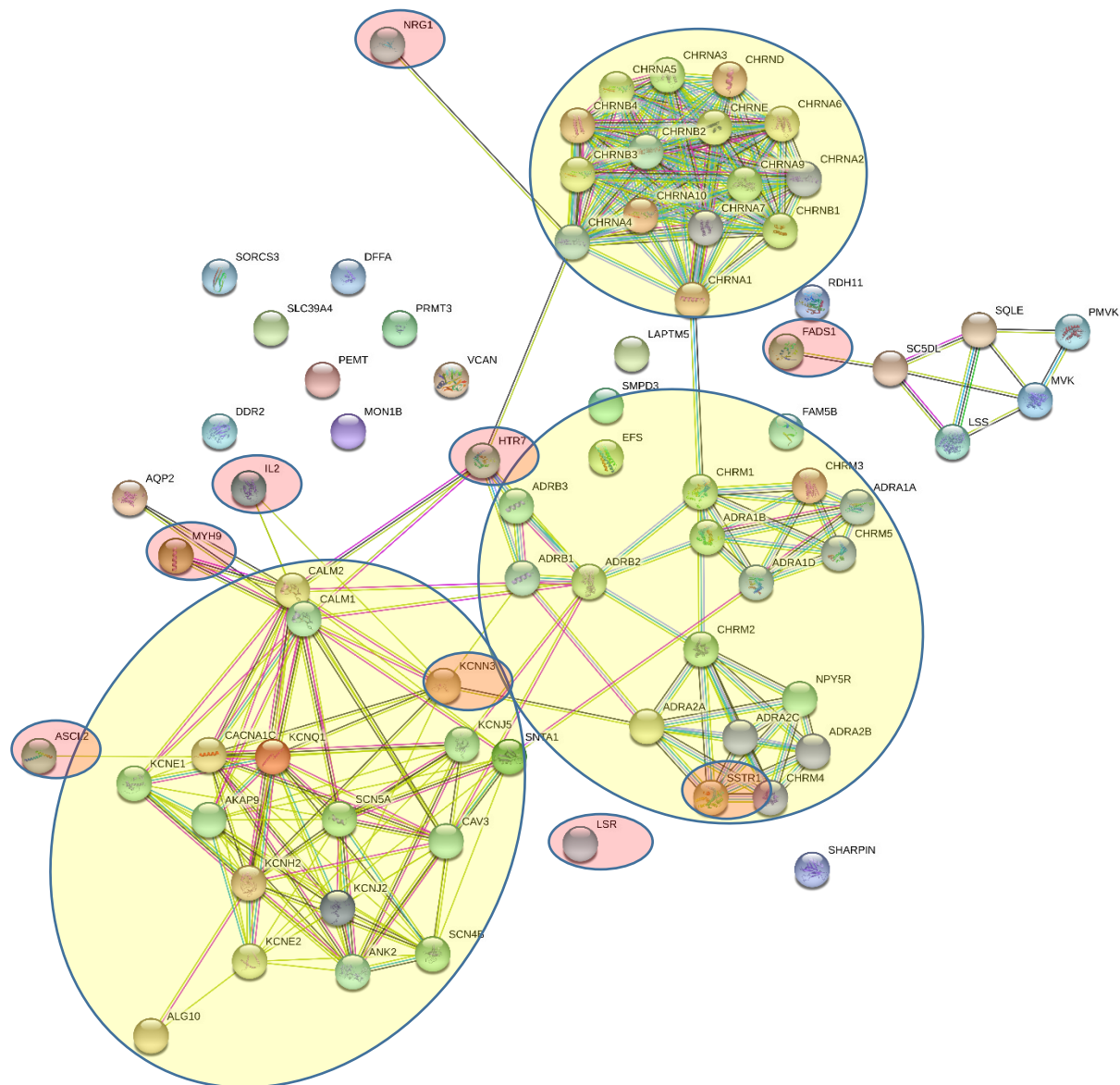
Section 3.3.39.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inducers

In Figure 51, genes associated with cLQTS are highlighted in yellow at the top center left. Genes associated with the ANS are connected and highlighted yellow at the bottom center right and top right.

KCNN3 is a potassium channel that was differentially expressed in this group. Mean expression of KCNN3 was lower in the QT group compared to the NQT group.

IL2 and **HTR7** are associated with immune responses. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

LSR and **FADS1** are associated with fatty acid metabolism. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

NRG1 is associated with MAPK activity. Mean expression of NRG1 was lower in the QT group compared to the NQT group.

SSTR1 is associated with G protein activity. Mean expression of SSTR1 was lower in the QT group compared to the NQT group.

Section 3.3.40: Cytochrome P-450 CYP3A Inhibitors

Table XLVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_012600_PROBE1	ME1	Malic enzyme 1
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
M30596_PROBE1	ME1	Malic enzyme 1
AI176781_PROBE1	FDFT1	Farnesyl-diphosphate farnesyltransferase 1
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
AF320509_PROBE1	FADS1	Fatty acid desaturase 1
D00569_PROBE1	DECR1	2,4-dienoyl-CoA reductase 1
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
BF555949_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
M29472_PROBE1	MVK	Mevalonate kinase
NM_019157_PROBE1	AQP7	Aquaporin 7
AA849497_PROBE1	ACSS2	Acyl-CoA synthetase short chain family member 2
NM_013134_PROBE1	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
AI137259_PROBE1	LSS	Lanosterol synthase
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
BF282437_PROBE1	TBC1D10A	TBC1 domain family member 10A
BF397726_PROBE1	NFE2	Nuclear factor, erythroid 2
D85435_PROBE1	CAVIN3	Caveolae associated protein 3
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
NM_012941_PROBE1	CYP51A1	Cytochrome P450 family 51 subfamily A member 1
NM_017014_PROBE1	GSTM1	Glutathione S-transferase mu 1
NM_019286_PROBE1	ADH1A	Alcohol dehydrogenase 1A (class I), alpha polypeptide
U53706_PROBE1	MVD	Mevalonate diphosphate decarboxylase
BF561196_PROBE1	RDH11	Retinol dehydrogenase 11 (all-trans/9-cis/11-cis)
X86789_PROBE1	SNCG	Synuclein gamma
D90219_PROBE1	NPPC	Natriuretic peptide C
NM_019243_PROBE1	PTGFRN	Prostaglandin F2 receptor inhibitor
BF408022_PROBE1	MYH9	Myosin heavy chain 9
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
AF071501_PROBE1	EBP	Emopamil binding protein (sterol isomerase)
AA859343_PROBE1	SRPK1	SRSF protein kinase 1
AI234678_PROBE1	ERMP1	Endoplasmic reticulum metallopeptidase 1

Figure 52: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors

Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000293217%250D9606.ENSP00000222271%250D9606.ENSP00000220584%250D9606.ENSP00000312436%250D96
06.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000228510%250D9606.ENSP00000209668%250D960
6.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000301012%250D9606.
ENSP00000384996%250D9606.ENSP00000312663%250D9606.ENSP00000304290%250D9606.ENSP00000250699%250D9606.E
NSP00000155840%250D9606.ENSP00000211122%250D9606.ENSP00000289957%250D9606.ENSP00000297988%250D9606.EN
SP00000355377%250D9606.ENSP00000340427%250D9606.ENSP00000306490%250D9606.ENSP00000266376%250D9606.ENS
P00000361087%250D9606.ENSP00000328968%250D9606.ENSP00000276410%250D9606.ENSP00000385026%250D9606.ENSP
00000359285%250D9606.ENSP00000220764%250D9606.ENSP00000305372%250D9606.ENSP00000287936%250D9606.ENSP0
0000266483%250D9606.ENSP00000386069%250D9606.ENSP00000253382%250D9606.ENSP00000285093%250D9606.ENSP00
000309871%250D9606.ENSP00000319984%250D9606.ENSP00000216181%250D9606.ENSP00000261751%250D9606.ENSP000
00348762%250D9606.ENSP00000349588%250D9606.ENSP00000362931%250D9606.ENSP00000003100%250D9606.ENSP0000
0368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000357461%250D9606.ENSP00000
370750%250D9606.ENSP00000264027%250D9606.ENSP00000311469%250D9606.ENSP00000387281%250D9606.ENSP000003
39960%250D9606.ENSP00000315602%250D9606.ENSP00000307292%250D9606.ENSP00000269143%250D9606.ENSP0000037
2750%250D9606.ENSP00000407546%250D9606.ENSP00000357452%250D9606.ENSP00000369960%250D9606.ENSP00000272
298%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP000003768
99%250D9606.ENSP00000341940%250D9606.ENSP00000295440%250D9606.ENSP00000337255%250D9606.ENSP0000026218
6%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000358719%250D9606.ENSP00000299565
%250D9606.ENSP00000322229%250D9606.ENSP00000293780%250D9606.ENSP00000293190%250D9606.ENSP00000417052%
250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.40.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors

In Figure 53, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the center right and center left.

ME1, **ACAA2**, **ACOX1**, and **FADS1** are examples of proteins associated with fatty acid metabolism. Mean expression for all of these was lower in the QT group compared to the same probes in the NQT group.

DECR1 is associated with mitochondrial beta oxidation metabolism. Mean expression of DECR1 was lower in the QT group compared to the NQT group.

GSTA3, **GSTM1**, and **GRIN2C** associated with glutathione. Mean expression of all three of these was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.41: Cytochrome P-450 Enzyme Inhibitors

Table XLVIII: Differentially Expressed Genes Used as Input from using Drugs Classified in DrugBank as Cytochrome P-450 Enzyme Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW533663_PROBE1	PRODH	Proline dehydrogenase 1
AW862653_PROBE1	NUDT4	Nudix hydrolase 4
NM_012545_PROBE1	NUDT4	Nudix hydrolase 4
D85035_PROBE1	DPYD	Dihydropyrimidine dehydrogenase
NM_017084_PROBE1	GNMT	Glycine N-methyltransferase
AW523642_PROBE1	KMT5B	Lysine methyltransferase 5B
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
D70816_PROBE1	CPLX2	Complexin 2
AA963282_PROBE1	NMNAT3	Nicotinamide nucleotide adenylyltransferase 3
J04112_PROBE1	FBP1	Fructose-bisphosphatase 1
X55995_PROBE1	DMGDH	Dimethylglycine dehydrogenase
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
AW917211_PROBE1	QPRT	Quinolinate phosphoribosyltransferase
M35266_PROBE1	CDO1	Cysteine dioxygenase type 1
NM_012550_PROBE1	EDNRA	Endothelin receptor type A
U16686_PROBE1	DEFA1	Defensin alpha 1
AI406275_PROBE1	CBX7	Chromobox 7
AF268030_PROBE1	SLC31A1	Solute carrier family 31 member 1
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
NM_017264_PROBE1	PSME1	Proteasome activator subunit 1
BF556833_PROBE1	RNF2	Ring finger protein 2
D55627_PROBE1	RBL2	RB transcriptional corepressor like 2
NM_012592_PROBE1	IVD	Isovaleryl-CoA dehydrogenase
AF292116_PROBE1	TPRA1	Transmembrane protein adipocyte associated 1
NM_012844_PROBE1	EPHX1	Epoxide hydrolase 1
NM_012984_PROBE1	MYO9B	Myosin IXB
BF398332_PROBE1	SLU7	SLU7 homolog, splicing factor
AI103106_PROBE1	LMNB1	Lamin B1
X68640_PROBE1	SULT1A1	Sulfotransferase family 1A member 1
AI045074_PROBE1	GLB1	Galactosidase beta 1
NM_012567_PROBE1	GJA1	Gap junction protein alpha 1

Figure 53: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Cytochrome P-450 Enzyme Inhibitors
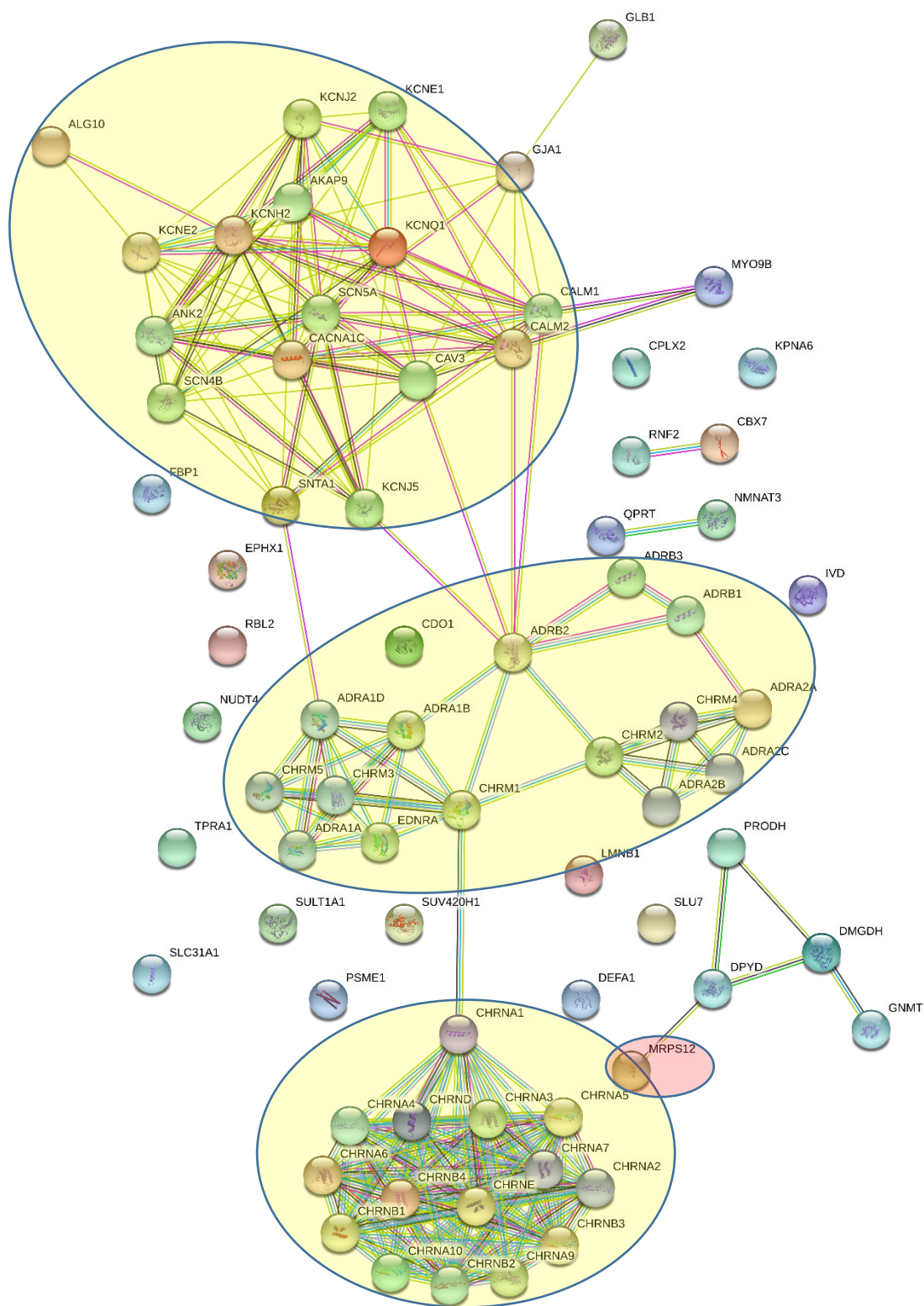
Permanent Link:

Section 3.3.41.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Cytochrome P-450 Enzyme Inhibitors

In Figure 53, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the center right and center left.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

Section 3.3.42: Dermatologicals

Table XLIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Dermatologicals

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF084241_PROBE1	ADORA2B	Adenosine A2b receptor
BF405883_PROBE1	DHX16	DEAH-box helicase 16
NM_017161_PROBE1	ADORA2B	Adenosine A2b receptor
U69279_PROBE1	EFNA5	Ephrin A5
X89963_PROBE1	THBS4	Thrombospondin 4
AI406275_PROBE1	CBX7	Chromobox 7
AF046886_PROBE1	AXL	AXL receptor tyrosine kinase
U77880_PROBE1	PDE7A	Phosphodiesterase 7A
NM_012758_PROBE1	SYK	Spleen associated tyrosine kinase
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
AA874881_PROBE1	ADNP	Activity dependent neuroprotector homeobox
AW918068_PROBE1	LMBRD1	LMBR1 domain containing 1
BF408424_PROBE1	RRP9	Ribosomal RNA processing 9, U3 small nucleolar RNA binding protein
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
AW915713_PROBE1	MYO1G	Myosin IG
AB003042_PROBE1	C5AR1	Complement C5a receptor 1
L34049_PROBE1	LRP2	LDL receptor related protein 2
NM_019311_PROBE1	INPP5D	Inositol polyphosphate-5-phosphatase D
AI235192_PROBE1	ABCF2	ATP binding cassette subfamily F member 2
AI176814_PROBE1	ILK	Integrin linked kinase
AB016160_PROBE1	GABBR1	Gamma-aminobutyric acid type B receptor subunit 1
AI555457_PROBE1	CTNNAL1	Catenin alpha like 1
X57514_PROBE1	GABRG1	Gamma-aminobutyric acid type A receptor gamma1 subunit
AF004811_PROBE1	MSN	Moesin
BF544320_PROBE1	KIF2A	Kinesin family member 2A
NM_012490_PROBE1	ACR	Acrosin
U83896_PROBE1	CYTH2	Cytohesin 2
AB003400_PROBE1	AOC1	Amine oxidase, copper containing 1

Figure 54: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Dermatologicals

Permanent Link: http://bit.ly/2w9Fswm
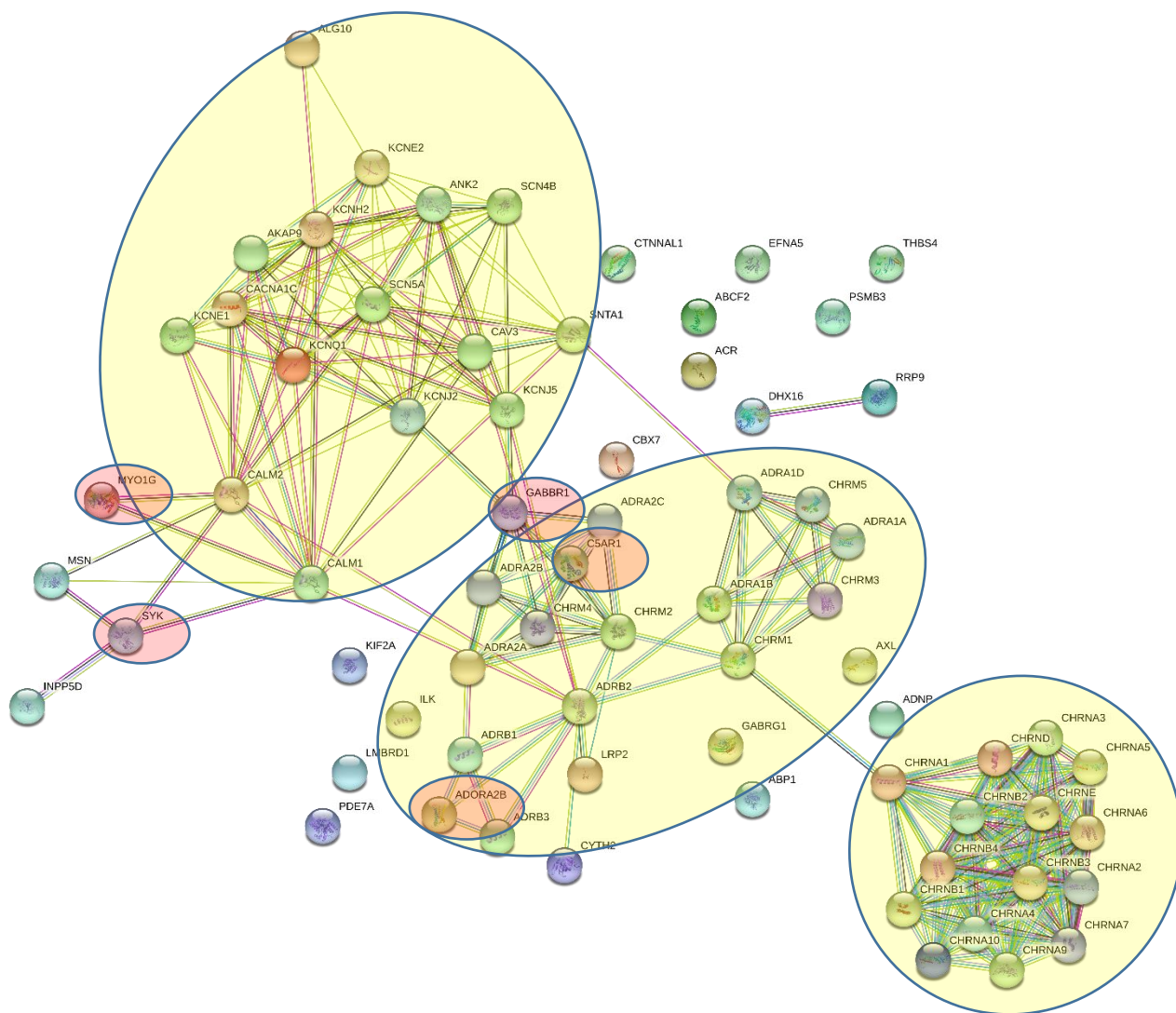
Section 3.3.42.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Dermatologicals

In Figure 54, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the center right and center left.

MYO1G, **C5AR1**, and **SYK** are associated with immune responses. Mean expression of MYO1G and C5AR1 were lower in the QT group compared to the same probes in the NQT group. Mean expression of SYK was higher in the QT group compared to the NQT group.

GABBR1 and **ADORA2B** are associated with G protein activity. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.43: Drugs for Acid Related Disorders

Table L: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Drugs for Acid Related Disorders

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_017223_PROBE1	SLC20A2	Solute carrier family 20 member 2
AB046592_PROBE1	LAPTM5	Lysosomal protein transmembrane 5
L09653_PROBE1	TGFBR2	Transforming growth factor beta receptor 2
NM_017268_PROBE1	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
NM_019149_PROBE1	MATR3	Matrin 3
U38938_PROBE1	ATF2	Activating transcription factor 2
AF178669_PROBE1	AAGAB	Alpha and gamma adaptin binding protein
D44481_PROBE1	CRK	CRK proto-oncogene, adaptor protein
U73142_PROBE1	MAPK14	Mitogen-activated protein kinase 14
U83895_PROBE1	CYTH1	Cytohesin 1
NM_013223_PROBE1	EIF2AK1	Eukaryotic translation initiation factor 2 alpha kinase 1
NM_021262_PROBE1	ACP1	Acid phosphatase 1, soluble
AJ271837_PROBE1	PPM1B	Protein phosphatase, Mg2+/Mn2+ dependent 1B
BF564940_PROBE1	IFIT2	Interferon induced protein with tetratricopeptide repeats 2
U17253_PROBE1	NAB1	NGFI-A binding protein 1
AI113190_PROBE1	THAP11	THAP domain containing 11
AJ000556_PROBE1	JAK1	Janus kinase 1
D29632_PROBE1	MET	MET proto-oncogene, receptor tyrosine kinase
D90109_PROBE1	ACSL1	Acyl-CoA synthetase long chain family member 1
X07365_PROBE1	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1
AW915859_PROBE1	FBXW2	F-box and WD repeat domain containing 2
D85100_PROBE1	SLC27A2	Solute carrier family 27 member 2
AF239045_PROBE1	KIDINS220	Kinase D interacting substrate 220
AF295405_PROBE1	SCAMP2	Secretory carrier membrane protein 2
D90164_PROBE1	PPP1CB	Protein phosphatase 1 catalytic subunit beta
L18889_PROBE1	CANX	Calnexin
M65148_PROBE1	ATF2	Activating transcription factor 2
NM_019302_PROBE1	CRK	CRK proto-oncogene, adaptor protein
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
AF068202_PROBE1	AKAP1	A-kinase anchoring protein 1
AF111268_PROBE1	CD36	CD36 molecule
AF139055_PROBE1	MYH10	Myosin heavy chain 10
AI137819_PROBE1	YME1L1	YME1 like 1 ATPase
AJ277423_PROBE1	MASP1	Mannan binding lectin serine peptidase 1
NM_012569_PROBE1	GLS	Glutaminase
U75409_PROBE1	NUCB1	Nucleobindin 1
BF395415_PROBE1	DPT	Dermatopontin
BE100014_PROBE1	SNX18	Sorting nexin 18
M18467_PROBE1	GOT2	Glutamic-oxaloacetic transaminase 2

Figure 55: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Drugs for Acid Related Disorders

Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000281455%250D9606.ENSP00000356791%250D9606.ENSP00000322706%250D9606.ENSP00000258385%250D96
06.ENSP00000304689%250D9606.ENSP00000217381%250D9606.ENSP00000337736%250D9606.ENSP00000349467%250D960
6.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606
.ENSP00000351905%250D9606.ENSP00000250699%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.
ENSP00000360891%250D9606.ENSP00000261880%250D9606.ENSP00000354398%250D9606.ENSP00000247461%250D9606.E
NSP00000363036%250D9606.ENSP00000263273%250D9606.ENSP00000317332%250D9606.ENSP00000318480%250D9606.EN
SP00000199389%250D9606.ENSP00000306490%250D9606.ENSP00000272065%250D9606.ENSP00000266376%250D9606.ENS
P00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000359285%250D9606.ENSP
00000305372%250D9606.ENSP00000336894%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP0
0000319984%250D9606.ENSP00000229794%250D9606.ENSP00000269243%250D9606.ENSP00000261751%250D9606.ENSP00
000317379%250D9606.ENSP00000349588%250D9606.ENSP00000294507%250D9606.ENSP00000368766%250D9606.ENSP000
00296122%250D9606.ENSP00000290310%250D9606.ENSP00000296280%250D9606.ENSP00000409378%250D9606.ENSP0000
0245206%250D9606.ENSP00000357461%250D9606.ENSP00000256707%250D9606.ENSP00000264027%250D9606.ENSP00000
340465%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP000003
72750%250D9606.ENSP00000317272%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP0000036
9960%250D9606.ENSP00000322460%250D9606.ENSP00000358301%250D9606.ENSP00000243457%250D9606.ENSP00000354
346%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000343204%250D9606.ENSP000002641
10%250D9606.ENSP00000282412%250D9606.ENSP00000262186%250D9606.ENSP00000161559%250D9606.ENSP0000025538
0%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000308165%250D9606.ENSP00000293780
%250D9606.ENSP00000267842%250D9606.ENSP00000306662%250D9606.ENSP00000268099%250D9606.ENSP00000348573%
250D9606.ENSP00000300574

Section 3.3.43.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Drugs for Acid Related Disorders

In Figure 55, genes associated with cLQTS are highlighted in yellow at the top right. Genes

associated with the ANS are connected and highlighted yellow at the center right and center left.

IFIT2, **CANX**, **JAK1** and **CD36** are associated with immune responses. CD36 is also associated

with fatty acid metabolism. Mean expression for all of these was lower in the QT group compared to the

same probes in the NQT group.

MAPK14 is a member of the MAPK family which is involved with immune responses such as

inflammation. Mean expression of MAPK14 was lower in the QT group compared to the NQT group.

Section 3.3.44: Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

Table LI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

Probe ID	Gene Symbol	Human Equivalent Gene Name
NM_017223_PROBE1	SLC20A2	Solute carrier family 20 member 2
AB046592_PROBE1	LAPTM5	Lysosomal protein transmembrane 5
L09653_PROBE1	TGFBR2	Transforming growth factor beta receptor 2
NM_017268_PROBE1	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
NM_019149_PROBE1	MATR3	Matrin 3
U38938_PROBE1	ATF2	Activating transcription factor 2
AF178669_PROBE1	AAGAB	Alpha and gamma adaptin binding protein
D44481_PROBE1	CRK	CRK proto-oncogene, adaptor protein
U73142_PROBE1	MAPK14	Mitogen-activated protein kinase 14
U83895_PROBE1	CYTH1	Cytohesin 1
NM_013223_PROBE1	EIF2AK1	Eukaryotic translation initiation factor 2 alpha kinase 1
NM_021262_PROBE1	ACP1	Acid phosphatase 1, soluble
AJ271837_PROBE1	PPM1B	Protein phosphatase, Mg2+/Mn2+ dependent 1B
BF564940_PROBE1	IFIT2	Interferon induced protein with tetratricopeptide repeats 2
U17253_PROBE1	NAB1	NGFI-A binding protein 1
AI113190_PROBE1	THAP11	THAP domain containing 11
AJ000556_PROBE1	JAK1	Janus kinase 1
D29632_PROBE1	MET	MET proto-oncogene, receptor tyrosine kinase
D90109_PROBE1	ACSL1	Acyl-CoA synthetase long chain family member 1
X07365_PROBE1	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1
AW915859_PROBE1	FBXW2	F-box and WD repeat domain containing 2
D85100_PROBE1	SLC27A2	Solute carrier family 27 member 2
AF239045_PROBE1	KIDINS220	Kinase D interacting substrate 220
AF295405_PROBE1	SCAMP2	Secretory carrier membrane protein 2
D90164_PROBE1	PPP1CB	Protein phosphatase 1 catalytic subunit beta
L18889_PROBE1	CANX	Calnexin
M65148_PROBE1	ATF2	Activating transcription factor 2
NM_019302_PROBE1	CRK	CRK proto-oncogene, adaptor protein
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
AF068202_PROBE1	AKAP1	A-kinase anchoring protein 1
AF111268_PROBE1	CD36	CD36 molecule
AF139055_PROBE1	MYH10	Myosin heavy chain 10
AI137819_PROBE1	YME1L1	YME1 like 1 ATPase
AJ277423_PROBE1	MASP1	Mannan binding lectin serine peptidase 1
NM_012569_PROBE1	GLS	Glutaminase
U75409_PROBE1	NUCB1	Nucleobindin 1
BF395415_PROBE1	DPT	Dermatopontin
BE100014_PROBE1	SNX18	Sorting nexin 18
M18467_PROBE1	GOT2	Glutamic-oxaloacetic transaminase 2

Figure 56: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000281455%250D9606.ENSP00000356791%250D9606.ENSP00000322706%250D9606.ENSP00000258385%250D9606.ENSP00000304689%250D9606.ENSP00000217381%250D9606.ENSP00000337736%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000351905%250D9606.ENSP00000250699%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000360891%250D9606.ENSP00000261880%250D9606.ENSP00000354398%250D9606.ENSP00000247461%250D9606.ENSP00000363036%250D9606.ENSP00000263273%250D9606.ENSP00000317332%250D9606.ENSP00000318480%250D9606.ENSP00000199389%250D9606.ENSP00000306490%250D9606.ENSP00000272065%250D9606.ENSP00000266376%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000336894%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000319984%250D9606.ENSP00000229794%250D9606.ENSP00000269243%250D9606.ENSP00000261751%250D9606.ENSP00000317379%250D9606.ENSP00000349588%250D9606.ENSP00000294507%250D9606.ENSP00000368766%250D9606.ENSP00000296122%250D9606.ENSP00000290310%250D9606.ENSP00000296280%250D9606.ENSP00000409378%250D9606.ENSP00000245206%250D9606.ENSP00000357461%250D9606.ENSP00000256707%250D9606.ENSP00000264027%250D9606.ENSP00000340465%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000317272%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000322460%250D9606.ENSP00000358301%250D9606.ENSP00000243457%250D9606.ENSP00000354346%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000343204%250D9606.ENSP00000264110%250D9606.ENSP00000282412%250D9606.ENSP00000262186%250D9606.ENSP00000161559%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000308165%250D9606.ENSP00000293780%250D9606.ENSP00000267842%250D9606.ENSP00000306662%250D9606.ENSP00000268099%250D9606.ENSP00000348573%250D9606.ENSP00000300574

Section 3.3.44.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

In Figure 56, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the center right and center left.

IFIT2, **CANX**, **JAK1** and **CD36** are associated with immune responses. CD36 is also associated with fatty acid metabolism. Mean expression for all of these was lower in the QT group compared to the same probes in the NQT group.

MAPK14 is a member of the MAPK family which is involved with immune responses such as inflammation. Mean expression of MAPK14 was lower in the QT group compared to the NQT group.

Section 3.3.45: Enzyme Inhibitors

Table LII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Enzyme Inhibitors

Probe ID	Gene symbol	Human Equivalent Gene Name
D13121_PROBE1	LUC7L2	LUC7 like 2, pre-mRNA splicing factor
NM_019237_PROBE1	PCOLCE	Procollagen C-endopeptidase enhancer
AA801076_PROBE1	SLC44A1	Solute carrier family 44 member 1
AI176781_PROBE1	FDFT1	Farnesyl-diphosphate farnesyltransferase 1
AW920527_PROBE1	ADHFE1	Alcohol dehydrogenase, iron containing 1
BF524415_PROBE1	RASGRP2	RAS guanyl releasing protein 2
X13295_PROBE1	LCN2	Lipocalin 2
D87839_PROBE1	ABAT	4-aminobutyrate aminotransferase
NM_017208_PROBE1	LBP	Lipopolysaccharide binding protein
BE329450_PROBE1	FAHD2A	Fumarylacetoacetate hydrolase domain containing 2A
AW918255_PROBE1	DGAT2	Diacylglycerol O-acyltransferase 2
BF550769_PROBE1	DDX41	DEAD-box helicase 41
NM_012855_PROBE1	JAK3	Janus kinase 3
L18948_PROBE1	S100A9	S100 calcium binding protein A9
NM_017051_PROBE1	SOD2	Superoxide dismutase 2
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
D28508_PROBE1	JAK3	Janus kinase 3
AB052846_PROBE1	SC5D	Sterol-C5-desaturase
AI103106_PROBE1	LMNB1	Lamin B1
AI012951_PROBE1	PEX13	Peroxisomal biogenesis factor 13
AF290194_PROBE1	COMMD5	COMM domain containing 5
AJ242554_PROBE1	ASIC4	Acid sensing ion channel subunit family member 4
AW144233_PROBE1	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
U42976_PROBE1	CHRNB4	Cholinergic receptor nicotinic beta 4 subunit
AA892824_PROBE1	TNC	Tenascin C
AW916592_PROBE1	NDUFB7	NADH:ubiquinone oxidoreductase subunit B7
AF029109_PROBE1	APBA3	Amyloid beta precursor protein binding family A member 3
AF032872_PROBE1	PIAS3	Protein inhibitor of activated STAT 3
BF414266_PROBE1	SART3	Squamous cell carcinoma antigen recognized by T-cells 3
AF161588_PROBE1	GABARAP	GABA type A receptor-associated protein
AI137259_PROBE1	LSS	Lanosterol synthase
AI045074_PROBE1	GLB1	Galactosidase beta 1
U01914_PROBE1	AKAP8	A-kinase anchoring protein 8
BE102111_PROBE1	TOR2A	Torsin family 2 member A
NM_012834_PROBE1	COMP	Cartilage oligomeric matrix protein

Figure 57: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Enzyme Inhibitors

Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000295030%250D9606.ENSP00000222271%250D9606.ENSP00000326627%250D9606.ENSP00000422753%250D9606.ENSP00000220584%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000225276%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000376765%250D9606.ENSP00000379865%250D9606.ENSP00000223061%250D9606.ENSP00000268251%250D9606.ENSP00000306866%250D9606.ENSP00000306490%250D9606.ENSP00000266376%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000228027%250D9606.ENSP00000315136%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000357727%250D9606.ENSP00000319984%250D9606.ENSP00000261751%250D9606.ENSP00000233379%250D9606.ENSP00000261366%250D9606.ENSP00000348762%250D9606.ENSP00000349588%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000357461%250D9606.ENSP00000391676%250D9606.ENSP00000228284%250D9606.ENSP00000264027%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000306920%250D9606.ENSP00000357452%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000347005%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000362381%250D9606.ENSP00000356022%250D9606.ENSP00000338864%250D9606.ENSP00000363852%250D9606.ENSP00000262186%250D9606.ENSP00000304544%250D9606.ENSP00000255380%250D9606.ENSP00000265131%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000217407%250D9606.ENSP00000277480%250D9606.ENSP00000293780%250D9606.ENSP00000356574%250D9606.ENSP00000215565%250D9606.ENSP00000269701%250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.45.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Enzyme Inhibitors

In Figure 57, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the center right and bottom left.

S100A9 and **RASGRP2** are associated immune responses with with RASGRP2 having possible links to muscarinic cholinergic activity. Mean expression for both was lower in the QT group compared to the same probes in the NQT groups.

SOD2 is a mitochondrial protein associated with detoxifying oxygen free radicals. Mean expression of SOD2 in the QT group was lower compared to the NQT group.

CHRNB4 is a nicotinic cholinergic receptor associated with the autonomic nervous system. Mean expression of CHRNB4 was lower in the QT group compared to the NQT group.

Section 3.3.46: Estrogen Antagonists

Table LIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Estrogen Antagonists

Probe ID	Gene Symbol	Human Equivalent Gene Name
D00913_PROBE1	ICAM1	Intercellular adhesion molecule 1
NM_017034_PROBE1	PIM1	Pim-1 proto-oncogene, serine/threonine kinase
U72660_PROBE1	NINJ1	Ninjurin 1
AI716480_PROBE1	GTPBP1	GTP binding protein 1
BF408022_PROBE1	MYH9	Myosin heavy chain 9
BF558742_PROBE1	NF2	Neurofibromin 2
NM_012931_PROBE1	BCAR1	BCAR1, Cas family scaffolding protein
BF564219_PROBE1	PI4K2A	Phosphatidylinositol 4-kinase type 2 alpha
M55601_PROBE1	PTN	Pleiotrophin
X12355_PROBE1	PDIA3	Protein disulfide isomerase family A member 3
D26178_PROBE1	ICK	Intestinal cell kinase
BE109525_PROBE1	EHMT2	Euchromatic histone lysine methyltransferase 2
M23674_PROBE1	AP2M1	Adaptor related protein complex 2 mu 1 subunit
AW916819_PROBE1	NCKIPSD	NCK interacting protein with SH3 domain
AI704755_PROBE1	GNG2	G protein subunit gamma 2
NM_017135_PROBE1	AK3	Adenylate kinase 3
AW919578_PROBE1	TERF2IP	TERF2 interacting protein
U35776_PROBE1	ARFGAP1	ADP ribosylation factor GTPase activating protein 1
D30040_PROBE1	AKT1	AKT serine/threonine kinase 1
NM_013112_PROBE1	APOA2	Apolipoprotein A2
NM_019331_PROBE1	FURIN	Furin, paired basic amino acid cleaving enzyme
AA818128_PROBE1	FBXO11	F-box protein 11
AA943578_PROBE1	EXOSC5	Exosome component 5
AA946063_PROBE1	UBL3	Ubiquitin like 3
AI412625_PROBE1	ELMOD1	ELMO domain containing 1
AI412949_PROBE1	STAP2	Signal transducing adaptor family member 2
AI556246_PROBE1	TRIM26	Tripartite motif containing 26
AJ236911_PROBE1	ARHGEF1	Rho guanine nucleotide exchange factor 1
NM_017323_PROBE1	NR2C2	Nuclear receptor subfamily 2 group C member 2
U14533_PROBE1	NR1H2	Nuclear receptor subfamily 1 group H member 2
U20195_PROBE1	PGM1	Phosphoglucomutase 1
AI171088_PROBE1	SRM	Spermidine synthase
BF408385_PROBE1	CTDNEP1	CTD nuclear envelope phosphatase 1
AB003104_PROBE1	BFSP1	Beaded filament structural protein 1
BF400781_PROBE1	AP3D1	Adaptor related protein complex 3 delta 1 subunit

Figure 58: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Estrogen Antagonists
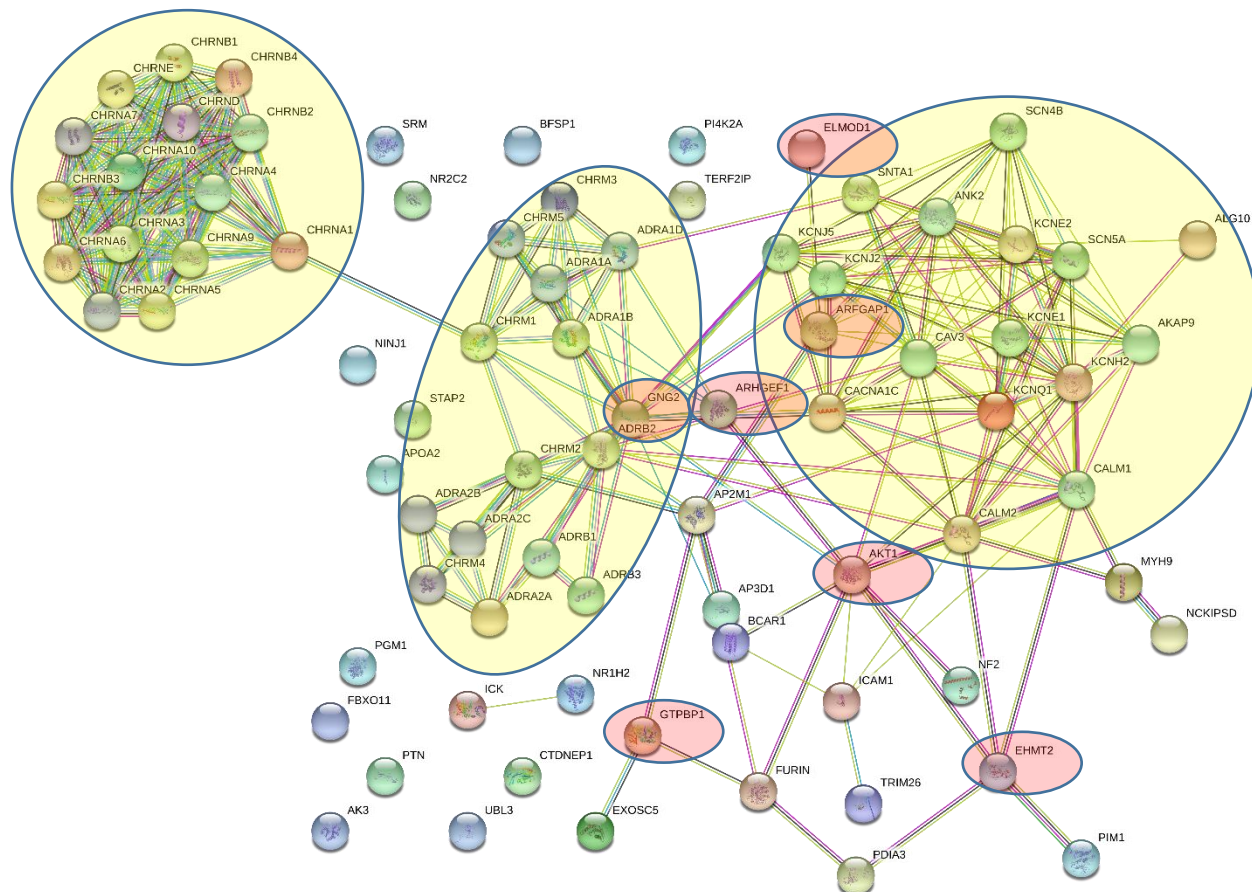
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000360124%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D9606.ENSP00000391669%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000265840%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000300289%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000391879%250D9606.ENSP00000367104%250D9606.ENSP00000314615%250D9606.ENSP00000341170%250D9606.ENSP00000263043%250D9606.ENSP00000268171%250D9606.ENSP00000221233%250D9606.ENSP00000306490%250D9606.ENSP00000320447%250D9606.ENSP00000266376%250D9606.ENSP00000294129%250D9606.ENSP00000253727%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00003359285%250D9606.ENSP00000366156%250D9606.ENSP00000305372%250D9606.ENSP00000344666%250D9606.ENSP00000356969%250D9606.ENSP00000266483%250D9606.ENSP00000321732%250D9606.ENSP00000386069%250D9606.ENSP00000319984%250D9606.ENSP00000362608%250D9606.ENSP00000216181%250D9606.ENSP00000270202%250D9606.ENSP00000261751%250D9606.ENSP00000349588%250D9606.ENSP00000216044%250D9606.ENSP00000344055%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000357461%250D9606.ENSP00000359665%250D9606.ENSP00000387281%250D9606.ENSP00000317912%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000364595%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00003369960%250D9606.ENSP00003358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000370055%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000364687%250D9606.ENSP00000299565%250D9606.ENSP00000264832%250D9606.ENSP00000293780%250D9606.ENSP00000292807%250D9606.ENSP00000371230%250D9606.ENSP00000334448%250D9606.ENSP00000300086%250D9606.ENSP00000337261%250D9606.ENSP00000306662%250D9606.ENSP00000348573%250D9606.ENSP00000384823

Section 3.3.46.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Estrogen Antagonists

In Figure 58, genes associated with cLQTS are highlighted in yellow on the right side. Genes associated with the ANS are connected and highlighted yellow at the center and left.

GTPBP1, **GNG2**, **ELMOD1**, **ARFGAP1**, and **ARHGEF1** are associated with G proteins. Mean expression for GTPBP1, ELMOD1, ARFGAP1 and ARHGEF1 were lower in the QT group compared to the same probes in the NQT group. Mean expression of GNG2 was higher in the QT group compared to the NQT group.

AKT1 is associated with glucose transport which suggests a possible link to diabetes, and it also interacts with MAPK35 to prevent apoptosis. Mean expression for AKT1 was lower in the QT group compared to the NQT group.

Section 3.3.47: Fluoroquinolones

Table LIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Fluoroquinolones

Probe ID	Gene Symbol	Human Equivalent Gene Name
J04636_PROBE1	CHRNB3	Cholinergic receptor nicotinic beta 3 subunit
AI137569_PROBE1	UCK1	Uridine-cytidine kinase 1
NM_017034_PROBE1	PIM1	Pim-1 proto-oncogene, serine/threonine kinase
X53427_PROBE1	GSK3A	Glycogen synthase kinase 3 alpha
AI169160_PROBE1	ELAC2	ElaC ribonuclease Z 2
D85760_PROBE1	GNA12	G protein subunit alpha 12
AB023781_PROBE1	CTSZ	Cathepsin Z
AA799476_PROBE1	TMX2	Thioredoxin related transmembrane protein 2
AW915580_PROBE1	PCF11	PCF11 cleavage and polyadenylation factor subunit
AA819488_PROBE1	PDCD6	Programmed cell death 6
AW916655_PROBE1	WWOX	WW domain containing oxidoreductase
AI012235_PROBE1	CXCL11	C-X-C motif chemokine ligand 11
AI009197_PROBE1	VKORC1	Vitamin K epoxide reductase complex subunit 1
D83792_PROBE1	CDKN1B	Cyclin dependent kinase inhibitor 1B
AW251612_PROBE1	TARS2	Threonyl-tRNA synthetase 2, mitochondrial (putative)
J04811_PROBE1	GHR	Growth hormone receptor
AI178158_PROBE1	RBBP6	RB binding protein 6, ubiquitin ligase
U96638_PROBE1	UNC50	Unc-50 inner nuclear membrane RNA binding protein
NM_012818_PROBE1	AANAT	Aralkylamine N-acetyltransferase
AI229655_PROBE1	CTDSP1	CTD small phosphatase 1
BE114123_PROBE1	CEP85	Centrosomal protein 85
AF255305_PROBE1	CCS	Copper chaperone for superoxide dismutase
AF069306_PROBE1	TALDO1	Transaldolase 1

Figure 59: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Fluoroquinolones

Permanent Link: http://bit.ly/2w9rElv
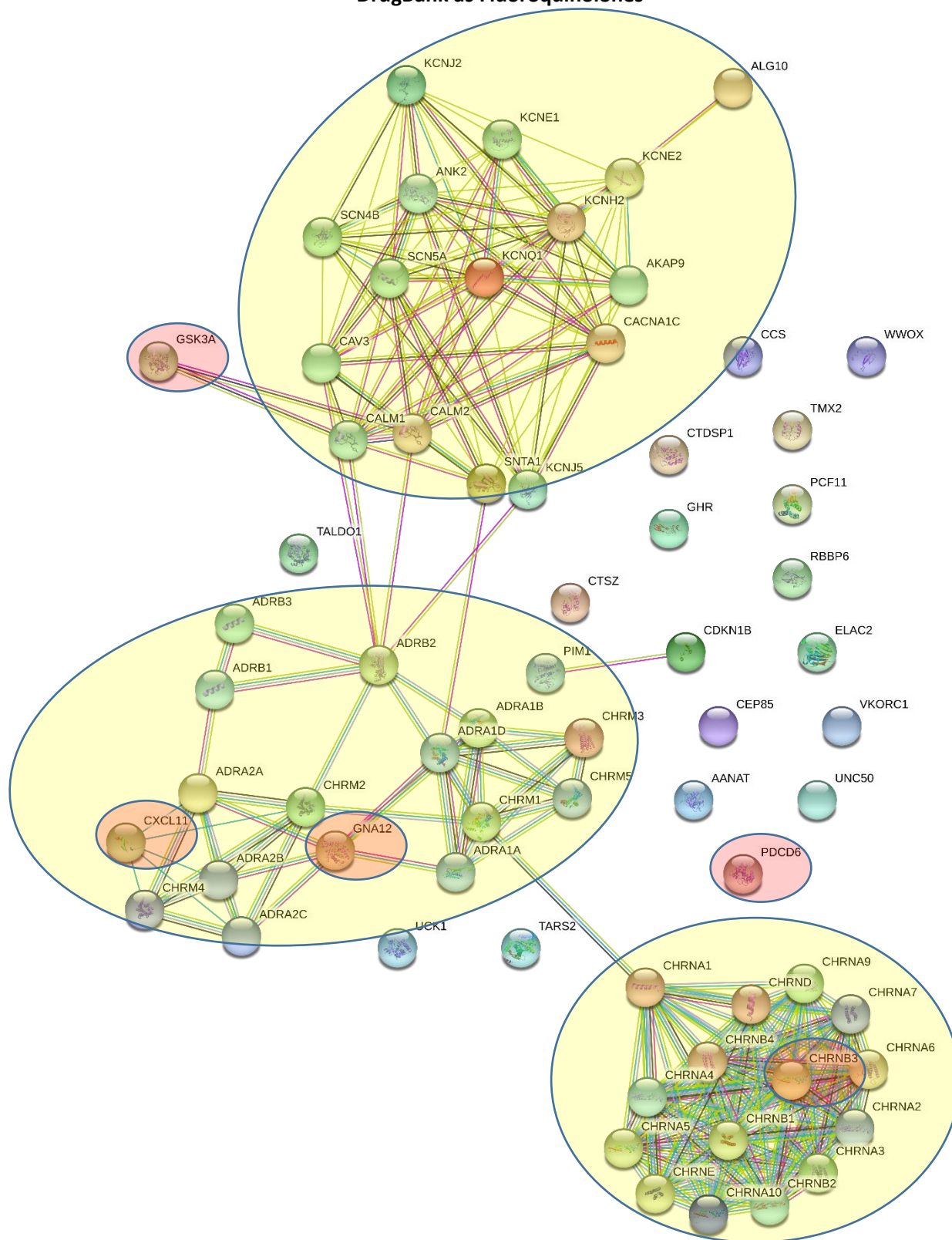
Section 3.3.47.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Fluoroquinolones

In Figure 59, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and lower right.

GNA12 is associated with G proteins. Mean expression of GNA12 was higher in the QT group compared to the NQT group.

CXCL11 and **PDCD6** are associatetd with apoptosis and immune responses. Mean expression of CXCL11 was lower in the QT group compared to the NQT group. Mean expression of PDCD6 was higher in the QT group compared to the same probes in the NQT group.

CHRNB3 is a nicotinic cholinergic receptor which is part of the autonomic nervous system. Mean expression of CHRNB3 was lower in the QT group compared to the NQT group.

GSK3A is associated with glycogen synthase which might suggest a potential link to diabetes, and GSK3A is also associated with apoptosis. Mean expression of GSK3A was higher in the QT group compared to the NQT group.

Section 3.3.48: Gastrointestinal Agents

Table LV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Gastrointestinal Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
AI454913_PROBE1	CXXC5	CXXC finger protein 5
BF284127_PROBE1	NIF3L1	NGG1 interacting factor 3 like 1
L24116_PROBE1	PGGT1B	Protein geranylgeranyltransferase type I subunit beta
X97831_PROBE1	SLC25A20	Solute carrier family 25 member 20
AI176713_PROBE1	DLC1	DLC1 Rho GTPase activating protein
AB049151_PROBE1	IP6K1	Inositol hexakisphosphate kinase 1
NM_012733_PROBE1	RBP1	Retinol binding proteinc 1
AA944036_PROBE1	SLC25A17	Solute carrier family 25 member 17
AI410079_PROBE1	NSMAF	Neutral sphingomyelinase activation associated factor
AB032739_PROBE1	UBE2N	Ubiquitin conjugating enzyme E2 N
AA799691_PROBE1	SLC12A7	Solute carrier family 12 member 7
AA892376_PROBE1	ZFAND6	Zinc finger AN1-type containing 6
AA925469_PROBE1	CBLL1	Cbl proto-oncogene like 1
AB017260_PROBE1	SLC22A5	Solute carrier family 22 member 5
AI102486_PROBE1	TRIM35	Tripartite motif containing 35
AI105145_PROBE1	ZNRF1	Zinc and ring finger 1
AI454081_PROBE1	NCOA1	Nuclear receptor coactivator 1
AW254369_PROBE1	PLEKHB2	Pleckstrin homology domain containing B2
AW862653_PROBE1	NUDT4	Nudix hydrolase 4
BE103543_PROBE1	RFC1	Replication factor C subunit 1
NM_012818_PROBE1	AANAT	Aralkylamine N-acetyltransferase
NM_019302_PROBE1	CRK	CRK proto-oncogene, adaptor protein
AI406667_PROBE1	GGA3	RAB5A, member RAS oncogene family
AI411501_PROBE1	DND1	DND microRNA-mediated repression inhibitor 1
BE107610_PROBE1	GGA3	Golgi associated, gamma adaptin ear containing, ARF binding protein 3
M64300_PROBE1	MAPK1	Mitogen-activated protein kinase 1
AA894259_PROBE1	HIGD2A	HIG1 hypoxia inducible domain family member 2A
Y13400_PROBE1	CCR3	C-C motif chemokine receptor 3
AJ303456_PROBE1	WIPF1	WAS/WASL interacting protein family member 1
NM_012770_PROBE1	GUCY1B2	Guanylate cyclase 1 soluble subunit beta 2 (pseudogene)
X89383_PROBE1	SNRK	SNF related kinase
AI412298_PROBE1	DNPEP	Aspartyl aminopeptidase

Figure 60: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Gastrointestinal Agents

Permanent Link: http://bit.ly/2w926oA
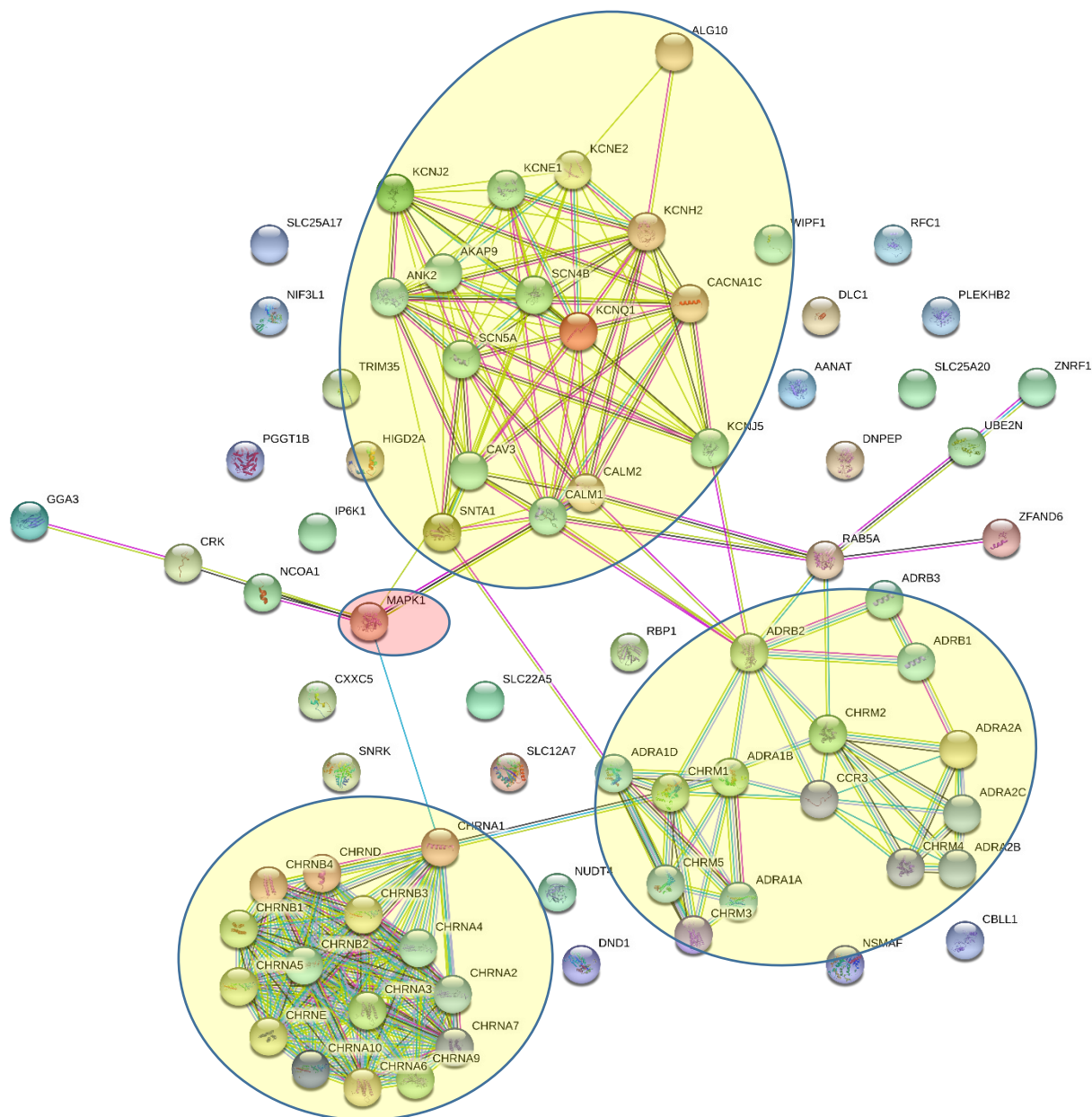
Section 3.3.48.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Gastrointestinal Agents

In Figure 60, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the lower left and lower right.

MAPK1 is a member of the MAPK family having associations with several apoptosis proteins. Mean expression of MAPK1 was lower in the QT group compared to the NQT group.

Section 3.3.49: Heterocyclic Compounds

Table LVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Heterocyclic Compounds

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF046886_PROBE1	AXL	AXL receptor tyrosine kinase
L11319_PROBE1	SEC11A	SEC11 homolog A, signal peptidase complex subunit
AW918255_PROBE1	DGAT2	Diacylglycerol O-acyltransferase 2
Y00497_PROBE1	SOD2	Superoxide dismutase 2
AB029559_PROBE1	SLC7A9	Solute carrier family 7 member 9
NM_019157_PROBE1	AQP7	Aquaporin 7
NM_017243_PROBE1	PRPS1	Phosphoribosyl pyrophosphate synthetase 1
X57764_PROBE1	EDNRB	Endothelin receptor type B
X13295_PROBE1	LCN2	Lipocalin 2
BE108272_PROBE1	SLC7A6	Solute carrier family 7 member 6
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
AW144233_PROBE1	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
BF285834_PROBE1	WASF1	WAS protein family member 1
NM_019237_PROBE1	PCOLCE	Procollagen C-endopeptidase enhancer
AF245227_PROBE1	SNAP25	Synaptosome associated protein 25
NM_017208_PROBE1	LBP	Lipopolysaccharide binding protein
AJ242554_PROBE1	ASIC4	Acid sensing ion channel subunit family member 4
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
BE103518_PROBE1	PLXNA3	Plexin A3
M88096_PROBE1	CCKAR	Cholecystokinin A receptor
NM_017077_PROBE1	FOXA3	Forkhead box A3
U10697_PROBE1	ESS2	Ess-2 splicing factor homolog
U42976_PROBE1	CHRNB4	Cholinergic receptor nicotinic beta 4 subunit
NM_021262_PROBE1	ACP1	Acid phosphatase 1, soluble
U55995_PROBE1	KCNMA1	Potassium calcium-activated channel subfamily M alpha 1
AI406275_PROBE1	CBX7	Chromobox 7
AA892918_PROBE1	TJP1	Tight junction protein 1
BF396247_PROBE1	USP54	Ubiquitin specific peptidase 54
AW531902_PROBE1	ZFHX4	Zinc finger homeobox 4
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1

Figure 61: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Heterocyclic Compounds

Permanent Link: http://bit.ly/2w9sIpv

Section 3.3.49.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Heterocyclic Compounds

In Figure 61, genes associated with cLQTS are highlighted in yellow on the left. Genes associated with the ANS are connected and highlighted yellow at the upper and lower right.

EDNRB is associated with G protein activity. Mean expression of EDNRB was lower in the QT group compared to the NQT group.

CACNA1S and **KCNMA1** are CA^{2+} and K^+, ion channels, respectively, that were differentially expressed in this group. Mean expression of both of these was downregulated in the QT group compared to the same probes in the NQT group.

GRIN2C and **GSTA3** are associated with glutamate and glutathione. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

SOD2 is associated with detoxification of oxygen free radicals. Mean expression of SOD2 was lower in the QT group compared to theNQT group.

CHRNB4 is a nicotinic cholinergic receptor associated with the autonomic nervous system. Mean expression of CHRNB4 was lower in the QT group compared to the NQT group.

Section 3.3.50: Heterocyclic Compounds – 1 Ring

Table LVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Heterocyclic Compounds – 1 Ring

Probe ID	Gene Symbol	Human Equivalent Gene Name
AI715955_PROBE1	STAC3	SH3 and cysteine rich domain 3
U02096_PROBE1	FABP7	Fatty acid binding protein 7
AW253902_PROBE1	MMP15	Matrix metallopeptidase 15
M63991_PROBE1	SERPINA7	Serpin family A member 7
BF407194_PROBE1	ITGB1BP2	Integrin subunit beta 1 binding protein 2
NM_013069_PROBE1	CD74	CD74 molecule
BF557572_PROBE1	FGFR2	Fibroblast growth factor receptor 2
AI172464_PROBE1	TSPAN3	tetraspanin 3
NM_019311_PROBE1	INPP5D	Inositol polyphosphate-5-phosphatase D
D38104_PROBE1	CTSE	Cathepsin E
AB029559_PROBE1	SLC7A9	Solute carrier family 7 member 9
BF283556_PROBE1	PLXNC1	Plexin C1
AW253409_PROBE1	ITM2C	Integral membrane protein 2C
AI176648_PROBE1	AEBP2	AE binding protein 2
AW915616_PROBE1	PIP4K2A	Phosphatidylinositol-5-phosphate 4-kinase type 2 alpha
NM_017180_PROBE1	PHLDA1	Pleckstrin homology like domain family A member 1
L22339_PROBE1	SULT1C2	Sulfotransferase family 1C member 2
AI232273_PROBE1	RCL1	RNA terminal phosphate cyclase like 1
BF524415_PROBE1	RASGRP2	RAS guanyl releasing protein 2
AW918493_PROBE1	PGLS	6-phosphogluconolactonase
BE105855_PROBE1	CYB5R2	Cytochrome b5 reductase 2
AF046886_PROBE1	AXL	AXL receptor tyrosine kinase
AW531675_PROBE1	GPSM3	G protein signaling modulator 3
AA799707_PROBE1	NDUFB5	NADH:ubiquinone oxidoreductase subunit B5
U25808_PROBE1	KDM6A	Lysine demethylase 6A
AF013144_PROBE1	DUSP5	Dual specificity phosphatase 5
NM_019255_PROBE1	CACNG1	Calcium voltage-gated channel auxiliary subunit gamma 1
AF097723_PROBE1	CPQ	Carboxypeptidase Q
J03734_PROBE1	CLEC4F	C-type lectin domain family 4 member F

Figure 62: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Heterocyclic Compounds – 1 Ring
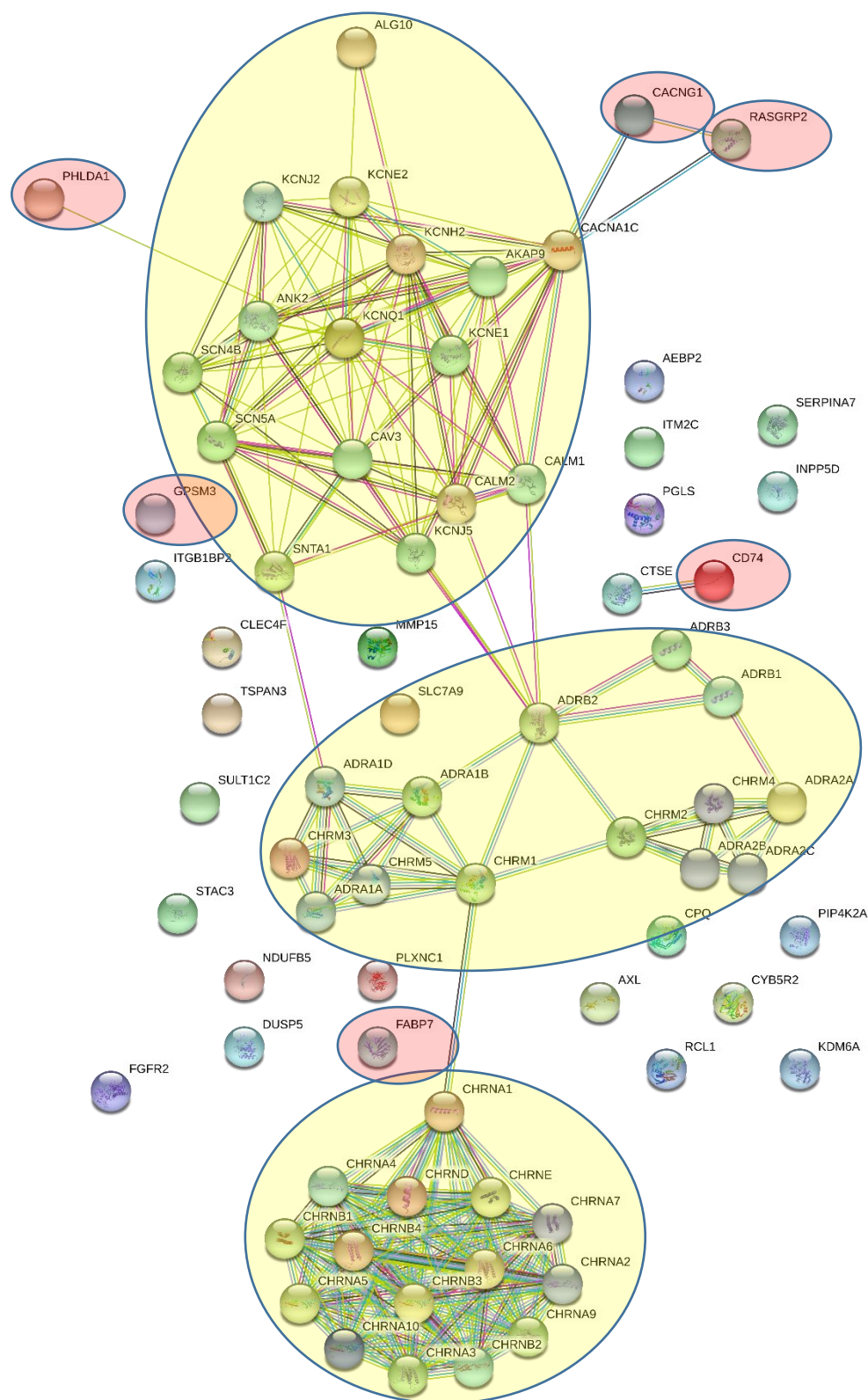
Section 3.3.50.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Heterocyclic Compounds – 1 Ring

In Figure 62, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom.

FABP7 is associated with fatty acid metabolism. Mean expression of FABP7 was lower in the QT group compared to the NQT group.

GPSM3 is associated with G proteins. Mean expression of GPSM3 was lower in the QT group compared to the NQT group.

PHLDA1 is associated witdh apoptosis. Mean expression of PHLDA1 was lower in the QT group compared to the NQT group.

RASGRP2 is associated with RAS-related immune responses. Mean expression of RASGRP2 was lower in the QT group compared to the NQT group.

CACNG1 is a subuint of a CA^{2+} ion channel. Mean expression of CACNG1 was lower in the QT group compared to the NQT group.

CD74 is a cell surface antigen associated with immune responses. Mean expression of CD74 was lower in the QT group compared to the NQT group.

Section 3.3.51: Heterocyclic Compounds – 2 Ring

Table LVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring

Probe ID	Gene Symbol	Human Equivalent Gene Name
X68191_PROBE1	SLC8A1	Solute carrier family 8 member A1
BF290076_PROBE1	GEM	GTP binding protein overexpressed in skeletal muscle
J00696_PROBE1	ORM1	Orosomucoid 1
L04535_PROBE1	SSTR5	Somatostatin receptor 5
BE103518_PROBE1	PLXNA3	Plexin A3
BE108272_PROBE1	SLC7A6	Solute carrier family 7 member 6
M18340_PROBE1	TAT	Tyrosine aminotransferase
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1
J03933_PROBE1	THRB	Thyroid hormone receptor beta
AF070065_PROBE1	CIT	Citron rho-interacting serine/threonine kinase
X77933_PROBE1	SCNN1G	Sodium channel epithelial 1 gamma subunit
AA849743_PROBE1	ALPK3	Alpha kinase 3
AI102086_PROBE1	NDUFA9	NADH:ubiquinone oxidoreductase subunit A9
J03960_PROBE1	ALOX5	Arachidonate 5-lipoxygenase
NM_012940_PROBE1	CYP1B1	Cytochrome P450 family 1 subfamily B member 1
AA818743_PROBE1	DST	Dystonin
AW144649_PROBE1	KLHL22	Kelch like family member 22
NM_021747_PROBE1	ACRV1	Acrosomal vesicle protein 1
U26033_PROBE1	CROT	Carnitine O-octanoyltransferase
AF245172_PROBE1	GDA	Guanine deaminase
L08812_PROBE1	TFEC	Transcription factor EC
M99418_PROBE1	CCKBR	Cholecystokinin B receptor
NM_012668_PROBE1	TAT	Tyrosine aminotransferase
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
AI598486_PROBE1	DPYSL3	Dihydropyrimidinase like 3
M84488_PROBE1	VCAM1	Vascular cell adhesion molecule 1
M60655_PROBE1	ADRA1B	Adrenoceptor alpha 1B
D10354_PROBE1	GPT	Glutamic--pyruvic transaminase
AW144233_PROBE1	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2
AF075383_PROBE1	SOCS3	Suppressor of cytokine signaling 3
D00833_PROBE1	GLRA1	Glycine receptor alpha 1
J03863_PROBE1	SDS	Serine dehydratase
L11319_PROBE1	SEC11A	SEC11 homolog A, signal peptidase complex subunit

Figure 63: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring

Permanent Link: http://bit.ly/2w9Bh3G
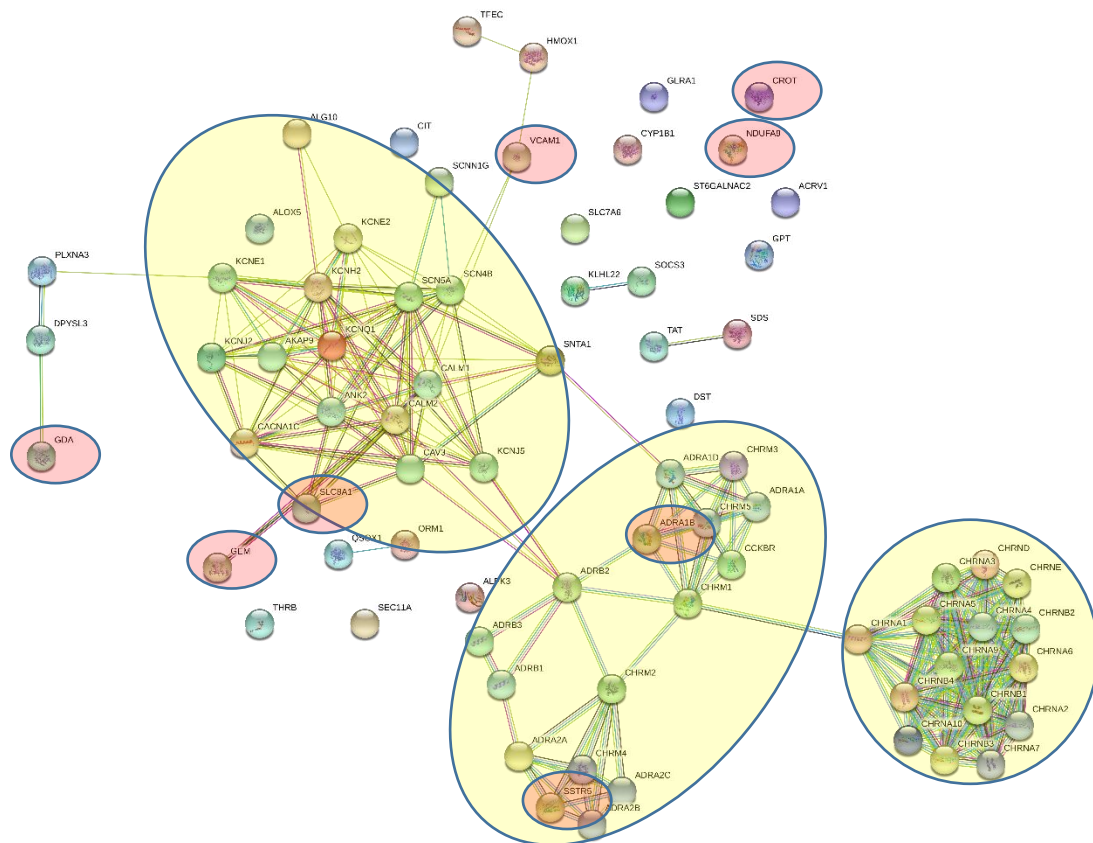
Section 3.3.51.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring

In Figure 63, genes associated with cLQTS are highlighted in yellow at the top center. Genes associated with the ANS are connected and highlighted yellow at the lower center and bottom right.

VCAM1 is associated with immune responses. Mean expression of VCAM1 was lower in the QT group compared to the NQT group.

SLC8A1 mediates cytoplasmic Ca^{2+} ion concentrations through exchange with Na^+ ions across the plasma membrane. Mean expression of SLC8A1 was lower in the QT group compared to the NQT group.

GDA, **GEM**, and **SSTR5** are associated with G proteins. Mean expression of all three was lower in the QT group compared to the same probes in the NQT group

NDUFA9 is associated with electron transport processes. Mean expression of NDUFA9 was lower in the QT group compared to the NQT group.

CROT is associated with fatty acid metabolism. Mean expression of CROT was higher in the QT group compared to the NQT group.

ADRA1B is an adrenergic autonomic nervous system receptor that was differentially expressed in this group. Mean expression of ACRA1B was lower in the QT group compared to the NQT group.

Section 3.3.52: Hormone Antagonists

Table LIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hormone Antagonists

Probe ID	Gene Symbol	Human Equivalent Gene Name
AJ003004_PROBE1	ABCB6	ATP binding cassette subfamily B member 6 (Langereis blood group)
AW523642_PROBE1	KMT5B	Lysine methyltransferase 5B
NM_012903_PROBE1	ANP32A	Acidic nuclear phosphoprotein 32 family member A
D70816_PROBE1	CPLX2	Complexin 2
J05132_PROBE1	UGT1A6	UDP glucuronosyltransferase family 1 member A6
NM_012545_PROBE1	DDC	Dopa decarboxylase
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
NM_012846_PROBE1	FGF1	Fibroblast growth factor 1
AW141873_PROBE1	MRPL14	Mitochondrial ribosomal protein L14
NM_017129_PROBE1	CTF1	Cardiotrophin 1
BF287032_PROBE1	WBP2	WW domain binding protein 2
BF285991_PROBE1	DENND5A	DENN domain containing 5A
BF399993_PROBE1	PURB	Purine rich element binding protein B
M22923_PROBE1	MS4A2	Membrane spanning 4-domains A2
M23674_PROBE1	AP2M1	Adaptor related protein complex 2 mu 1 subunit
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
AI232098_PROBE1	CRYZ	Crystallin zeta
AF007108_PROBE1	CYB5A	Cytochrome b5 type A
AI704799_PROBE1	CDK5RAP2	CDK5 regulatory subunit associated protein 2
M91563_PROBE1	GRIN2C	(Gutamate ionotropic receptor NMDA type subunit 2C
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
AW917831_PROBE1	FECH	Ferrochelatase
NM_017353_PROBE1	SLC7A5	Solute carrier family 7 member 5
BF392344_PROBE1	MTMR7	Myotubularin related protein 7
AW918068_PROBE1	LMBRD1	LMBR1 domain containing 1
AI103106_PROBE1	LMNB1	Lamin B1
AW141073_PROBE1	UBE2E2	Ubiquitin conjugating enzyme E2
AW862653_PROBE1	NUDT4	Nudix hydrolase 4
NM_012719_PROBE1	SSTR1	Somatostatin receptor 1
X05341_PROBE1	ACAA2	Acetyl-CoA acyltransferase 2
NM_020098_PROBE1	PCLO	Piccolo presynaptic cytomatrix protein

Figure 64: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hormone Antagonists

Permanent Link: http://bit.ly/2w93Yh6
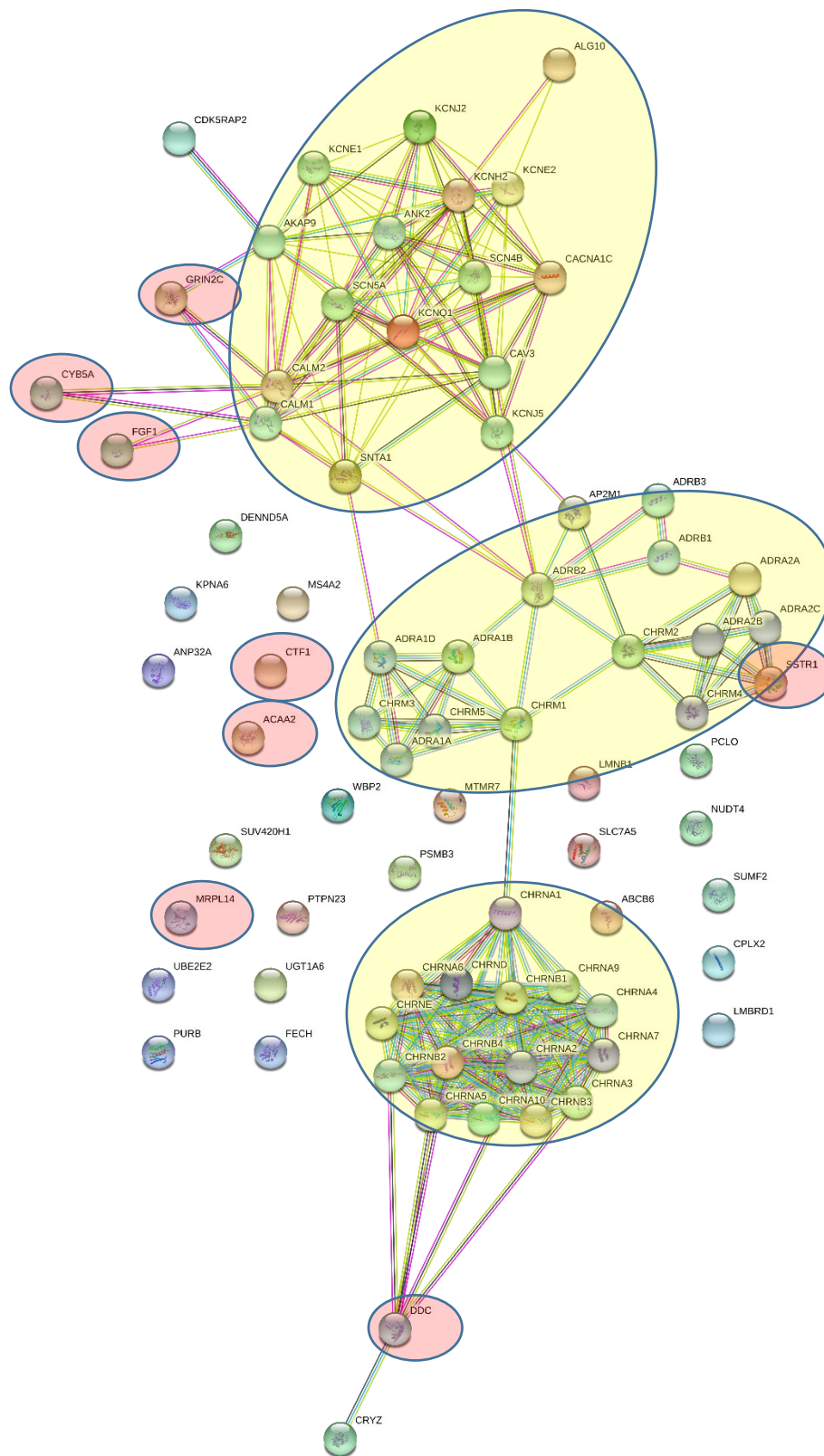
Section 3.3.52.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hormone Antagonists

In Figure 64, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom.

ACAA2 is associated with fatty acid metabolism. Mean expression of ACAA2 was lower in the QT group compared to the NQT group.

MRPL14 is a mitochondrial ribosomal protein. Mean expression of MRPL14 was lower in the QT group compared to the NQT group.

FGF1 is associated with MAPK activity. Mean expression of FGF1 was lower in the QT group compared to the NQT group.

GRIN2C and **SSTR1** are associated with G proteins. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

CYB5A is a membrane bound electron carrier associated with membrane bound oxygenases. Mean expression of CYB5A was lower in the QT group compared to the NQT group.

DDC is associated with catecholamine biosynthesis. Mean expression of DDC was lower in the QT group compared to the NQT group.

CTF1 is associated with multiple forms of heart disease. Mean expression of CTF1 was lower in the QT group compared to the NQT group.

Section 3.3.53: Hormones, Hormone Substitutes, and Hormone Antagonists

Table LX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
NM_019157_PROBE1	AQP7	Aquaporin 7
NM_020098_PROBE1	PCLO	Piccolo presynaptic cytomatrix protein
AW523642_PROBE1	KMT5B	Lysine methyltransferase 5B
NM_017353_PROBE1	SLC7A5	Solute carrier family 7 member 5
AW917831_PROBE1	FECH	Ferrochelatase
BF282899_PROBE1	CDKN2C	Cyclin dependent kinase inhibitor 2C
BF402596_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
BF405468_PROBE1	ZDHHC2	Zinc finger DHHC-type containing 2
M22923_PROBE1	MS4A2	Membrane spanning 4-domains A2
M26125_PROBE1	EPHX1	Epoxide hydrolase 1
NM_012719_PROBE1	SSTR1	Somatostatin receptor 1
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
BF285991_PROBE1	DENND5A	DENN domain containing 5A
M91563_PROBE1	GRIN2C	Glutamate ionotropic receptor NMDA type subunit 2C
NM_019291_PROBE1	CA2	Carbonic anhydrase 2
NM_017000_PROBE1	NQO1	NAD(P)H quinone dehydrogenase 1
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
NM_012903_PROBE1	ANP32A	Acidic nuclear phosphoprotein 32 family member A
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
BF405883_PROBE1	DHX16	DEAH-box helicase 16
NM_017129_PROBE1	CTF1	Cardiotrophin 1
AA891834_PROBE1	COL4A5	Collagen type IV alpha 5 chain
AW918068_PROBE1	LMBRD1	LMBR1 domain containing 1
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
NM_019149_PROBE1	MATR3	Matrin 3
BF398680_PROBE1	MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4
NM_012664_PROBE1	SYP	Synaptophysin
L09647_PROBE1	FOXD1	Forkhead box D1
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2

Figure 65: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists

Permanent Link: http://bit.ly/2w9t1kf
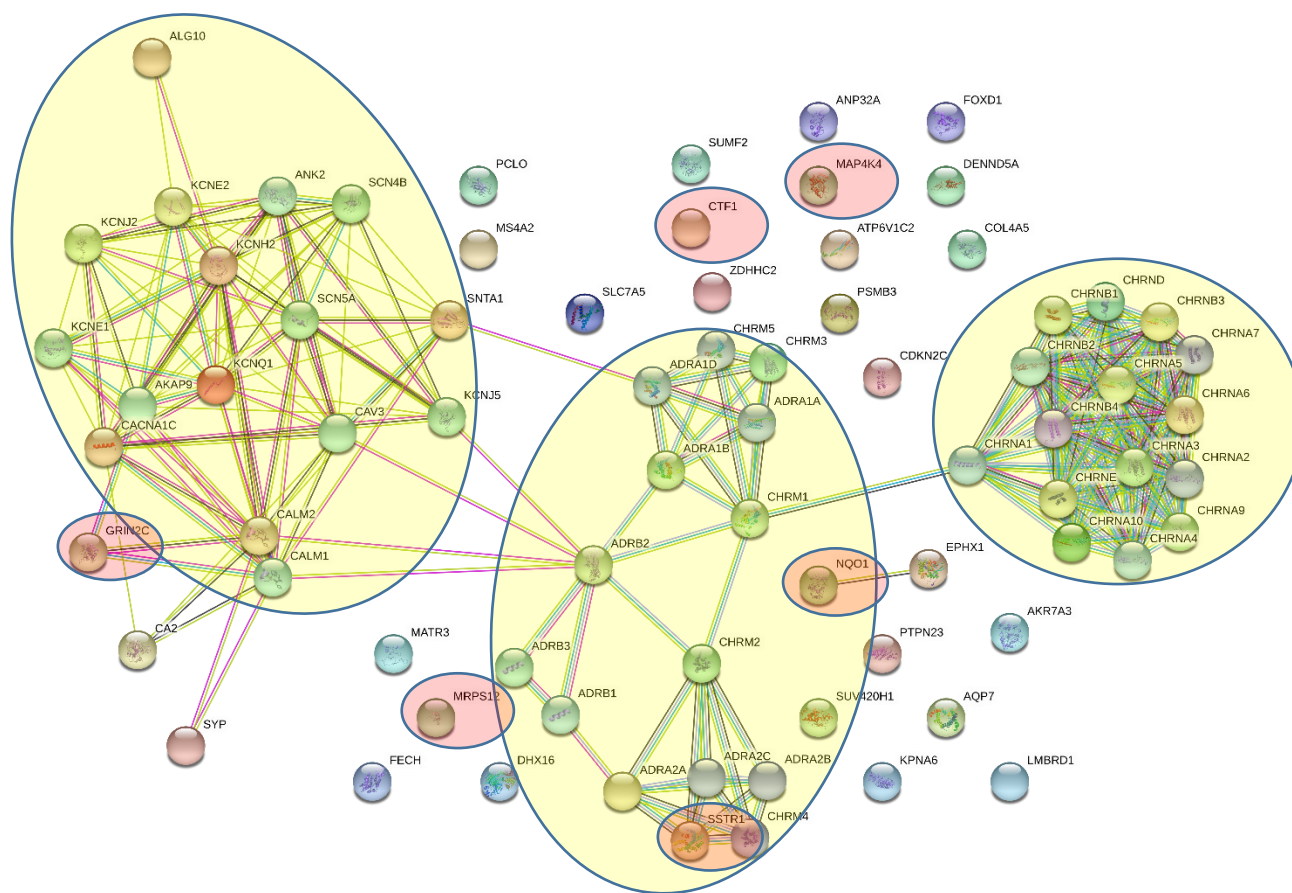
Section 3.3.53.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists

In Figure 65, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom.

GRIN2C is associated with glutathion and **NQO1** is associated with electron transport. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

SSTR1 is associated with G proteins. Mean expression of SSTR1 was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

MAP4K4 is a member of the MAPK family. Mean expression of MAP4K4 was lower in the QT group compared to the NQT group.

CTF1 is associated with multiple forms of heart disease. Mean expression of CTF1 was lower in the QT group compared to the NQT group.

Section 3.3.54: Hydrocarbons

Table LXI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hydrocarbons

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
BF412111_PROBE1	GDPD2	Glycerophosphodiester phosphodiesterase domain containing 2
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2
AF107723_PROBE1	GPSM1	G protein signaling modulator 1
AF110021_PROBE1	AQP2	Aquaporin 2
NM_012519_PROBE1	CAMK2D	Calcium/calmodulin dependent protein kinase II delta
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
X65083_PROBE1	EPHX2	Epoxide hydrolase 2
NM_019355_PROBE1	SYNE1	Spectrin repeat containing nuclear envelope protein 1
AF031384_PROBE1	KCNK3	Potassium two pore domain channel subfamily K member 3
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
BF417292_PROBE1	KCNMA1	Potassium calcium-activated channel subfamily M alpha 1
NM_021739_PROBE1	CAMK2B	Calcium/calmodulin dependent protein kinase II beta
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
NM_012490_PROBE1	ACR	Acrosin
NM_012863_PROBE1	BHLHA15	Basic helix-loop-helix family member a15
AA899304_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AF111268_PROBE1	CD36	CD36 molecule
NM_017075_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
M21208_PROBE1	CYP17A1	Cytochrome P450 family 17 subfamily A member 1
BE115600_PROBE1	XPO5	Exportin 5
AF051425_PROBE1	CNMD	Chondromodulin
NM_021841_PROBE1	GABRA6	Gamma-aminobutyric acid type A receptor alpha6 subunit
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
AA849721_PROBE1	STUB1	STIP1 homology and U-box containing protein 1
X76996_PROBE1	GZMB	Granzyme B

Figure 66: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hydrocarbons

Permanent Link: http://bit.ly/2w9xRh7
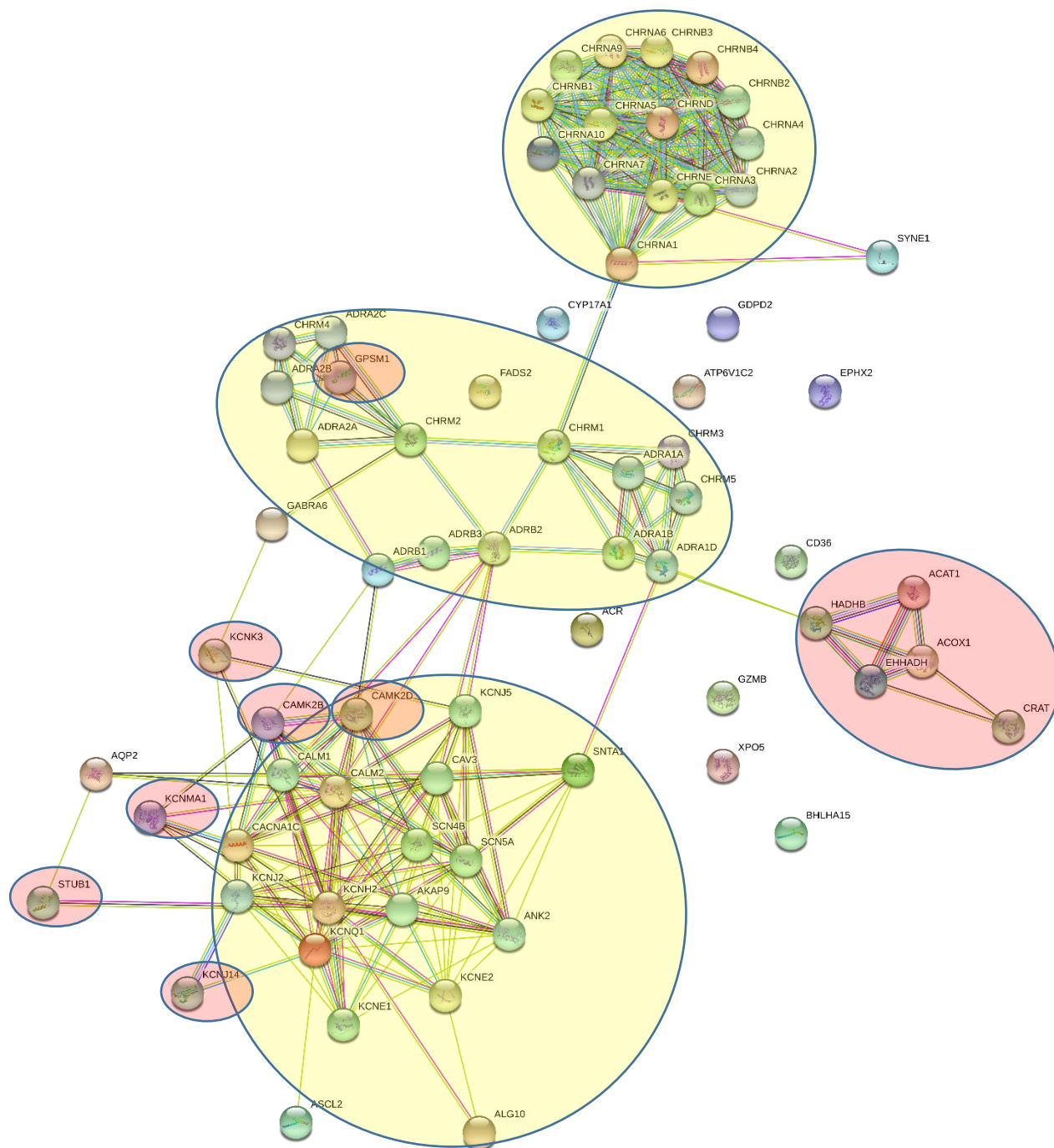
Section 3.3.54.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hydrocarbons

In Figure 66, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom.

FADS2, **EHHADH**, **HADHB**, **ACAT1**, **CRAT**, and **ACOX1** were examples of genes that are associated with fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

GPSM1 is associated with G proteins. Mean expression of GPSM1 was lower in the QT group compared to the NQT group.

KCNJ14, **KCNK3**, and **KCNMA1** are all potassium ion channels which were differentially expressed in this group. Mean expression of all three of these was lower in the QT group compared to the same probes in the NQT group.

CAMK2B and **CAMK2D** are involved with Ca^{2+} ion concentration regulation. Expression of both of these was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.55: Hydrocarbons, Aromatic

Table LXII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hydrocarbons, Aromatic

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
U13253_PROBE1	COL4A1	Collagen type IV alpha 1 chain
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
AB032243_PROBE1	SCD5	Stearoyl-CoA desaturase 5
NM_017135_PROBE1	AK3	Adenylate kinase 3
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
Y00090_PROBE1	SPN	Sialophorin
AW916819_PROBE1	NCKIPSD	NCK interacting protein with SH3 domain
AF110021_PROBE1	AQP2	Aquaporin 2
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2
AA899304_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AW916776_PROBE1	MSRB2	Methionine sulfoxide reductase B2
AF107723_PROBE1	GPSM1	G protein signaling modulator 1
AI233199_PROBE1	FMO5	Flavin containing monooxygenase 5
NM_012519_PROBE1	CAMK2D	Calcium/calmodulin dependent protein kinase II delta
AF057025_PROBE1	TLR4	Toll like receptor 4
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
D88190_PROBE1	STK39	Serine/threonine kinase 39
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
NM_021739_PROBE1	CAMK2B	Calcium/calmodulin dependent protein kinase II beta
D11444_PROBE1	CXCL1	C-X-C motif chemokine ligand 1
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
AI412625_PROBE1	ELMOD1	ELMO domain containing 1
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
AF031384_PROBE1	KCNK3	Potassium two pore domain channel subfamily K member 3
AI411194_PROBE1	PNPLA2	Patatin like phospholipase domain containing 2
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36

Figure 67: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hydrocarbons, Aromatic

Permanent Link: http://bit.ly/2w9zA6e
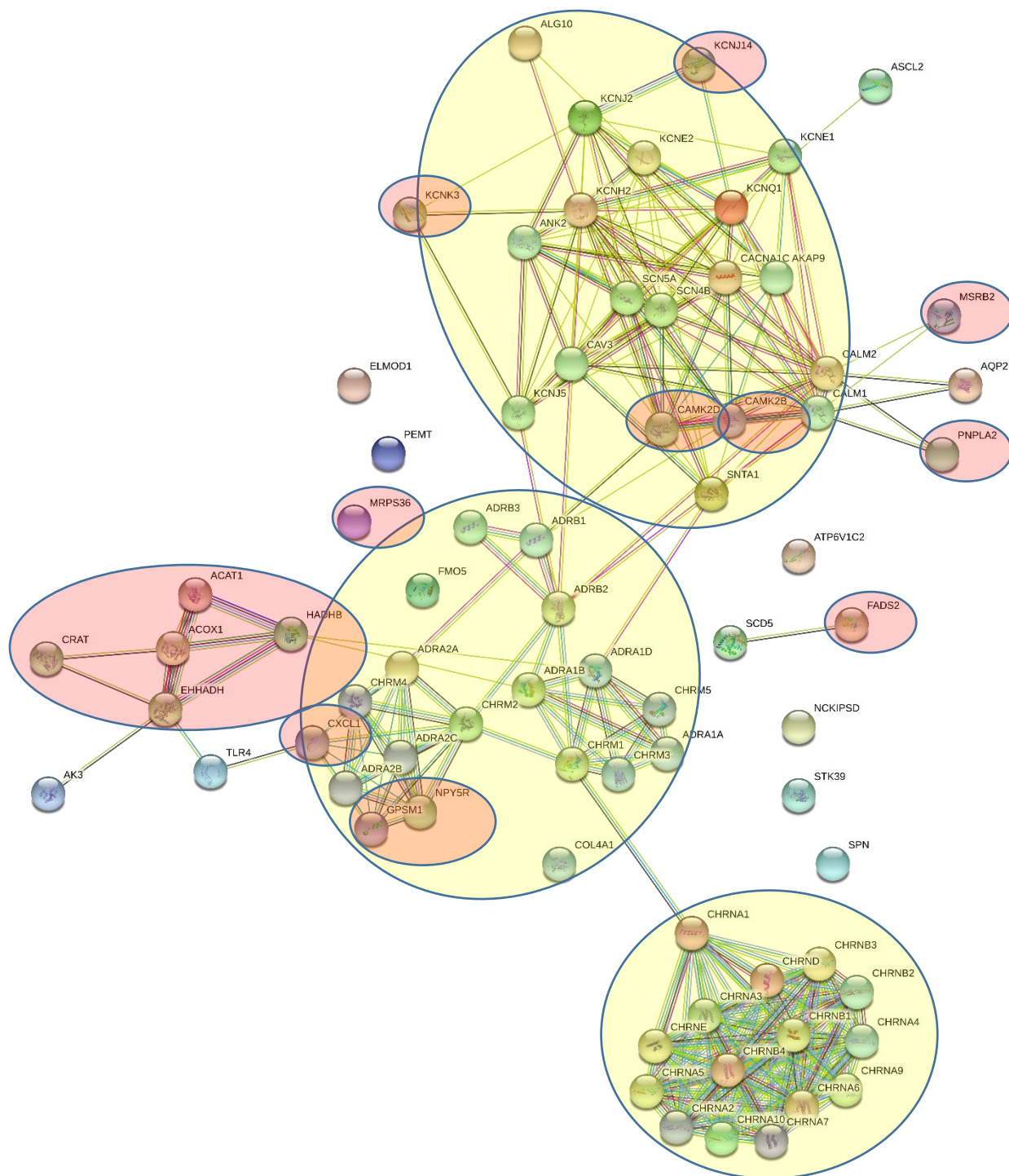
Section 3.3.55.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hydrocarbons, Aromatic

Gin Figure 67, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom.

FADS2, **EHHADH**, **ACAT1**, **ACOX1**, **PMPLA2**, and **CRAT** are examples of proteins associated with fatty acid metabolism. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

KCNJ14 and **KCNK3** are potassium ion channels which were differentially expressed in this group. Mean expression of both of these was lower in the QT group compared to the same probes in the NQT group.

CAMK2D and **CAMK2B** are associated with Ca^{2+} ion concentration modulation. Mean expression for both of these was lower in the QT gropu compared to the same probes in the NQT group.

CXCL11 is associated with T-cell mediated immune responses. Mean expression of CXCL11 was lower in the QT group compared ot the NQT group.

GPSM1 is associated with G protein activity. Mean expression of GPSM1 was lower in the QT group compared to the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was lower in the QT group compared to the NQT group.

MSRB2 is associated with preserving mitochondrial integrity through reduction of reactive oxygen species. Mean expression of MSRB2 was lower in the QT group compared to the NQT group.

Section 3.3.56: Hydrocarbons, Cyclic

Table LXIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hydrocarbons, Cyclic

Probe ID	Gene Symbol	Human Equivalent Gene Name
AB021980_PROBE1	FADS2	Fatty acid desaturase 2
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
BF412111_PROBE1	GDPD2	Glycerophosphodiester phosphodiesterase domain containing 2
K03249_PROBE1	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase
AF110021_PROBE1	AQP2	Aquaporin 2
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2
AF107723_PROBE1	GPSM1	G protein signaling modulator 1
AF031384_PROBE1	KCNK3	Potassium two pore domain channel subfamily K member 3
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
X65083_PROBE1	EPHX2	Epoxide hydrolase 2
D16479_PROBE1	HADHB	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit
NM_021739_PROBE1	CAMK2B	Calcium/calmodulin dependent protein kinase II beta
AA800303_PROBE1	PLSCR3	Phospholipid scramblase 3
NM_012519_PROBE1	CAMK2D	Calcium/calmodulin dependent protein kinase II delta
NM_012490_PROBE1	ACR	Acrosin
NM_019355_PROBE1	SYNE1	Spectrin repeat containing nuclear envelope protein 1
NM_017075_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AA899304_PROBE1	ACAT1	Acetyl-CoA acetyltransferase 1
AI411194_PROBE1	PNPLA2	Patatin like phospholipase domain containing 2
M21208_PROBE1	CYP17A1	Cytochrome P450 family 17 subfamily A member 1
AI411979_PROBE1	CRAT	Carnitine O-acetyltransferase
NM_012863_PROBE1	BHLHA15	Basic helix-loop-helix family member a15
AF111268_PROBE1	CD36	CD36 molecule
BF417292_PROBE1	KCNMA1	Potassium calcium-activated channel subfamily M alpha 1
AA849721_PROBE1	STUB1	STIP1 homology and U-box containing protein 1
AI764464_PROBE1	PHYHIP	Phytanoyl-CoA 2-hydroxylase interacting protein
NM_021841_PROBE1	GABRA6	Gamma-aminobutyric acid type A receptor alpha6 subunit
NM_012891_PROBE1	ACADVL	Acyl-CoA dehydrogenase, very long chain
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
X92069_PROBE1	P2RX5	Purinergic receptor P2X 5
AA817860_PROBE1	ATF7IP	Activating transcription factor 7 interacting protein

Figure 68: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hydrocarbons, Cyclic

Permanent Link: http://bit.ly/2w99Re3
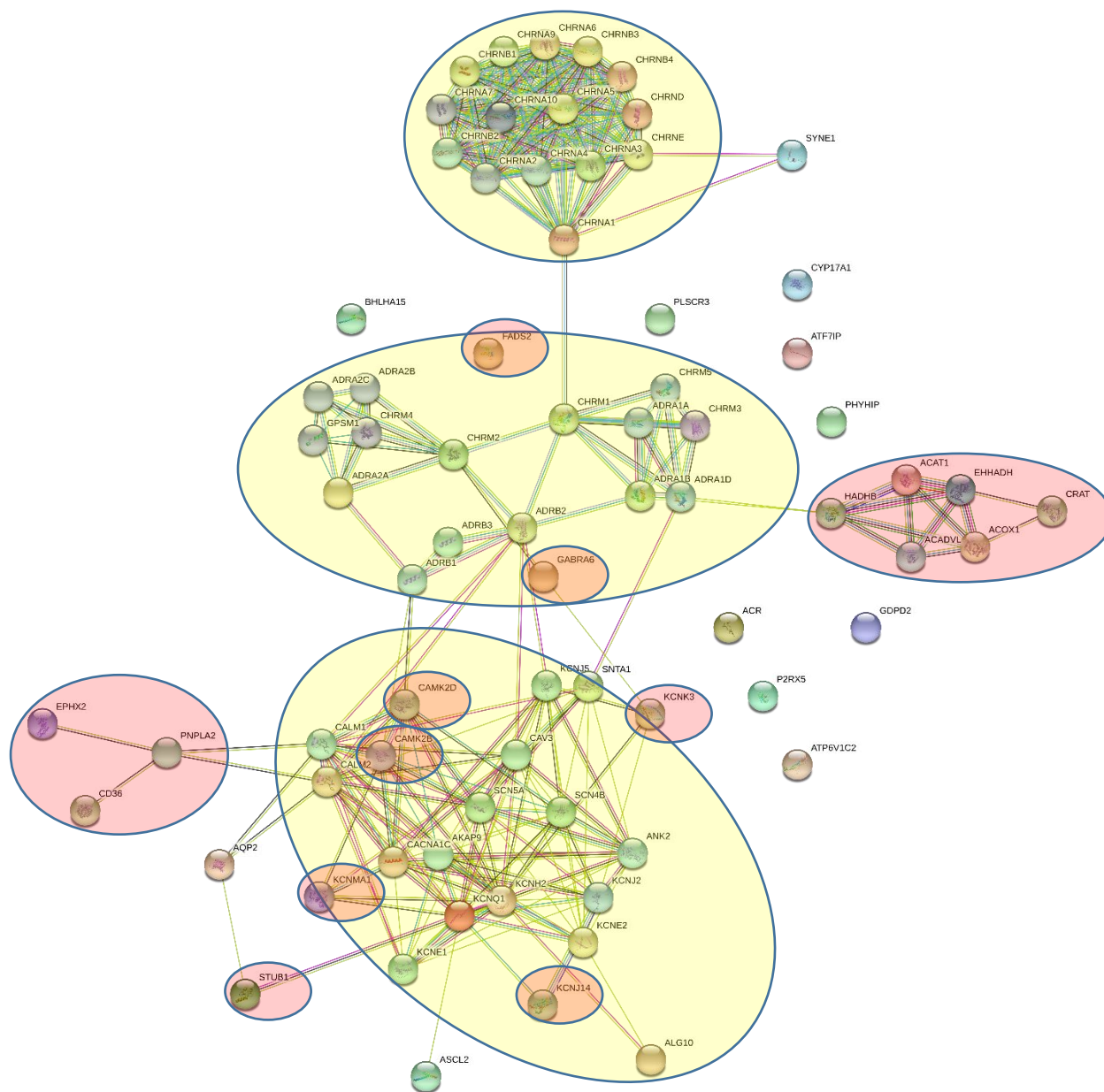
Section 3.3.56.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hydrocarbons, Cyclic

In Figure 68, genes associated with cLQTS are highlighted in yellow at the bottom. Genes associated with the ANS are connected and highlighted yellow at the center and top.

FADS2, **EHHADH**, **HADHB**, **ACOX1**, **ACADVL**, **ACAT1**, **CRAT**, **EPHX2**, and **PNPLA2** are proteins associated with fatty acid metabolism. Mean expression for all of these was lower in the QT group compared to the same probes in the NQT group.

CD36 is associated with fatty acid metabolism, diabetes, and heart disease. Mean expression of CD36 was lower in the QT group compared to the NQT group.

CAMK2B and **CAMK2D** are involved with Ca^{2+} ion concentration modulation. Mean expression for both of these was lower in the QT group compared to the same probes in the NQT group.

KCNJ14, **KCNK3**, are **KCNMA1** all potassium ion channels which were differentially expressed in this group. Mean expression for all three of these was lower in the QT group compared to the same probes in the NQT group.

GPSM1 is associated with G proteins. Mean exposure of GPSM1 was lower in the QT group compared to the NQT group.

STUB1 is associated with immune responses. Mean exposure of STUB1 was lower in the QT group compared to the NQT group.

Section 3.3.57: Hyperglycemia-Associated Agents

Table LXIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hyperglycemia-Associated Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
BE110722_PROBE1	GTF2H3	General transcription factor IIH subunit 3
BE109599_PROBE1	THRAP3	Thyroid hormone receptor associated protein 3
J00696_PROBE1	ORM1	Orosomucoid 1
BF415760_PROBE1	PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2
D13061_PROBE1	AK2	Adenylate kinase 2
NM_012550_PROBE1	EDNRA	Endothelin receptor type A
NM_017116_PROBE1	CAPN2	Calpain 2
U94856_PROBE1	PON1	Paraoxonase 1
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
AF222712_PROBE1	CTBP2	C-terminal binding protein 2
AJ010200_PROBE1	STAU1	Staufen double-stranded RNA binding protein 1
NM_019387_PROBE1	HGS	Hepatocyte growth factor-regulated tyrosine kinase substrate
Z14030_PROBE1	SSR3	Signal sequence receptor subunit 3
NM_016990_PROBE1	ADD1	Adducin 1
X13722_PROBE1	LDLR	Low density lipoprotein receptor
L06482_PROBE1	PRX	Periaxin
NM_021763_PROBE1	ARFIP1	ADP ribosylation factor interacting protein 1
U75409_PROBE1	NUCB1	Nucleobindin 1
AF110267_PROBE1	GORASP2	Golgi reassembly stacking protein 2
BF407480_PROBE1	SMYD2	SET and MYND domain containing 2
AI409841_PROBE1	PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2
Y18208_PROBE1	PPP1R3B	Protein phosphatase 1 regulatory subunit 3B
M29787_PROBE1	ITPKA	Inositol-trisphosphate 3-kinase A
J03808_PROBE1	ACACA	Acetyl-CoA carboxylase alpha
M58716_PROBE1	GP2	Glycoprotein 2
AJ236911_PROBE1	ARHGEF1	Rho guanine nucleotide exchange factor 1
U72353_PROBE1	LMNB1	Lamin B1
X77237_PROBE1	PPP5C	protein phosphatase 5 catalytic subunit
AF181992_PROBE1	DYNC1LI1	Dynein cytoplasmic 1 light intermediate chain 1
NM_012738_PROBE1	APOA1	Apolipoprotein A1
NM_012790_PROBE1	DSPP	Dentin sialophosphoprotein
NM_019140_PROBE1	PTPRD	Protein tyrosine phosphatase, receptor type D
AF139055_PROBE1	MYH10	Myosin heavy chain 10
AJ002942_PROBE1	RARB	Retinoic acid receptor beta
AI070123_PROBE1	SLURP1	Secreted LY6/PLAUR domain containing 1
BF419646_PROBE1	RARB	Retinoic acid receptor beta
NM_013064_PROBE1	HCRTR1	Hypocretin receptor 1
BE109057_PROBE1	DCX	Doublecortin
AW921151_PROBE1	NHP2	NHP2 ribonucleoprotein
AI171617_PROBE1	DUSP22	Dual specificity phosphatase 22
AW526136_PROBE1	HDAC5	Histone deacetylase 5
U40188_PROBE1	TAF9B	TATA-box binding protein associated factor 9b

Figure 69: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hyperglycemia-Associated Agents
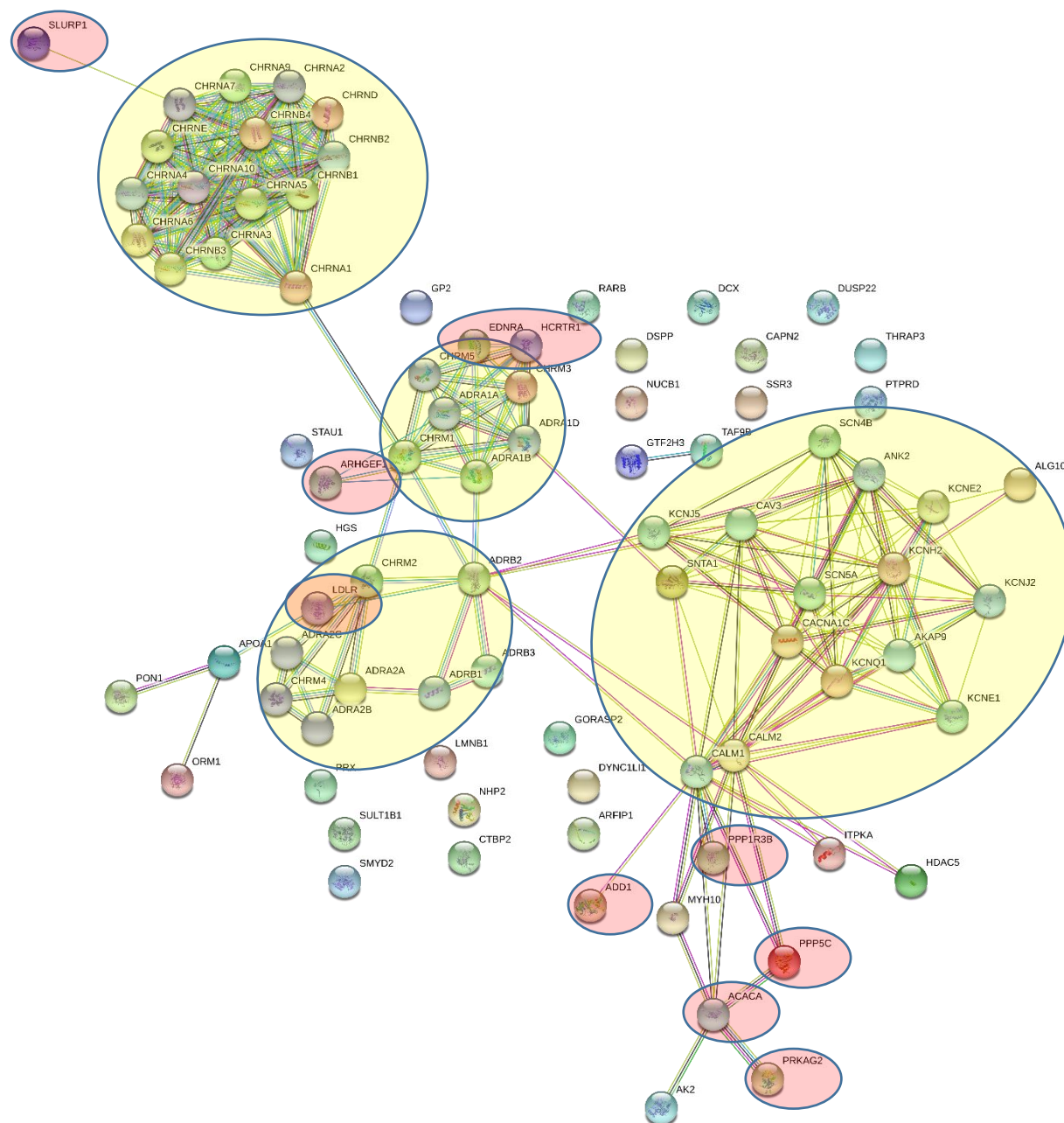
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000454071%250D9606.ENSP00000225983%250D9606.ENSP00000345281%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000346921%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000265044%250D9606.ENSP00000287878%250D9606.ENSP00000250699%250D9606.ENSP00000331201%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000263273%250D9606.ENSP00000355924%250D9606.ENSP00000306490%250D9606.ENSP00000315011%250D9606.ENSP00000266376%250D9606.ENSP00000370767%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000273130%250D9606.ENSP00000385026%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000236850%250D9606.ENSP00000386069%250D9606.ENSP00000319984%250D9606.ENSP00000269243%250D9606.ENSP00000261751%250D9606.ENSP00000261366%250D9606.ENSP00000222381%250D9606.ENSP00000308770%250D9606.ENSP00000346634%250D9606.ENSP00000349588%250D9606.ENSP00000344789%250D9606.ENSP00000362810%250D9606.ENSP00000246515%250D9606.ENSP00000368766%250D9606.ENSP00000295006%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000326018%250D9606.ENSP00000357461%250D9606.ENSP00000337697%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000296557%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000322460%250D9606.ENSP00000358301%250D9606.ENSP00000243457%250D9606.ENSP00000341940%250D9606.ENSP00000274606%250D9606.ENSP00000337255%250D9606.ENSP00000282478%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000308318%250D9606.ENSP00000360922%250D9606.ENSP00000234160%250D9606.ENSP00000348812%250D9606.ENSP00000260386%250D9606.ENSP00000339917%250D9606.ENSP00000293780%250D9606.ENSP00000264758%250D9606.ENSP00000445162%250D9606.ENSP00000337261%250D9606.ENSP00000332296%250D9606.ENSP00000306662%250D9606.ENSP00000259396%250D9606.ENSP00000012443%250D9606.ENSP00000311825%250D9606.ENSP00000348573

Section 3.3.57.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hyperglycemia-Associated Agents

In Figure 69, genes associated with cLQTS are highlighted in yellow at the bottom right. Genes associated with the ANS are connected and highlighted yellow in the two clusters at the center and the one cluster at the top.

PPP1R3B is associated with glycogen metabolism and diabetes. Mean expression of PP1R3B was lower in the QT group compared to the NQT group.

PPP5C is associated with MAPK activity. Mean expression of PPP5C was lower in the QT group compared to the NQT group.

LDLR and **ACACA** are associated with lipid and fatty acid metabolism. Mean expression for both of these was lower in the QT group compared to the NQT group.

ARHGEF1 is associated with G proteins. Mean expression of ARHGEF1 was lower in the QT group compared to the NQT group.

222

ENDRA is associated with G proteins and a Ca^{2+} second messenger system. Mean expression of ENDRA was lower in the QT group compared to the NQT group.

PRKAG2 mutations have been associated with ventricular preexcitation, progressive cardiac conduction system disease and cardiac hypertrophy. Mean expression of PRKAG2 was lower in the QT group compared to the NQT group.

SLURP1 is associated with Ca^{2+} regulation in T cells, suggesting a possible link to the immune system. Mean expression of SLURP1 was lower in the QT group compared to the NQT group.

HCRTR1 is associated with cytoplasmic Ca^{2+} release. Mean exposure of HCTR1 was lower in the QT gropu compared to the NQT group.

Section 3.3.58: Hypotensive Agents

Table LXV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Hypotensive Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
AJ011607_PROBE1	PRIM2	DNA primase subunit 2
BE109599_PROBE1	THRAP3	Thyroid hormone receptor associated protein 3
X74835_PROBE1	CHRND	Cholinergic receptor nicotinic delta subunit
AF030243_PROBE1	IL3RA	Interleukin 3 receptor subunit alpha
NM_017010_PROBE1	GRIN1	Glutamate ionotropic receptor NMDA type subunit 1
BF284878_PROBE1	TMEM69	Transmembrane protein 69
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
U75405_PROBE1	COL1A1	Collagen type I alpha 1 chain
AF148210_PROBE1	RAB6A	RAB6A, member RAS oncogene family
U16858_PROBE1	TES	Testin LIM domain protein
BF551318_PROBE1	HERC4	HECT and RLD domain containing E3 ubiquitin protein ligase 4
AA944079_PROBE1	ADAM8	ADAM metallopeptidase domain 8
L29259_PROBE1	ELOC	Elongin C
U08290_PROBE1	NNAT	Neuronatin
X94186_PROBE1	DUSP7	Dual specificity phosphatase 7
AF235993_PROBE1	BAX	BCL2 associated X, apoptosis regulator
AW921151_PROBE1	NHP2	NHP2 ribonucleoprotein
AJ011608_PROBE1	PRIM1	DNA primase subunit 1
X96394_PROBE1	ABCC1	ATP binding cassette subfamily C member 1
AF029757_PROBE1	SLC11A2	Solute carrier family 11 member 2
U89282_PROBE1	TEP1	Telomerase associated protein 1
M86705_PROBE1	ARF4	ADP ribosylation factor 4
BE108396_PROBE1	CNOT9	CCR4-NOT transcription complex subunit 9
NM_017327_PROBE1	GNAO1	G protein subunit alpha o1
NM_019179_PROBE1	TYMS	Thymidylate synthetase
U12309_PROBE1	ITGB1	Integrin subunit beta 1
U21954_PROBE1	EPHA7	EPH receptor A7
AI060118_PROBE1	NDST2	N-deacetylase and N-sulfotransferase 2
AI011704_PROBE1	CASC4	Cancer susceptibility 4
BE329061_PROBE1	UQCRC2	Ubiquinol-cytochrome c reductase core protein II
BF287209_PROBE1	POP4	POP4 homolog, ribonuclease P/MRP subunit
NM_017000_PROBE1	NQO1	NAD(P)H quinone dehydrogenase 1
AF177477_PROBE1	CDK5RAP1	CDK5 regulatory subunit associated protein 1
D49977_PROBE1	NUDT1	Nudix hydrolase 1

Figure 70: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Hypotensive Agents

Permanent Link: http://bit.ly/2xoFWNF
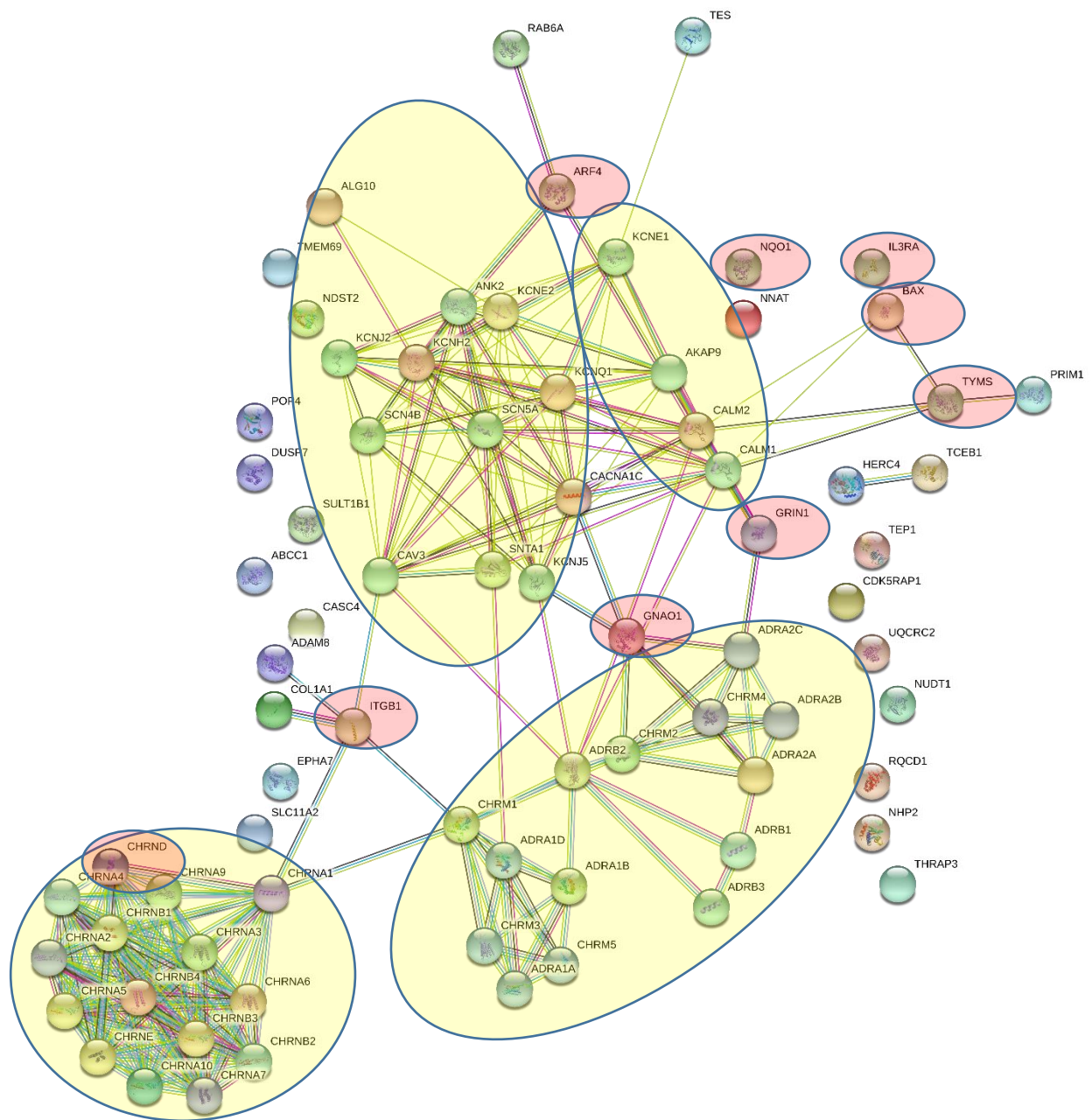
Section 3.3.58.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Hypotensive Agents

In Figure 70, genes associated with cLQTS are highlighted in yellow at the bottom right. Genes associated with the ANS are connected and highlighted yellow in the two clusters at the center and the one cluster at the top.

GNAO1 and **ARF4** are associated with G proteins. Mean expression for both of these was lower in the QT group compared to the same probes in the NQT group.

IL3RA and **BAX** are associated witdh immune responses and apoptosis. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

GRIN1 is glutamate receptor that may be linked to glutathione. Mean expression of GRIN1 was lower in the QT group compared to the NQT group.

NQO1 is associated with electron transport. Mean expression of NQO1 was lower in the QT group compared to the NQT group.

TYMS is involved with mitochondrial metabolism. Mean expression of TYMS was lower in the QT group compared to the NQT group.

CHRND is a nicotinic cholinergic autonomic nervous system receptor which was differentially expressed in this group. Mean expression of CHRND was lower in the QT group compared to the NQT group.

Section 3.3.59: Imidazole Derivatives

Table LXVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Imidazole Derivatives

Probe ID	Gene Symbol	Human Equivalent Gene Name
AA946470_PROBE1	IPO11	Importin 11
AI180187_PROBE1	NET1	Neuroepithelial cell transforming 1
BF282395_PROBE1	VPS26A	VPS26, retromer complex component A

Figure 71: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Imidazole Derivatives
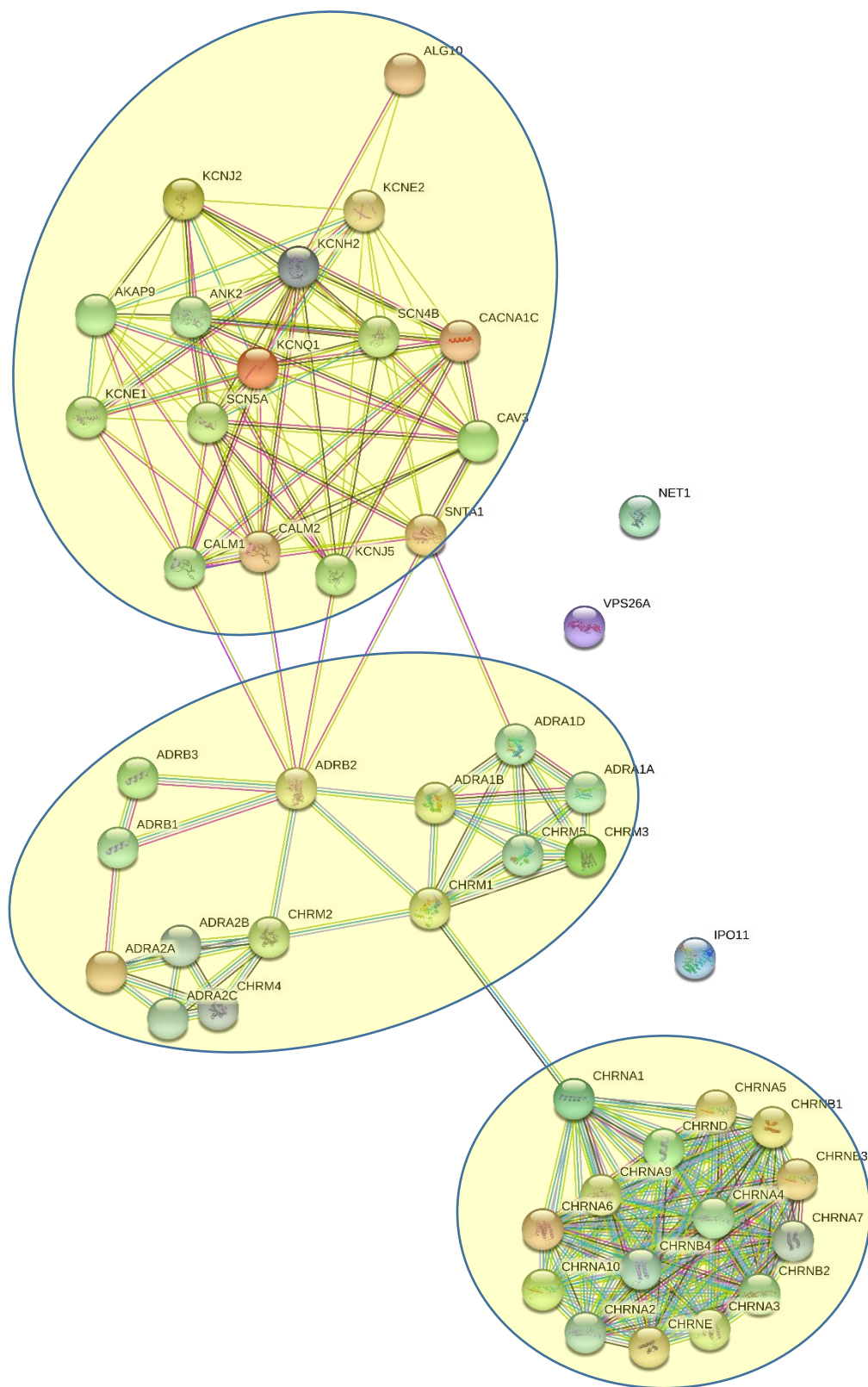
Permanent Link:

Section 3.3.59.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Imidazole Derivatives

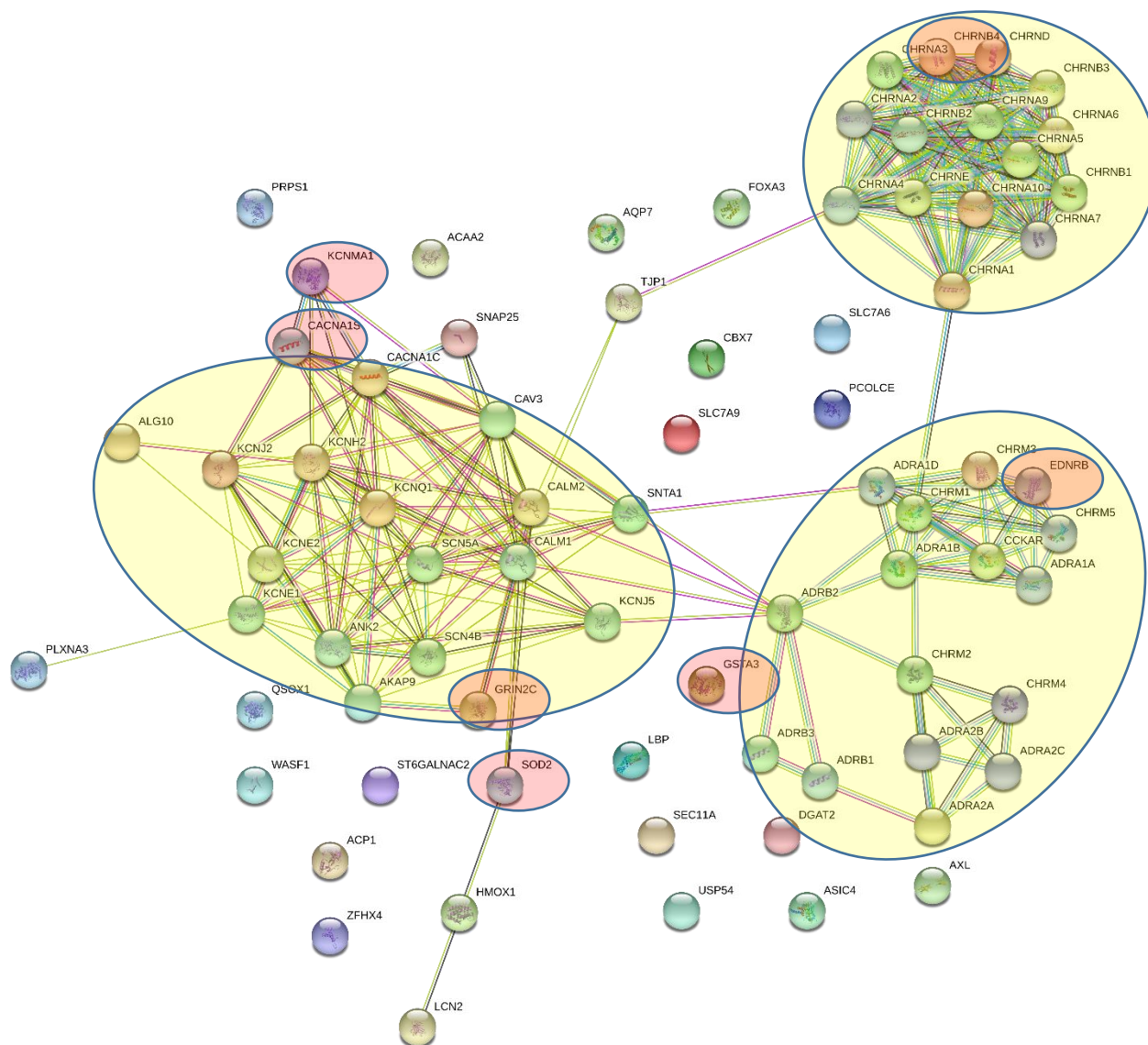In Figure 71, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom. There was an insufficient number of differentially expressed genes to generate a meaningful String model for this class.

Section 3.3.60: Inorganic Chemicals

Table LXVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Inorganic Chemicals

Probe ID	Gene Symbol	Human Equivalent Gene Name
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
D10233_PROBE1	RENBP	Renin binding protein
NM_017187_PROBE1	HMGB2	High mobility group box 2
BE115417_PROBE1	MTA2	Metastasis associated 1 family member 2
BF398680_PROBE1	MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
M18467_PROBE1	GOT2	Glutamic-oxaloacetic transaminase 2
U10894_PROBE1	AIF1	Allograft inflammatory factor 1
L09653_PROBE1	TGFBR2	Transforming growth factor beta receptor 2
AA850509_PROBE1	TRIP13	Thyroid hormone receptor interactor 13
AW253880_PROBE1	KIFC1	Kinesin family member C1
BE113076_PROBE1	NFATC4	Nuclear factor of activated T-cells 4
AI233916_PROBE1	HLTF	Helicase like transcription factor
BF281149_PROBE1	DLGAP5	DLG associated protein 5
D63834_PROBE1	SLC16A1	Solute carrier family 16 member 1
AA963234_PROBE1	TUBE1	Tubulin epsilon 1
AB033418_PROBE1	SLC2A8	Solute carrier family 2 member 8
NM_019179_PROBE1	TYMS	Thymidylate synthetase
L13722_PROBE1	CHM	CHM, Rab escort protein 1
U02315_PROBE1	NRG1	Neuregulin 1
U45986_PROBE1	MXD3	MAX dimerization protein 3
BF416285_PROBE1	ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif 9
BF566580_PROBE1	FANCD2	Fanconi anemia complementation group D2
AI101475_PROBE1	DCTPP1	dCTP pyrophosphatase 1
M22323_PROBE1	ACTA2	Actin, alpha 2, smooth muscle, aorta
U89282_PROBE1	TEP1	Telomerase associated protein 1
AI603128_PROBE1	CCNA2	Cyclin A2
AA892918_PROBE1	TJP1	Tight junction protein 1
AF276774_PROBE1	LIG1	DNA ligase 1
AI598467_PROBE1	CDCA8	Cell division cycle associated 8
U38376_PROBE1	PLA2G4A	Phospholipase A2 group IVA
U69550_PROBE1	PLD1	Phospholipase D1
NM_012627_PROBE1	PKIB	cAMP-dependent protein kinase inhibitor beta
NM_012964_PROBE1	HMMR	Hyaluronan mediated motility receptor
BF522212_PROBE1	SLC35B2	Solute carrier family 35 member B2
AF335281_PROBE1	STEAP3	STEAP3 metalloreductase
M69246_PROBE1	SERPINH1	Serpin family H member 1
AW914045_PROBE1	EPS8L2	EPS8 like 2
M64300_PROBE1	MAPK1	Mitogen-activated protein kinase 1

Figure 72: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Inorganic Chemicals

Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000346227%250D9606.ENSP00000296503%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D9606.ENSP00000320828%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000401867%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000351905%250D9606.ENSP00000365227%250D9606.ENSP00000250699%250D9606.ENSP00000355192%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000287647%250D9606.ENSP00000349275%250D9606.ENSP00000166345%250D9606.ENSP00000393963%250D9606.ENSP00000274026%250D9606.ENSP00000306490%250D9606.ENSP00000357651%250D9606.ENSP00000377401%250D9606.ENSP00000266376%250D9606.ENSP00000362469%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000350386%250D9606.ENSP00000385026%250D9606.ENSP00000263274%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000356436%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000376822%250D9606.ENSP00000224784%250D9606.ENSP00000314363%250D9606.ENSP00000377492%250D9606.ENSP00000319984%250D9606.ENSP00000215832%250D9606.ENSP00000261751%250D9606.ENSP00000281537%250D9606.ENSP00000308770%250D9606.ENSP00000349588%250D9606.ENSP00000350894%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000245206%250D9606.ENSP00000357461%250D9606.ENSP00000262715%250D9606.ENSP00000315644%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000322524%250D9606.ENSP00000315602%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000388910%250D9606.ENSP00000341940%250D9606.ENSP00000342793%250D9606.ENSP00000337255%250D9606.ENSP00000316121%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000358640%250D9606.ENSP00000377303%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000308944%250D9606.ENSP00000278823%250D9606.ENSP00000293780%250D9606.ENSP00000247191%250D9606.ENSP00000306662%250D9606.ENSP00000418735%250D9606.ENSP00000348573

Section 3.3.60.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Inorganic Chemicals

In Figure 72, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the center right and at the bottom.

MAP4K4, **MAPK1**, and **NRG1** are associated with MAPKs. Mean expression for all three of these was lower in the QT group compared to the same probes in the NQT group.

CACNA1S is a Ca^{2+} channel which was differentially expressed in this group. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

NFATC4 and **PLA2G4A** are associated with immune and inflammatory responses. Mean expression for both of these was lower in the QT group compared to the same probes in the NQT group.

TYMS1 is associated with mitochondrial metabolism. Mean expression of TYMS1 was lower in the QT group compared to the NQT group.

SLC2A8 is associated with glucose transport, which might suggest a potential link to diabetes. Mean expression of SLC2A8 was lower in the QT group compared to the NQT group.

Section 3.3.61: Nervous System

Table LXVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Nervous System

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF111160_PROBE1	MAPK1	Mitogen-activated protein kinase 1
AF187065_PROBE1	BEX3	Brain expressed X-linked 3
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
AA859768_PROBE1	MCM5	Minichromosome maintenance complex component 5
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
NM_019157_PROBE1	AQP7	Aquaporin 7
X98490_PROBE1	RPA2	Replication protein A2
AA851306_PROBE1	HMGN3	High mobility group nucleosomal binding domain 3
BE108837_PROBE1	CENPE	Centromere protein E
AA963234_PROBE1	TUBE1	Tubulin epsilon 1
AI556458_PROBE1	TACC3	Transforming acidic coiled-coil containing protein 3
BF398424_PROBE1	CD276	CD276 molecule
AA891839_PROBE1	MRPL50	Mitochondrial ribosomal protein L50
L11002_PROBE1	NFASC	Neurofascin
J05029_PROBE1	ACADL	Aacyl-CoA dehydrogenase, long chain
AI408960_PROBE1	PITRM1	Pitrilysin metallopeptidase 1
BF551349_PROBE1	TRPC2	Transient receptor potential cation channel subfamily C member 2, pseudogene
J02646_PROBE1	EIF2S1	Eukaryotic translation initiation factor 2 subunit alpha
NM_017305_PROBE1	GCLM	Glutamate-cysteine ligase modifier subunit
NM_019144_PROBE1	ACP5	Acid phosphatase 5, tartrate resistant
U63111_PROBE1	DSPP	Dentin sialophosphoprotein
X54862_PROBE1	MGMT	O-6-methylguanine-DNA methyltransferase
D30035_PROBE1	PRDX1	Peroxiredoxin 1
AJ011607_PROBE1	PRIM2	DNA primase subunit 2
AW526673_PROBE1	SAP130	Sin3A associated protein 130
NM_013226_PROBE1	RPL32	Ribosomal protein L32
NM_019179_PROBE1	TYMS	Thymidylate synthetase
AW252871_PROBE1	MKI67	Marker of proliferation Ki-67
BF282271_PROBE1	PNPT1	Polyribonucleotide nucleotidyltransferase 1
L20900_PROBE1	ICA1	Islet cell autoantigen 1
BE104266_PROBE1	KNTC1	Kinetochore associated 1

Figure 73: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Nervous System

Permanent Link: http://bit.ly/2xouSQA
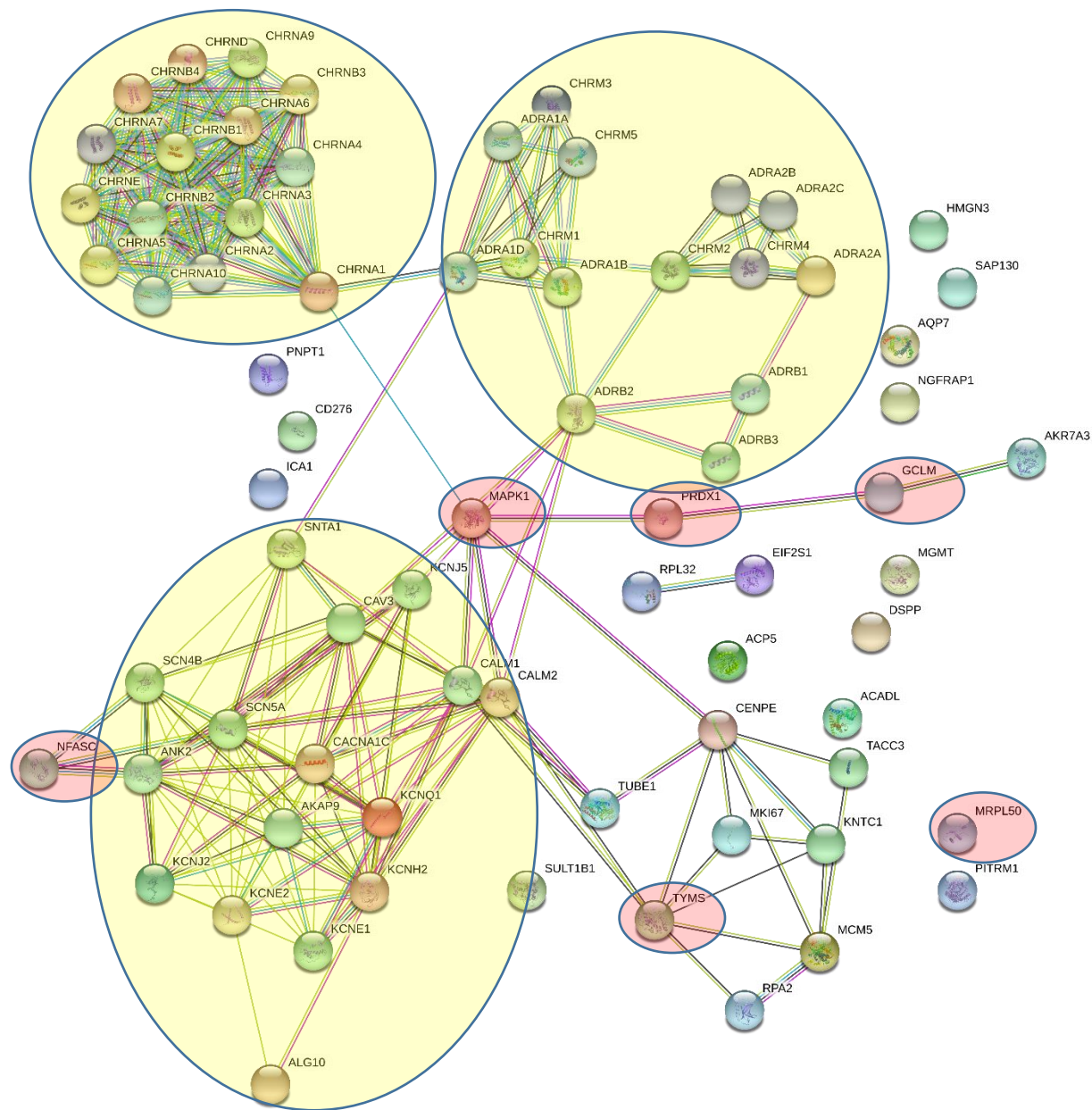
Section 3.3.61.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Nervous System

In Figure 73, genes associated with cLQTS are highlighted in yellow at the bottom. Genes associated with the ANS are connected and highlighted yellow at the top left and top right.

MAPK1 is associated with MAPKs. Mean expression of MAPK1 was lower in the QT group compared to the NQT group.

MRPL50 is a mitochondrial ribosomal protein. Mean expression of MRPL50 was lower in the QT group compared to the NQT group.

TYMS1 is associated with mitochondrial metabolism. Mean expression of TYMS1 was lower in the QT group compared to the NQT group.

GCLM is associated with glutamate and by extension possibly glutathione. Mean expression of GCLM was lower in the QT group compared to the NQT group.

PRDX1 is associated with electron transfer in peroxides. Mean expression of PRDX1 was lower in the QT group compared to the NQT group.

Section 3.3.62: Neurotransmitter Agents

Table LXIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Neurotransmitter Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
X68199_PROBE1	MYO1B	Myosin IB
AI412230_PROBE1	CRYZL1	Crystallin zeta like 1
NM_019157_PROBE1	AQP7	Aquaporin 7
AI598648_PROBE1	IPMK	Inositol polyphosphate multikinase
AW916474_PROBE1	CHD1L	Chromodomain helicase DNA binding protein 1 like
BE113398_PROBE1	KIFC3	Kinesin family member C3
AF016387_PROBE1	RXRG	Retinoid X receptor gamma
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
NM_017020_PROBE1	IL6R	Interleukin 6 receptor
NM_021850_PROBE1	BCL2L2	BCL2 like 2
AI105186_PROBE1	SLC39A8	Solute carrier family 39 member 8
AI234858_PROBE1	SF3B3	Splicing factor 3b subunit 3
X90710_PROBE1	ADH4	Alcohol dehydrogenase 4 (class II), pi polypeptide
AF235993_PROBE1	BAX	BCL2 associated X, apoptosis regulator
BE108396_PROBE1	CNOT9	CCR4-NOT transcription complex subunit 9
BF408285_PROBE1	BAIAP2	BAI1 associated protein 2
D29969_PROBE1	PTGER3	Prostaglandin E receptor 3
M85299_PROBE1	SLC9A1	Solute carrier family 9 member A1
NM_013215_PROBE1	AKR7A3	Aldo-keto reductase family 7 member A3
AF177477_PROBE1	CDK5RAP1	CDK5 regulatory subunit associated protein 1
BF283053_PROBE1	ATP6V1C2	ATPase H+ transporting V1 subunit C2
X71873_PROBE1	PEBP1	Phosphatidylethanolamine binding protein 1
AI598486_PROBE1	DPYSL3	Dihydropyrimidinase like 3
L22191_PROBE1	GCLM	Glutamate-cysteine ligase modifier subunit
L02121_PROBE1	CDK5	Cyclin dependent kinase 5
M69246_PROBE1	SERPINH1	Serpin family H member 1
AW918640_PROBE1	IVNS1ABP	Influenza virus NS1A binding protein
AI231776_PROBE1	NUDT21	Nudix hydrolase 21
AJ223083_PROBE1	RXRG	Retinoid X receptor gamma

Figure 74: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Neurotransmitter Agents

Permanent Link: http://bit.ly/2xoNhNo
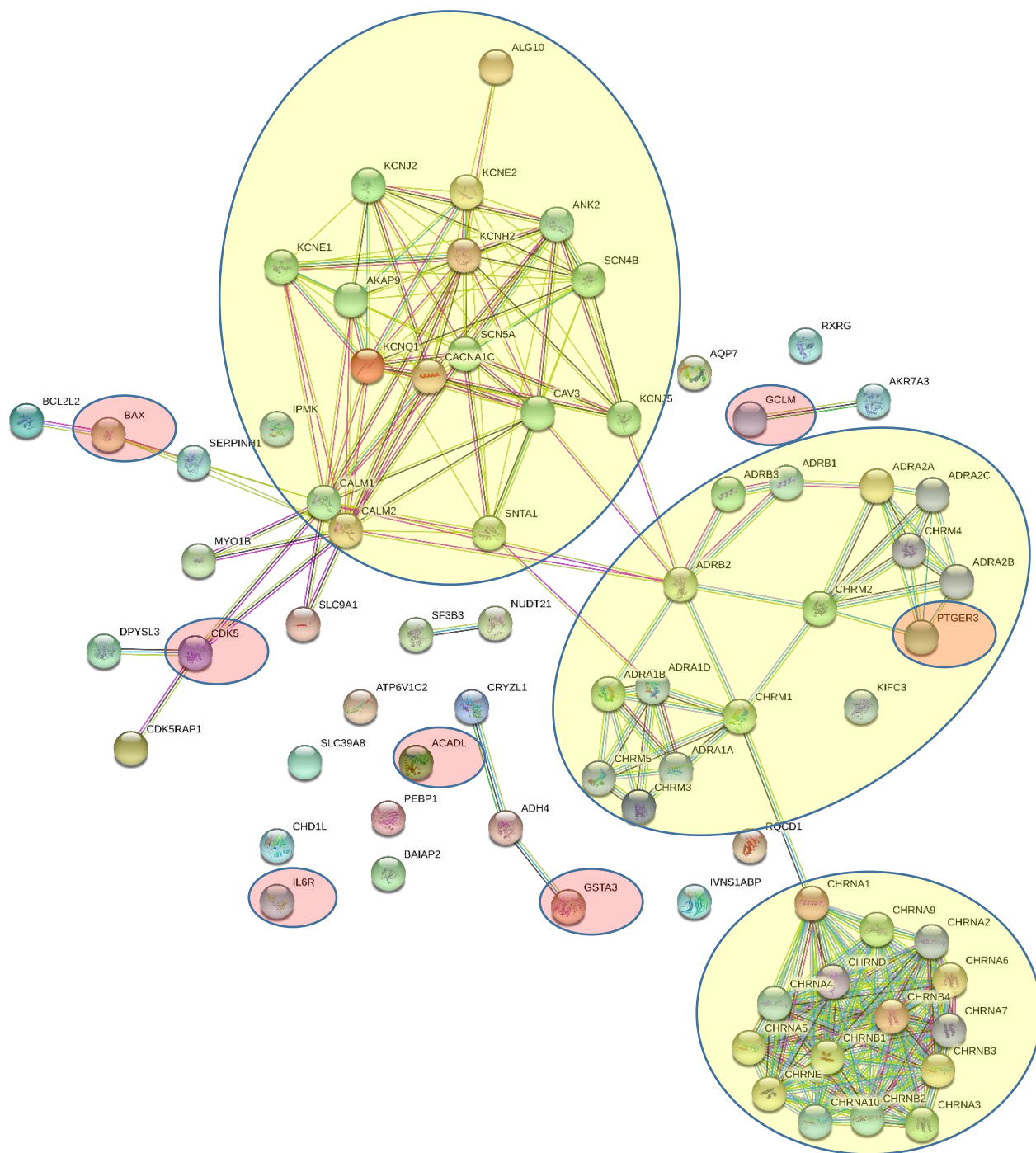
Section 3.3.62.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Neurotransmitter Agents

In Figure 74, genes associated with cLQTS are highlighted in yellow at the top center. Genes associated with the ANS are connected and highlighted yellow at the center right and bottom right.

GSTA3 and GCLM are assocated with glutamate and glutathione. Mean expression of GSTA3 was lower in the QT group compared to the NQT group.

ACADL is associated with fatty acid metabolism in the mitochondria. Mean expression of ACADL was lower in the QT group compared to the NQT group.

IL6R is an immunoglobulin receptor suggesting an association with immune responses. Mean expression of IL6R was higher in the QT group compared to the NQT group.

BAX is associated with apoptosis and **CDK5** may be involved with apoptosis. Mean expression of both BAX and CDK5 was lower in the QT group compared to the NQT group.

Section 3.3.63: Ophthalmologicals

Table LXX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Ophthalmologicals

Probe ID	Gene Symbol	Human Equivalent Gene Name
M76591_PROBE1	PGAM1	Phosphoglycerate mutase 1
AA819871_PROBE1	CDC16	Cell division cycle 16
AW521367_PROBE1	WDR41	WD repeat domain 41
AA799981_PROBE1	PRKCH	Protein kinase C eta
AW143101_PROBE1	SNAP29	Synaptosome associated protein 29
BF390910_PROBE1	DNAJB5	DnaJ heat shock protein family (Hsp40) member B5
BF548006_PROBE1	ANAPC1	Anaphase promoting complex subunit 1
NM_012919_PROBE1	CACNA2D1	Calcium voltage-gated channel auxiliary subunit alpha2delta 1
AA944451_PROBE1	OTUB1	OTU deubiquitinase, ubiquitin aldehyde binding 1
AI177590_PROBE1	COG4	Component of oligomeric Golgi complex 4
AF061442_PROBE1	CYP2E1	Cytochrome P450 family 2 subfamily E member 1
AA858518_PROBE1	RNF7	Ring finger protein 7
AI408517_PROBE1	PPP1R14B	Protein phosphatase 1 regulatory inhibitor subunit 14B
AI406533_PROBE1	CHSY1	Chondroitin sulfate synthase 1
NM_017283_PROBE1	PSMA6	Proteasome subunit alpha 6
BF418630_PROBE1	LRRFIP1	LRR binding FLII interacting protein 1
AF255305_PROBE1	CCS	Copper chaperone for superoxide dismutase
AI171242_PROBE1	TBC1D7	TBC1 domain family member 7
U91539_PROBE1	GOSR2	Golgi SNAP receptor complex member 2
BE109531_PROBE1	IFI35	Interferon induced protein 35
AA946349_PROBE1	NUDT3	Nudix hydrolase 3
NM_017035_PROBE1	PLCD1	Phospholipase C delta 1
U69702_PROBE1	ACVR1C	Activin A receptor type 1C
AF025424_PROBE1	POLR1B	RNA polymerase I subunit B
AW918535_PROBE1	PRKAR2A	Protein kinase cAMP-dependent type II regulatory subunit alpha
AW916776_PROBE1	MSRB2	Methionine sulfoxide reductase B2
BE329347_PROBE1	SSR2	Signal sequence receptor subunit 2
AI233133_PROBE1	MRPS7	Mitochondrial ribosomal protein S7
AI179993_PROBE1	PAXIP1	PAX interacting protein 1
AW921546_PROBE1	TMED7	Transmembrane p24 trafficking protein 7

Figure 75: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Ophthalmologicals
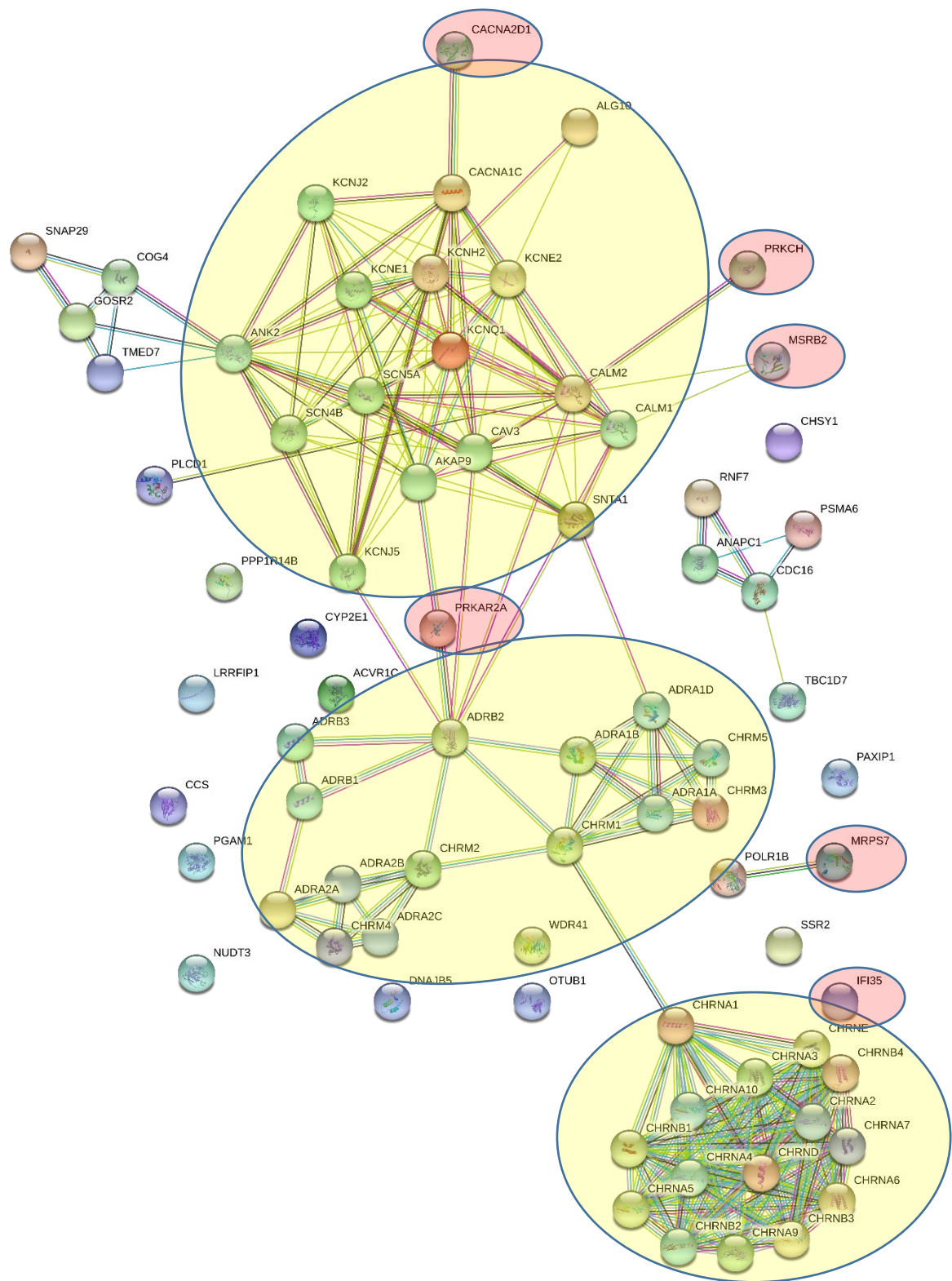
Section 3.3.63.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Ophthalmologicals

In Figure 75, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom right.

PRKAR2A is a protein kinase which is mediated by cAMP, which is a common second messenger. Mean expression of PRKAR2A was higher in the QT group compared to the NQT group.

CACNA2D1 is a Ca^{2+} ion channel which was differentially expressed in this group. Mean expression of CACNA2D1 was lower in the QT group compared to the NQT group.

IFI35 is associated with interferon which is part of an immune response. Mean expression of IFI35 was higher in the QT group compared to the NQT group.

PRKCH is associated with apoptosis. Mean expression of PRKCH was lower in the QT group compared to the NQT group.

MRPS7 is a mitochondrial ribosomal protein. Mean expression of MRPS7 was lower in the QT group compared to the NQT group.

MSRB2 is associated with preservation of mitochondrial integrity by reducing reactive oxygen species. Mean expression of MSRB2 was lower in the QT group compared to the NQT group.

Section 3.3.64: Peripheral Nervous System Agents

Table LXXI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Peripheral Nervous System Agents

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW141928_PROBE1	VNN1	Vanin 1
X65083_PROBE1	EPHX2	Epoxide hydrolase 2
AA800587_PROBE1	GPX2	Glutathione peroxidase 2
J00696_PROBE1	ORM1	Orosomucoid 1
M84203_PROBE1	KCNC2	Potassium voltage-gated channel subfamily C member 2
NM_017208_PROBE1	LBP	Lipopolysaccharide binding protein
U40628_PROBE1	NOL3	Nucleolar protein 3
AW915685_PROBE1	FKBP11	FK506 binding protein 11
U42976_PROBE1	CHRNB4	Cholinergic receptor nicotinic beta 4 subunit
U63111_PROBE1	DSPP	Dentin sialophosphoprotein
AF178974_PROBE1	DNASE2B	Deoxyribonuclease 2 beta
X13295_PROBE1	LCN2	Lipocalin 2
L02530_PROBE1	FZD2	Frizzled class receptor 2
U05014_PROBE1	EIF4EBP1	Eukaryotic translation initiation factor 4E binding protein 1
L18948_PROBE1	S100A9	S100 calcium binding protein A9
U52948_PROBE1	C9	Complement C9
U67136_PROBE1	AKAP5	A-kinase anchoring protein 5
AI105154_PROBE1	OGFRL1	Opioid growth factor receptor like 1
X74835_PROBE1	CHRND	Cholinergic receptor nicotinic delta subunit
NM_019341_PROBE1	RGS5	Regulator of G protein signaling 5
AF223642_PROBE1	CXCR3	C-X-C motif chemokine receptor 3
Y00497_PROBE1	SOD2	Superoxide dismutase 2
AW914408_PROBE1	PCK2	Phosphoenolpyruvate carboxykinase 2, mitochondrial
AB017260_PROBE1	SLC22A5	Solute carrier family 22 member 5
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
AA892897_PROBE1	PLOD2	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2
AJ242554_PROBE1	ASIC4	Acid sensing ion channel subunit family member 4
D28508_PROBE1	JAK3	Janus kinase 3
NM_012580_PROBE1	HMOX1	Heme oxygenase 1
NM_019237_PROBE1	PCOLCE	Procollagen C-endopeptidase enhancer
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
X97121_PROBE1	NTSR2	Neurotensin receptor 2
NM_017260_PROBE1	ALOX5AP	Arachidonate 5-lipoxygenase activating protein
U07201_PROBE1	ASNS	Asparagine synthetase (glutamine-hydrolyzing)
NM_012532_PROBE1	CP	Ceruloplasmin
U66470_PROBE1	CGREF1	Cell growth regulator with EF-hand domain 1

Figure 76: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Peripheral Nervous System Agents
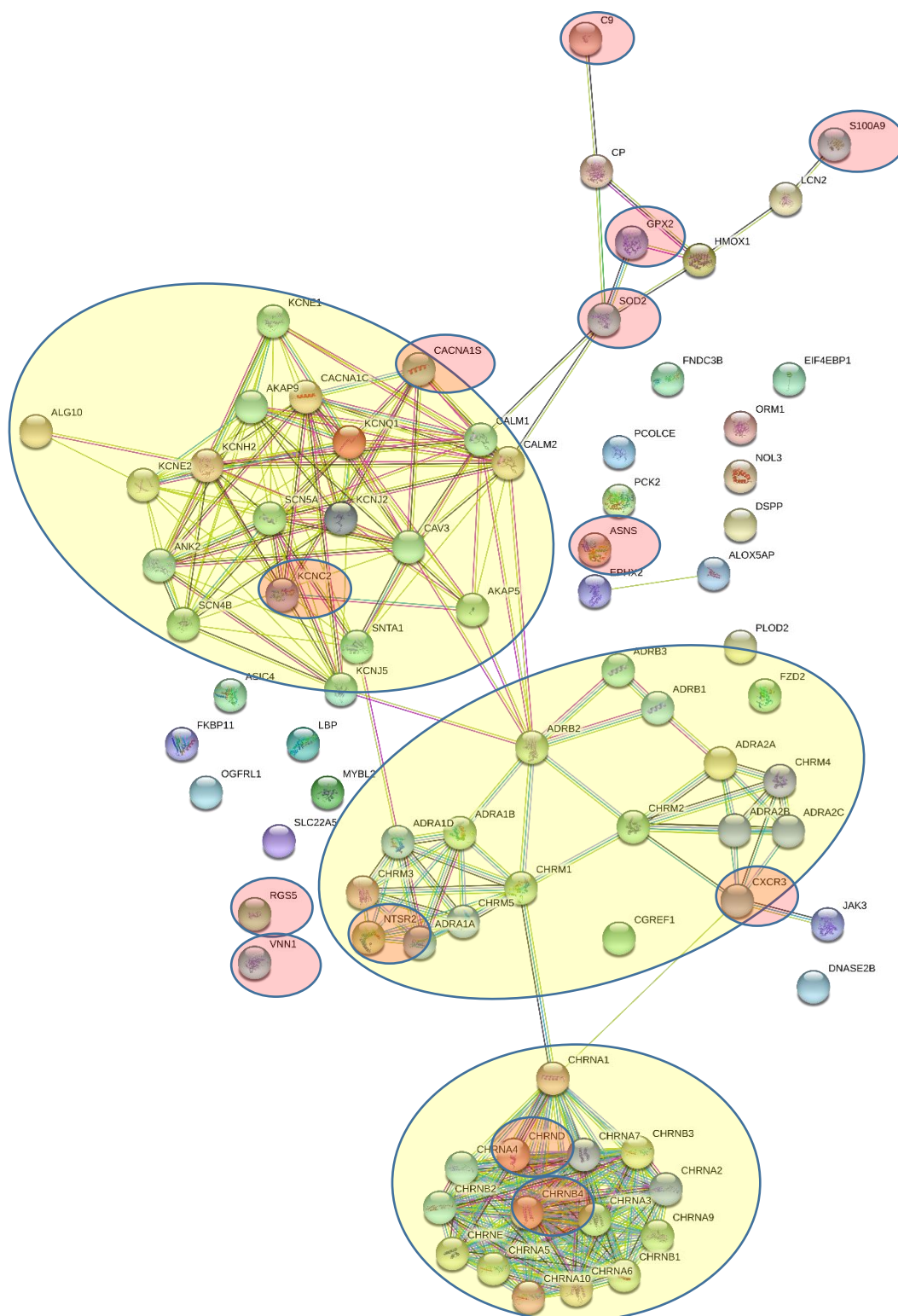
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9606.ENSP00000323901%250D9606.ENSP00000282903%250D9606.ENSP00000326627%250D9606.ENSP00000338523%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000369858%250D9606.ENSP00000449253%250D9606.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000303686%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000250699%250D9606.ENSP00000355192%250D9606.ENSP00000155840%250D9606.ENSP00000289957%250D9606.ENSP00000223061%250D9606.ENSP00000359464%250D9606.ENSP00000306490%250D9606.ENSP00000266376%250D9606.ENSP00000245407%250D9606.ENSP00000359699%250D9606.ENSP00000276410%250D9606.ENSP00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000324025%250D9606.ENSP00000359285%250D9606.ENSP00000305372%250D9606.ENSP00000175506%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000263408%250D9606.ENSP00000357727%250D9606.ENSP00000319984%250D9606.ENSP00000264613%250D9606.ENSP00000261751%250D9606.ENSP00000349588%250D9606.ENSP00000362795%250D9606.ENSP00000430269%250D9606.ENSP00000368766%250D9606.ENSP00000319308%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP00000216780%250D9606.ENSP00000357461%250D9606.ENSP00000391676%250D9606.ENSP00000268605%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP00000217026%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP00000243457%250D9606.ENSP00000340691%250D9606.ENSP00000315615%250D9606.ENSP00000356905%250D9606.ENSP00000341940%250D9606.ENSP00000337255%250D9606.ENSP00000282478%250D9606.ENSP00000356022%250D9606.ENSP00000216117%250D9606.ENSP00000374265%250D9606.ENSP00000449751%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP00000280155%250D9606.ENSP00000299565%250D9606.ENSP00000217407%250D9606.ENSP00000277480%250D9606.ENSP00000293780%250D9606.ENSP00000306662%250D9606.ENSP00000259396%250D9606.ENSP00000348573

Section 3.3.64.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Peripheral Nervous System Agents

In Figure 76, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the center and bottom center.

GPX2 and **ASNS** are associated with glutathione. Expression for both of these was lower in the QT group compared to the same probes in the NQT groups.

SOD2 is associated witdh oxygen free radicals. Mean expression of SOD2 was lower in the QT group compared to the NQT group.

RGS5, **CXCR3,** and **NTSR2** are associated with G proteins. Mean expression for all three was lower in the QT group compared to the same probes in the NQT group.

VNN1, **S100A9**, and **C9** are associated with immune responses. Mean expression for all three was lower in the QT group compared to the same probes in the NQT group.

KCNC2 and **CACNA1S** are K^+ and Ca^{2+} ion channels, respectively, which were differentially expressed in this group. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

**CHRNB4** and **CHRND** are nicotinic cholinergic receptors associated with the autonomic nervous system. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.65: P-Glycoprotein/ABCB1 Inducers

Table LXXII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inducers

Probe ID	Gene Symbol	Human Equivalent Gene Name
U13253_PROBE1	COL4A1	Collagen type IV alpha 1 chain
AW142276_PROBE1	MRPS36	Mitochondrial ribosomal protein S36
NM_013003_PROBE1	PEMT	Phosphatidylethanolamine N-methyltransferase
AF062402_PROBE1	VCAN	Versican
AB032243_PROBE1	SCD5	Stearoyl-CoA desaturase 5
AI171088_PROBE1	SRM	Spermidine synthase
AI704799_PROBE1	CDK5RAP2	CDK5 regulatory subunit associated protein 2
AJ003065_PROBE1	KCNJ14	Potassium voltage-gated channel subfamily J member 14
BE099800_PROBE1	SLC29A3	Solute carrier family 29 member 3
M76591_PROBE1	PGAM1	Phosphoglycerate mutase 1
X53003_PROBE1	ACACA	Acetyl-CoA carboxylase alpha
AJ277748_PROBE1	ENTPD6	Ectonucleoside triphosphate diphosphohydrolase 6 (putative)
M69056_PROBE1	FNTB	Farnesyltransferase, CAAX box, beta
AI411501_PROBE1	DND1	DND microRNA-mediated repression inhibitor 1
AF110021_PROBE1	AQP2	Aquaporin 2
U69884_PROBE1	KCNN3	Potassium calcium-activated channel subfamily N member 3
L20900_PROBE1	ICA1	Islet cell autoantigen 1
AA800535_PROBE1	ZDHHC3	Zinc finger DHHC-type containing 3
AB001075_PROBE1	LGALS2	Galectin 2
AI070394_PROBE1	BRINP2	BMP/retinoic acid inducible neural specific 2
M17069_PROBE1	CALM2	Calmodulin 2
NM_012751_PROBE1	SLC2A4	Solute carrier family 2 member 4
NM_017098_PROBE1	FABP6	Fatty acid binding protein 6
BF553500_PROBE1	CITED4	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4
AW531675_PROBE1	GPSM3	G protein signaling modulator 3
BE111512_PROBE1	SP1	Sp1 transcription factor
D13374_PROBE1	NME1	NME/NM23 nucleoside diphosphate kinase 1
NM_017332_PROBE1	FASN	Fatty acid synthase
AI138061_PROBE1	SLC50A1	Solute carrier family 50 member 1
BF558742_PROBE1	NF2	Neurofibromin 2

Figure 77: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inducers
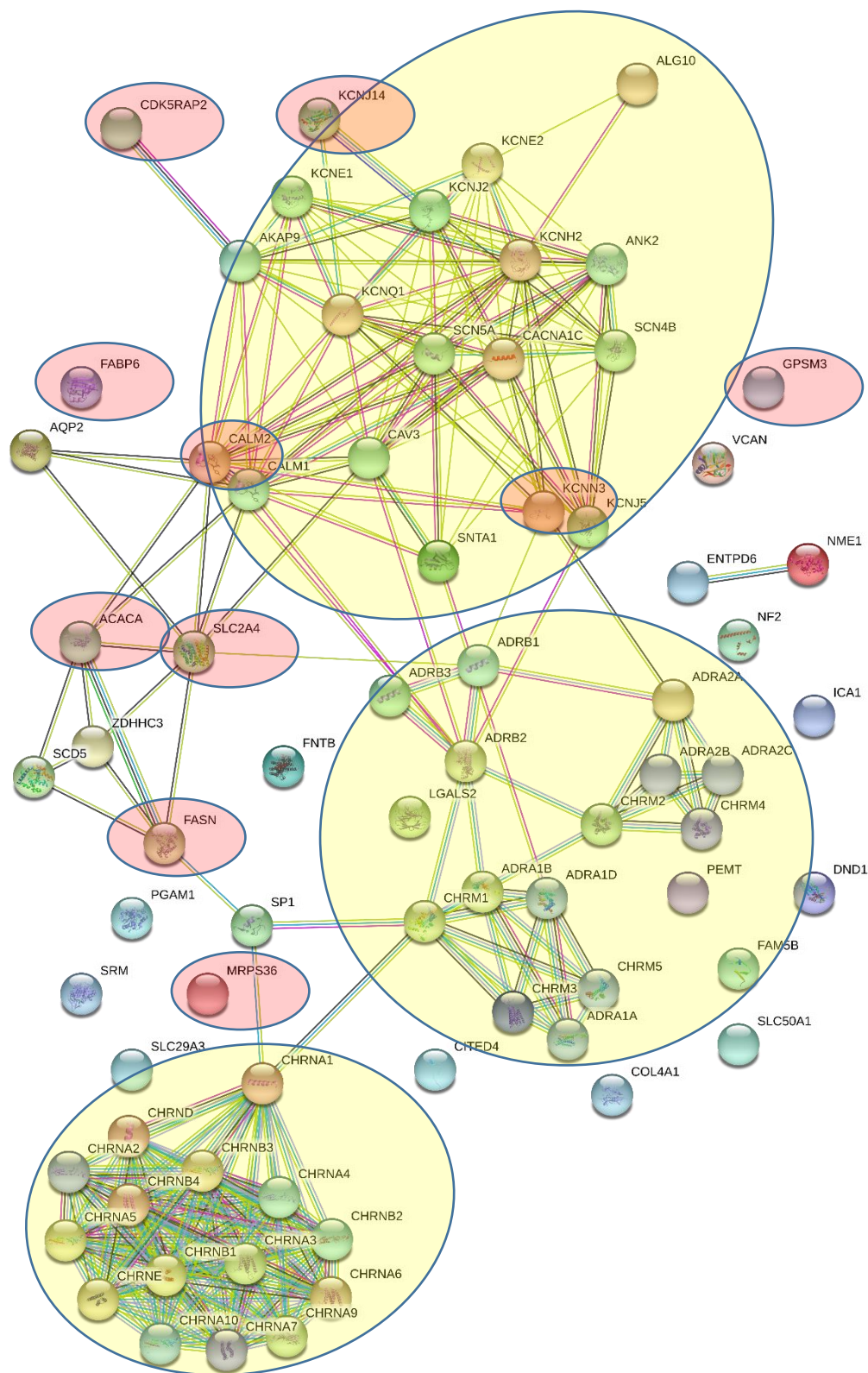
Section 3.3.65.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inducers

In Figure 77, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

KCNJ14 and **KCNN3** are potassium channels which were differentially expressed in this group. Mean expression for both was higher in the QT group compared to the same probes in the NQT group.

ACACA, **FABP6**, and **FASN** are associated with fatty acid metabolism. Mean expression for all three was lower in the QT group compared to the same probes in the NQT group.

GPSM3 is associated with G protein activity. Mean expression of GPSM3 was higher in the QT group compared to the NQT group.

MRPS36 is a mitochondrial ribosomal protein. Mean expression of MRPS36 was higher in the QT group compared to the NQT group.

CALM2 is a cLQTS proten differentially expressed in this group. Mean expression of CALM2 was expressed lower in the QT group compared to the NQT group.

SLC2A4 is an insulin-gated transporter associated with glucose metabolism, which might suggest a potential link to diabetes. Mean expression of SLC2A4 was lower in the QT group compared to the NQT group.

Section 3.3.66: P-Glycoprotein/ABCB1 Inhibitors

Table LXXIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AI104251_PROBE1	ABHD14A	Abhydrolase domain containing 14A
AI169278_PROBE1	KPNB1	Karyopherin subunit beta 1
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
D87839_PROBE1	ABAT	4-aminobutyrate aminotransferase
AA943578_PROBE1	EXOSC5	Exosome component 5
AI171632_PROBE1	TRIM11	Tripartite motif containing 11
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
AA850909_PROBE1	NECTIN2	Nectin cell adhesion molecule 2
AI169375_PROBE1	NUP93	Nucleoporin 93
AI177590_PROBE1	COG4	Component of oligomeric Golgi complex 4
AI317841_PROBE1	GRAMD2B	GRAM domain containing 2B
BF419241_PROBE1	MOCS1	Molybdenum cofactor synthesis 1
AI603128_PROBE1	CCNA2	Cyclin A2
U61729_PROBE1	PNRC1	Proline rich nuclear receptor coactivator 1
AI111840_PROBE1	PMVK	Phosphomevalonate kinase
AI409259_PROBE1	RACGAP1	Rac GTPase activating protein 1
U75916_PROBE1	TJP2	Tight junction protein 2
BF281149_PROBE1	DLGAP5	DLG associated protein 5
BE329450_PROBE1	FAHD2A	Fumarylacetoacetate hydrolase domain containing 2A
AI232784_PROBE1	BDH2	3-hydroxybutyrate dehydrogenase 2
BE100595_PROBE1	NCOA1	Nuclear receptor coactivator 1
NM_012964_PROBE1	NCOA1	Nuclear receptor coactivator 1
X15958_PROBE1	ECHS1	Enoyl-CoA hydratase, short chain 1
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
BE113034_PROBE1	ISCA1	Iron-sulfur cluster assembly 1
D30666_PROBE1	ACSL3	Acyl-CoA synthetase long chain family member 3
AI176781_PROBE1	FDFT1	Farnesyl-diphosphate farnesyltransferase 1
BE114586_PROBE1	CDKN1A	Cyclin dependent kinase inhibitor 1A
AF111268_PROBE1	CD36	CD36 molecule
AF245227_PROBE1	SNAP25	Synaptosome associated protein 25
AA892918_PROBE1	TJP1	Tight junction protein 1

Figure 78: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors

Permanent Link: http://bit.ly/2xoVi51
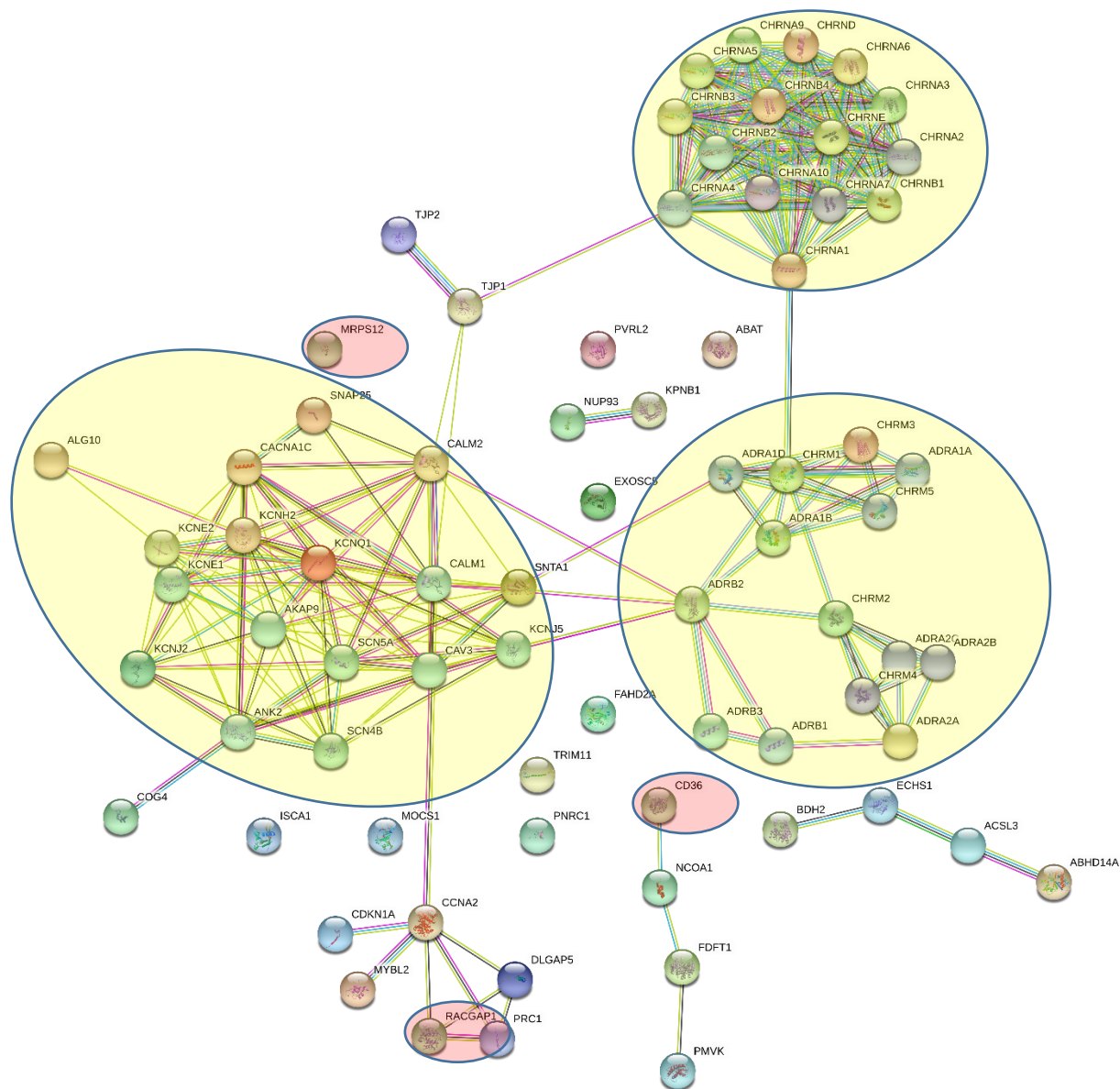
Section 3.3.66.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors

In Figure 78, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was higher in the QT group compared to the NQT group.

CD36 is associated with fatty acid metabolism and an immune response. Mean expression of CD36 was lower in the QT group compared to the NQT group.

RACGAP1 may be associated with G proteins. Mean expression of RACGAP1 was lower in the QT group compared to the NQT group.

Section 3.3.67: P-Glycoprotein/ABCB1 Substrates

Table LXXIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates

Probe ID	Gene Symbol	Human Equivalent Gene Name
X12355_PROBE1	PDIA3	Protein disulfide isomerase family A member 3
AJ245648_PROBE1	POLA2	DNA polymerase alpha 2, accessory subunit
AW525042_PROBE1	DHRS3	Dehydrogenase/reductase 3
NM_017243_PROBE1	PRPS1	Phosphoribosyl pyrophosphate synthetase 1
NM_017000_PROBE1	NQO1	NAD(P)H quinone dehydrogenase 1
NM_019292_PROBE1	CA3	Carbonic anhydrase 3
U69485_PROBE1	FKBP1A	FK506 binding protein 1A
AF285078_PROBE1	QSOX1	Quiescin sulfhydryl oxidase 1
X66539_PROBE1	TNF	Tumor necrosis factor
D00913_PROBE1	ICAM1	Intercellular adhesion molecule 1
NM_019239_PROBE1	MGAT3	Mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
U59245_PROBE1	ATP7A	ATPase copper transporting alpha
X96392_PROBE1	CYB5B	Cytochrome b5 type B
AA894189_PROBE1	TUBGCP6	Tubulin gamma complex associated protein 6
AA800303_PROBE1	PLSCR3	Phospholipid scramblase 3
AA892829_PROBE1	PAPSS1	3'-phosphoadenosine 5'-phosphosulfate synthase 1
BF415760_PROBE1	PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2
AA849987_PROBE1	USP7	Ubiquitin specific peptidase 7
AF087946_PROBE1	GPR37	G protein-coupled receptor 37
AJ222691_PROBE1	POLD1	DNA polymerase delta 1, catalytic subunit
BE113101_PROBE1	ATG4B	Autophagy related 4B cysteine peptidase
AW143190_PROBE1	BAIAP2	BAI1 associated protein 2
D00833_PROBE1	GLRA1	Glycine receptor alpha 1
BF553500_PROBE1	CITED4	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4
AF059530_PROBE1	PRMT3	Protein arginine methyltransferase 3
BF282987_PROBE1	SLC40A1	Solute carrier family 40 member 1
L20900_PROBE1	ICA1	Islet cell autoantigen 1
AW919666_PROBE1	LMCD1	LIM and cysteine rich domains 1

Figure 79: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates

Permanent Link: http://bit.ly/2xoNUWX
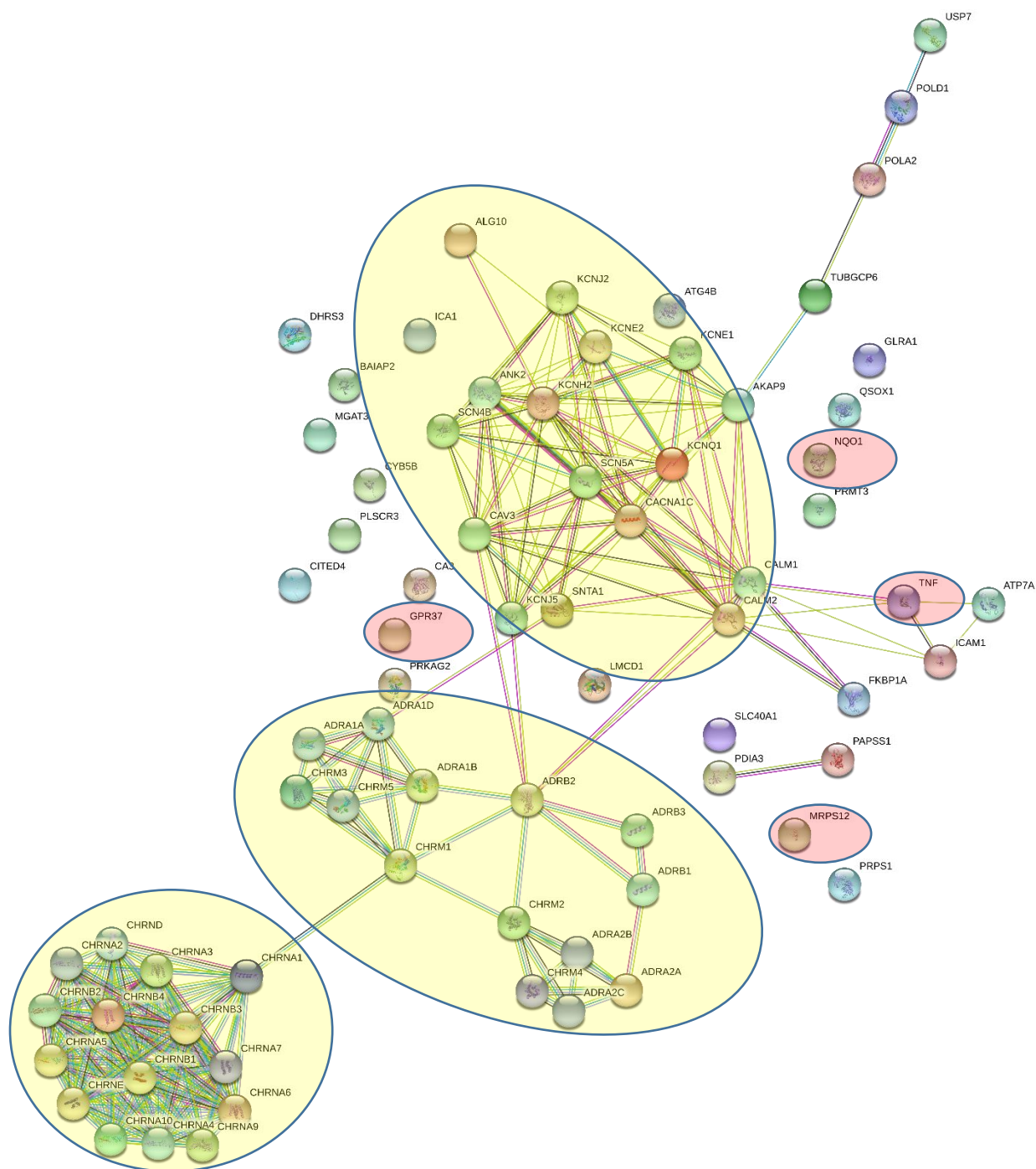
Section 3.3.67.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates

In Figure 79, genes associated with cLQTS are highlighted in yellow in the upper center. Genes associated with the ANS are connected and highlighted yellow at the lower center and bottom left.

TNF is associated with immune responses and cytokines. Mean expression of TNF was lower in the QT group compared to the NQT group.

NQO1 is asscociated with electron transport. Mean expression of NQO1 was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower compared to the NQT group.

GPR37 is associated with G protein activity. Mean expression of GPR37 was higher in the QT group compared to the NQT group.

Section 3.3.68: Piperazines

Table LXXV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Piperazines

Probe ID	Gene Symbol	Human Equivalent Gene Name
BF554229_PROBE1	PHF12	PHD finger protein 12
AI411742_PROBE1	SESN1	Sestrin 1
AW253902_PROBE1	MMP15	Matrix metallopeptidase 15
AW520823_PROBE1	AMOTL1	Angiomotin like 1
AW916201_PROBE1	SCCPDH	Saccharopine dehydrogenase (putative)
X68400_PROBE1	PRKCH	Protein kinase C eta
AA946470_PROBE1	IPO11	Importin 11
NM_012751_PROBE1	SLC2A4	Solute carrier family 2 member 4
AI412244_PROBE1	TBC1D14	TBC1 domain family member 14
D13127_PROBE1	ATP5O	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit
NM_019252_PROBE1	DPM2	Dolichyl-phosphate mannosyltransferase subunit 2, regulatory
AF109674_PROBE1	CRISPLD2	Cysteine rich secretory protein LCCL domain containing 2
AJ293617_PROBE1	MAGED2	MAGE family member D2
NM_013069_PROBE1	CD74	CD74 molecule
AF046886_PROBE1	AXL	AXL receptor tyrosine kinase
AF019109_PROBE1	SORT1	Sortilin 1
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
AW919920_PROBE1	HSPA12B	Heat shock protein family A (Hsp70) member 12B
M19044_PROBE1	ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide
M35052_PROBE1	ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex subunit B1
NM_012886_PROBE1	TIMP3	TIMP metallopeptidase inhibitor 3
U86379_PROBE1	C3AR1	Complement C3a receptor 1
AI172274_PROBE1	ECHDC2	Enoyl-CoA hydratase domain containing 2
X67654_PROBE1	GSTT1	Glutathione S-transferase theta 1
X95096_PROBE1	MST1	Macrophage stimulating 1

Figure 80: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Piperazines

Section 3.3.68.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Piperazines

In Figure 80, genes associated with cLQTS are highlighted in yellow in the upper center. Genes associated with the ANS are connected and highlighted yellow at the lower center and bottom left.

GSTT1 is associated with glutathione. Mean expression of GSTT1 was lower in the QT group compared to the NQT group.

SLC2A4 is an insulin-linked glucose transporter which might suggest a link to dabetes. Mean expression of SLC2A4 was lower in the QT group compared to the NQT group.

CD74 and **PRKCH** are associated with immune responses and apoptosis. Mean expression for both was higher in the QT group compared to the same probes in the NQT group.

C3AR1 is associated with immune responses and is coupled to a G protein. Mean expression of C3AR1 was higher in the QT group compared to the NQT group.

Section 3.3.69: Polycyclic Compounds

Table LXXVI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Polycyclic Compounds

Probe ID	Gene Symbol	Human Equivalent Gene Name
AF111268_PROBE1	CD36	CD36 molecule
NM_012886_PROBE1	TIMP3	TIMP metallopeptidase inhibitor 3
AJ224120_PROBE1	PEX11A	Peroxisomal biogenesis factor 11 alpha
U07201_PROBE1	ASNS	Asparagine synthetase (glutamine-hydrolyzing)
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
AI230228_PROBE1	PSAT1	Phosphoserine aminotransferase 1
NM_012930_PROBE1	CPT2	Carnitine palmitoyltransferase 2
AW919920_PROBE1	HSPA12B	Heat shock protein family A (Hsp70) member 12B
NM_012522_PROBE1	CBS	Cystathionine-beta-synthase
AI716502_PROBE1	SPHK2	Sphingosine kinase 2
NM_017064_PROBE1	STAT5A	Signal transducer and activator of transcription 5A
J00696_PROBE1	ORM1	Orosomucoid 1
AI170799_PROBE1	FBXW2	F-box and WD repeat domain containing 2
AI715257_PROBE1	ARRDC2	Arrestin domain containing 2
AF296131_PROBE1	DGAT1	Diacylglycerol O-acyltransferase 1
AA859343_PROBE1	SRPK1	SRSF protein kinase 1
AI411194_PROBE1	PNPLA2	Patatin like phospholipase domain containing 2
AF077354_PROBE1	HSPA4	Heat shock protein family A (Hsp70) member 4
NM_019283_PROBE1	SLC3A2	Solute carrier family 3 member 2
AB012759_PROBE1	PREP	Prolyl endopeptidase
L08814_PROBE1	SSRP1	Structure specific recognition protein 1
BF412111_PROBE1	GDPD2	Glycerophosphodiester phosphodiesterase domain containing 2
AW143909_PROBE1	REEP6	Receptor accessory protein 6
BF407480_PROBE1	SMYD2	SET and MYND domain containing 2
NM_013068_PROBE1	FABP2	Fatty acid binding protein 2
U17967_PROBE1	KCNAB1	Potassium voltage-gated channel subfamily A member regulatory beta subunit 1
BF396132_PROBE1	EML2	Echinoderm microtubule associated protein like 2
AI548730_PROBE1	AFG3L2	AFG3 like matrix AAA peptidase subunit 2
BF553500_PROBE1	CITED4	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4
NM_017340_PROBE1	ACOX1	Acyl-CoA oxidase 1
U02315_PROBE1	NRG1	Neuregulin 1
NM_017083_PROBE1	MYO5B	Myosin VB
AI233766_PROBE1	PSME3	Proteasome activator subunit 3
X61925_PROBE1	PNLIPRP1	Pancreatic lipase related protein 1

Figure 81: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Polycyclic Compounds
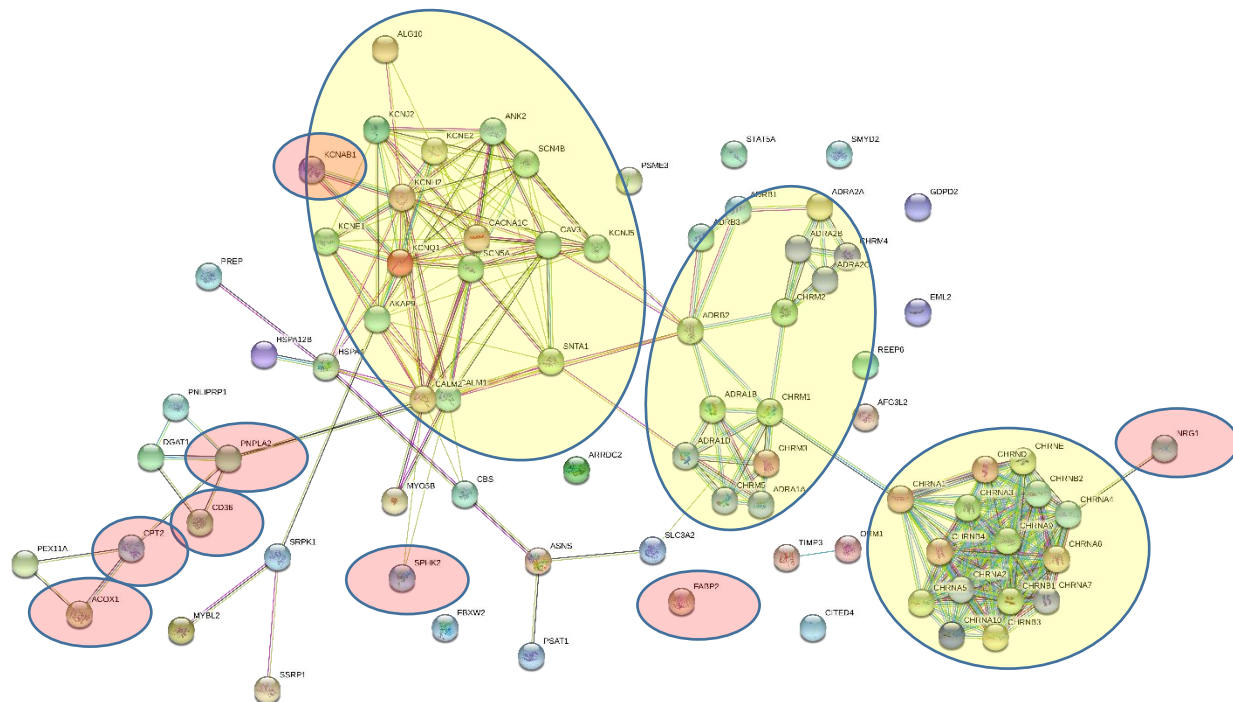
Permanent Link (Short link not provided by String): https://version-10-5.string-db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes =0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9 606.ENSP00000341208%250D9606.ENSP00000293217%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D96 06.ENSP00000349467%250D9606.ENSP00000343782%250D9606.ENSP00000261007%250D9606.ENSP00000304290%250D960 6.ENSP00000312663%250D9606.ENSP00000332258%250D9606.ENSP00000250699%250D9606.ENSP00000155840%250D9606 .ENSP00000289957%250D9606.ENSP00000222250%250D9606.ENSP00000363036%250D9606.ENSP00000349275%250D9606. ENSP00000278412%250D9606.ENSP00000355924%250D9606.ENSP00000245222%250D9606.ENSP00000306490%250D9606.E NSP00000419952%250D9606.ENSP00000266376%250D9606.ENSP00000360541%250D9606.ENSP00000276410%250D9606.EN SP00000328968%250D9606.ENSP00000233596%250D9606.ENSP00000385026%250D9606.ENSP00000359285%250D9606.ENS P00000274024%250D9606.ENSP00000305372%250D9606.ENSP00000175506%250D9606.ENSP00000367123%250D9606.ENSP 00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000319984%250D9606.ENSP00000361721%250D9606.ENSP0 0000261751%250D9606.ENSP00000285039%250D9606.ENSP00000349588%250D9606.ENSP00000362931%250D9606.ENSP00 000442365%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP00000409378%250D9606.ENSP000 00357461%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP00000315602%250D9606.ENSP0000 0269143%250D9606.ENSP00000217026%250D9606.ENSP00000372750%250D9606.ENSP00000407546%250D9606.ENSP00000 272298%250D9606.ENSP00000369960%250D9606.ENSP00000358301%250D9606.ENSP00000322460%250D9606.ENSP000002 43457%250D9606.ENSP00000344460%250D9606.ENSP00000341940%250D9606.ENSP00000254963%250D9606.ENSP0000036 5773%250D9606.ENSP00000337255%250D9606.ENSP00000300056%250D9606.ENSP00000351695%250D9606.ENSP00000293 362%250D9606.ENSP00000414019%250D9606.ENSP00000262186%250D9606.ENSP00000255380%250D9606.ENSP000002801 55%250D9606.ENSP00000299565%250D9606.ENSP00000337701%250D9606.ENSP00000308165%250D9606.ENSP0000026608 5%250D9606.ENSP00000293780%250D9606.ENSP00000302961%250D9606.ENSP00000306662%250D9606.ENSP00000259396 %250D9606.ENSP00000358106%250D9606.ENSP00000348573

Section 3.3.69.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Polycyclic Compounds

In Figure 81, genes associated with cLQTS are highlighted in yellow in the upper right. Genes associated with the ANS are connected and highlighted yellow at the center lower right.

KCNAB1 is a K^+ ion channel that binds NAPH, suggesting an association with electron transport activity, which was differentially expressed in this group. Mean expression of KCNAB1 was lower in the QT group compared to the NQT group.

CD36, **CPT2**, **FABP2**, **ACOX1**, **SPHK2**, and **PNPLA2** are associated with lipid and fatty acid metabolism. Mean expression for all of these was higher in the QT group compared to the same probes in the NQT group.

NRG1 is associatd with MAPKs. Mean expression of NRG1 was lower in the QT group compared to the NQT group.

Section 3.3.70: Psycholeptics

Table LXXVII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Psycholeptics

Probe ID	Gene Symbol	Human Equivalent Gene Name
BE113076_PROBE1	NFATC4	Nuclear factor of activated T-cells 4
J05029_PROBE1	ACADL	Acyl-CoA dehydrogenase, long chain
L13722_PROBE1	CHM	CHM, Rab escort protein 1
NM_012859_PROBE1	LIPE	Lipase E, hormone sensitive type
K03250_PROBE1	RPS11	Ribosomal protein S11
AA817860_PROBE1	ATF7IP	Activating transcription factor 7 interacting protein
AI598648_PROBE1	IPMK	Inositol polyphosphate multikinase
AF067728_PROBE1	PSMD9	Proteasome 26S subunit, non-ATPase 9
AJ293948_PROBE1	KLHL41	Kelch like family member 41
AW522122_PROBE1	TNNT2	Troponin T2, cardiac type
M25157_PROBE1	SOD1	Superoxide dismutase 1
X52311_PROBE1	CSDE1	Cold shock domain containing E1
NM_012585_PROBE1	HTR1A	5-hydroxytryptamine receptor 1A
U76997_PROBE1	LNPEP	Leucyl and cystinyl aminopeptidase
BF283760_PROBE1	LDB2	LIM domain binding 2
D86557_PROBE1	LDB2	LIM domain binding 2) Homo sapiens
M98327_PROBE1	VARS2	Valyl-tRNA synthetase 2, mitochondrial
AF235993_PROBE1	BAX	BCL2 associated X, apoptosis regulator
U08290_PROBE1	NNAT	Neuronatin
U12309_PROBE1	ITGB1	Integrin subunit beta 1
AA858930_PROBE1	PDE4B	Phosphodiesterase 4B
AF111160_PROBE1	GSTA3	Glutathione S-transferase alpha 3
AI406747_PROBE1	NRCAM	Neuronal cell adhesion molecule
NM_017153_PROBE1	RPS3A	Ribosomal protein S3A
U89282_PROBE1	TEP1	Telomerase associated protein 1
AI009656_PROBE1	PEF1	Penta-EF-hand domain containing 1

Figure 82: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Psycholeptics

Permanent Link: http://bit.ly/2w9A3Fm
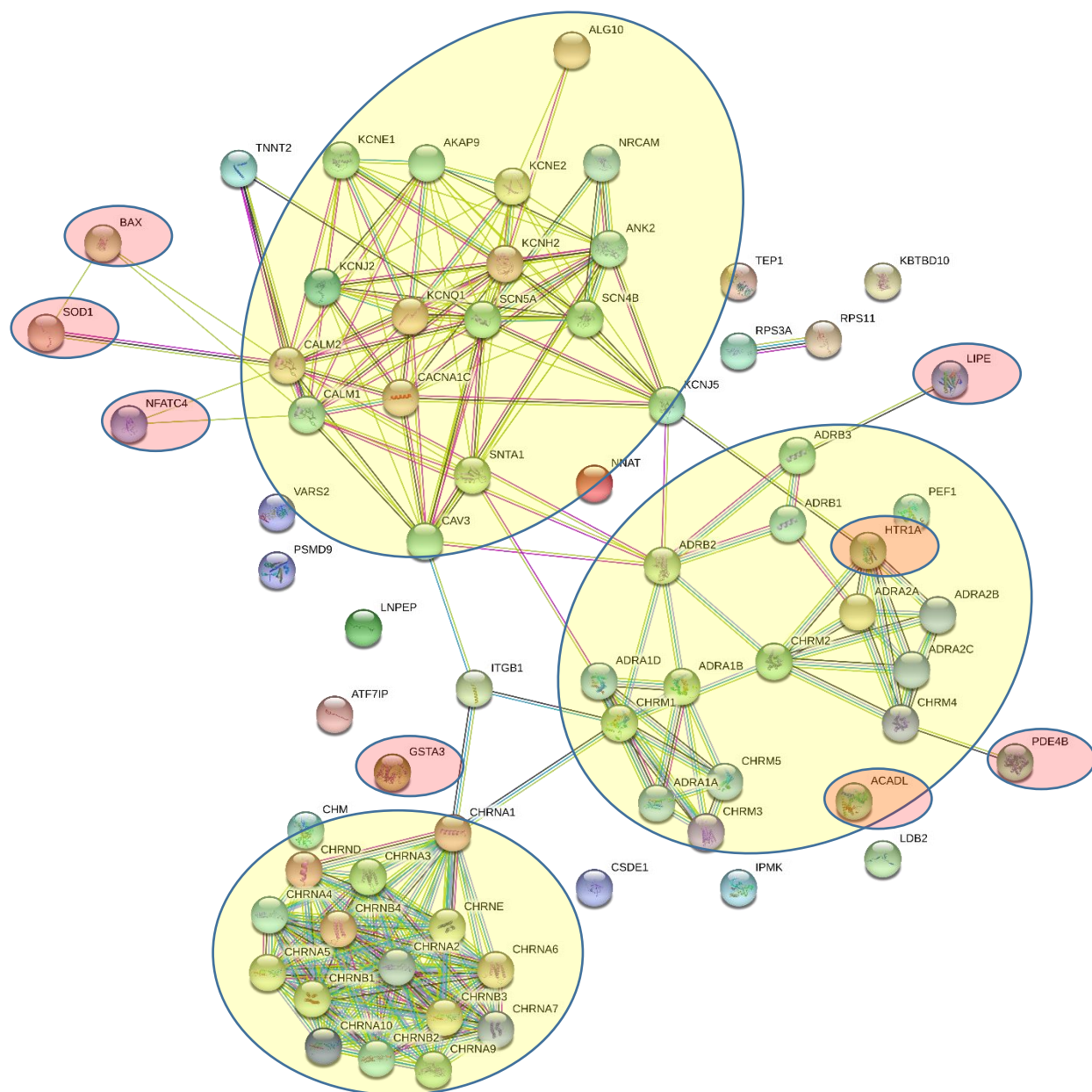
Section 3.3.70.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Psycholeptics

In Figure 82, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center right and bottom left.

BAX is associated with apoptosis. Mean expression of BAX was lower in the QT group compared to the NQT group.

SOD1 is associated with electron transport and detoxifying oxygen free radicals. Mean expression of SOD1 was lower in the QT group compared to the NQT group.

ACADL and **LIPE** are associated with fatty acid metabolism. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

NFATC4 and **PDE4B** are associated with cytokines and inflammatory responses. Mean expression of NFATC4 was lower in the QT group compared to the NQT group. Mean expression of PDE4B was higher in the QT group compared to the NQT group.

HTR1A is associated with G proteins and regulation of the release of Ca^{2+} ions from intracellular stores as a second messenger. Mean expression of HTR1A was higher in the QT group compared to the NQT group.

GSTA3 is associated with glutathione. Mean expression of GSTA3 was lower in the QT group compared to the NQT group.

Section 3.3.71: Respiratory System

Table LXXVIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Respiratory System

Probe ID	Gene Symbol	Human Equivalent Gene Name
AI177590_PROBE1	COG4	Component of oligomeric Golgi complex 4
AW253767_PROBE1	NKIRAS2	NFKB inhibitor interacting Ras like 2
AF231407_PROBE1	CALM3	Calmodulin 3
BF557871_PROBE1	FLT3	Fms related tyrosine kinase 3
AI179142_PROBE1	MBIP	MAP3K12 binding inhibitory protein 1
AF005099_PROBE1	NPTXR	Neuronal pentraxin receptor
NM_012656_PROBE1	SPARC	Secreted protein acidic and cysteine rich
AI170679_PROBE1	UGP2	UDP-glucose pyrophosphorylase 2
AI409218_PROBE1	SPRED2	Sprouty related EVH1 domain containing 2
AW917069_PROBE1	MRPS12	Mitochondrial ribosomal protein S12
AF022729_PROBE1	CHST10	Carbohydrate sulfotransferase 10
BE111773_PROBE1	TARBP2	TARBP2, RISC loading complex RNA binding subunit
M81687_PROBE1	SDC2	Syndecan 2
NM_012667_PROBE1	TACR1	Tachykinin receptor 1
BF283760_PROBE1	LDB2	LIM domain binding 2
AW536019_PROBE1	ARID1A	AT-rich interaction domain 1A
U41662_PROBE1	NLGN2	Neuroligin 2
AF234600_PROBE1	NPLOC4	NPL4 homolog, ubiquitin recognition factor
X01976_PROBE1	OTC	Ornithine carbamoyltransferase
NM_017194_PROBE1	CHRNE	Cholinergic receptor nicotinic epsilon subunit
AI639504_PROBE1	LDHD	Lactate dehydrogenase D
AF030253_PROBE1	SLC32A1	Solute carrier family 32 member 1
NM_013199_PROBE1	DNM2	Dynamin 2
BF282437_PROBE1	TBC1D10A	TBC1 domain family member 10A
AI716502_PROBE1	SPHK2	Sphingosine kinase 2
AI407555_PROBE1	FBXW9	F-box and WD repeat domain containing 9
AW914020_PROBE1	CHMP1A	Charged multivesicular body protein 1A
AW534383_PROBE1	MOB1A	MOB kinase activator 1A
AF089825_PROBE1	INHBE	Inhibin beta E subunit
AI170291_PROBE1	MTPN	Myotrophin

Figure 83: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Respiratory System
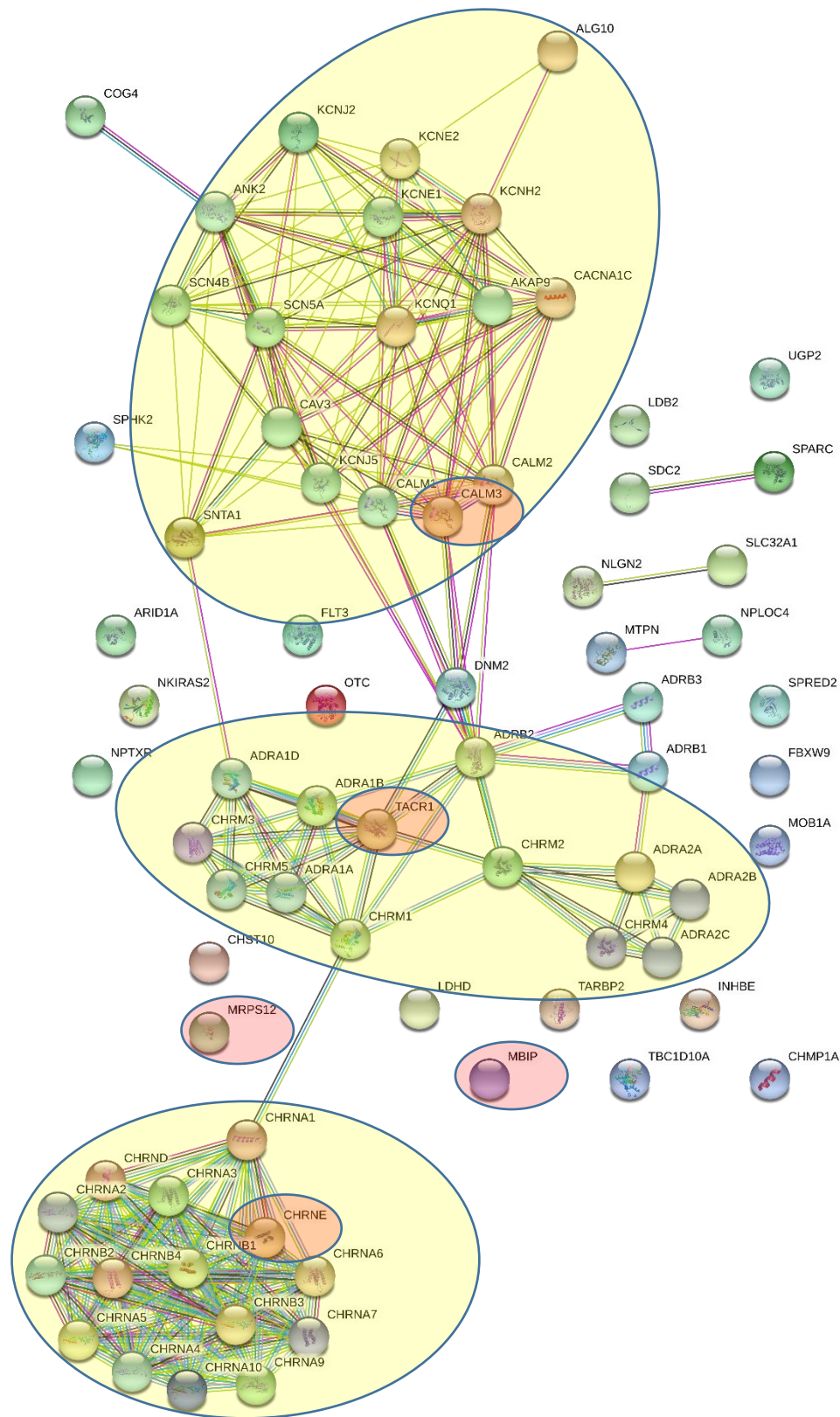
Section 3.3.71.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Respiratory System

In Figure 83, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

MBIP is associated with MAPK activity. Mean expression of MBIP was higher in the QT group compared to the NQT group.

TACR1 is associated with a G protein that uses Ca^{2+} as a second messenger. Mean expression of TACR1 was lower in the QT group compared to the NQT group.

CALM3 modulates Ca^{2+} ion concentrations. Mean expression of CALM3 was lower in the QT group compared to the NQT group.

MRPS12 is a mitochondrial ribosomal protein. Mean expression of MRPS12 was lower in the QT group compared to the NQT group.

CHRNE is a nicotinic cholinergic receptor which is part of the autonomic nervous system. Mean expression of CHRNE was lower in the QT group compared to the NQT group.

Section 3.3.72: Sensory Organs

Table LXXIX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Sensory Organs

Probe ID	Gene Symbol	Human Equivalent Gene Name
M76591_PROBE1	PGAM1	Phosphoglycerate mutase 1
BF548006_PROBE1	ANAPC1	Anaphase promoting complex subunit 1
AW143101_PROBE1	SNAP29	Synaptosome associated protein 29
AF061442_PROBE1	CYP2E1	Cytochrome P450 family 2 subfamily E member 1
BF390910_PROBE1	DNAJB5	DnaJ heat shock protein family (Hsp40) member B5
NM_017283_PROBE1	PSMA6	Proteasome subunit alpha 6
AA819871_PROBE1	CDC16	Cell division cycle 16
AA858518_PROBE1	RNF7	Ring finger protein 7
AA944451_PROBE1	OTUB1	OTU deubiquitinase, ubiquitin aldehyde binding 1
AW521367_PROBE1	WDR41	WD repeat domain 41
AI177590_PROBE1	COG4	Component of oligomeric Golgi complex 4
AI171242_PROBE1	TBC1D7	TBC1 domain family member 7
U91539_PROBE1	GOSR2	Golgi SNAP receptor complex member 2
BF418630_PROBE1	LRRFIP1	LRR binding FLII interacting protein 1
AA799981_PROBE1	PRKCH	Protein kinase C eta
AI408517_PROBE1	PPP1R14B	Protein phosphatase 1 regulatory inhibitor subunit 14B
NM_012919_PROBE1	CACNA2D1	Calcium voltage-gated channel auxiliary subunit alpha2delta 1
AI233133_PROBE1	MRPS7	Mitochondrial ribosomal protein S7
AI102591_PROBE1	SNRPD1	Small nuclear ribonucleoprotein D1 polypeptide
L19698_PROBE1	RALA	RAS like proto-oncogene A
AA946349_PROBE1	NUDT3	Nudix hydrolase 3
AF025424_PROBE1	POLR1B	RNA polymerase I subunit B
AF255305_PROBE1	CCS	Copper chaperone for superoxide dismutase
AI177104_PROBE1	SLC30A6	Solute carrier family 30 member 6
NM_013186_PROBE1	KCNB1	Potassium voltage-gated channel subfamily B member 1
X53724_PROBE1	ASCL2	Achaete-scute family bHLH transcription factor 2
AI406533_PROBE1	CHSY1	Chondroitin sulfate synthase 1
NM_017035_PROBE1	PLCD1	Phospholipase C delta 1
BE329347_PROBE1	SSR2	Signal sequence receptor subunit 2
NM_012670_PROBE1	TCP1	T-complex 1
AI179993_PROBE1	PAXIP1	PAX interacting protein 1

Figure 84: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Sensory Organs
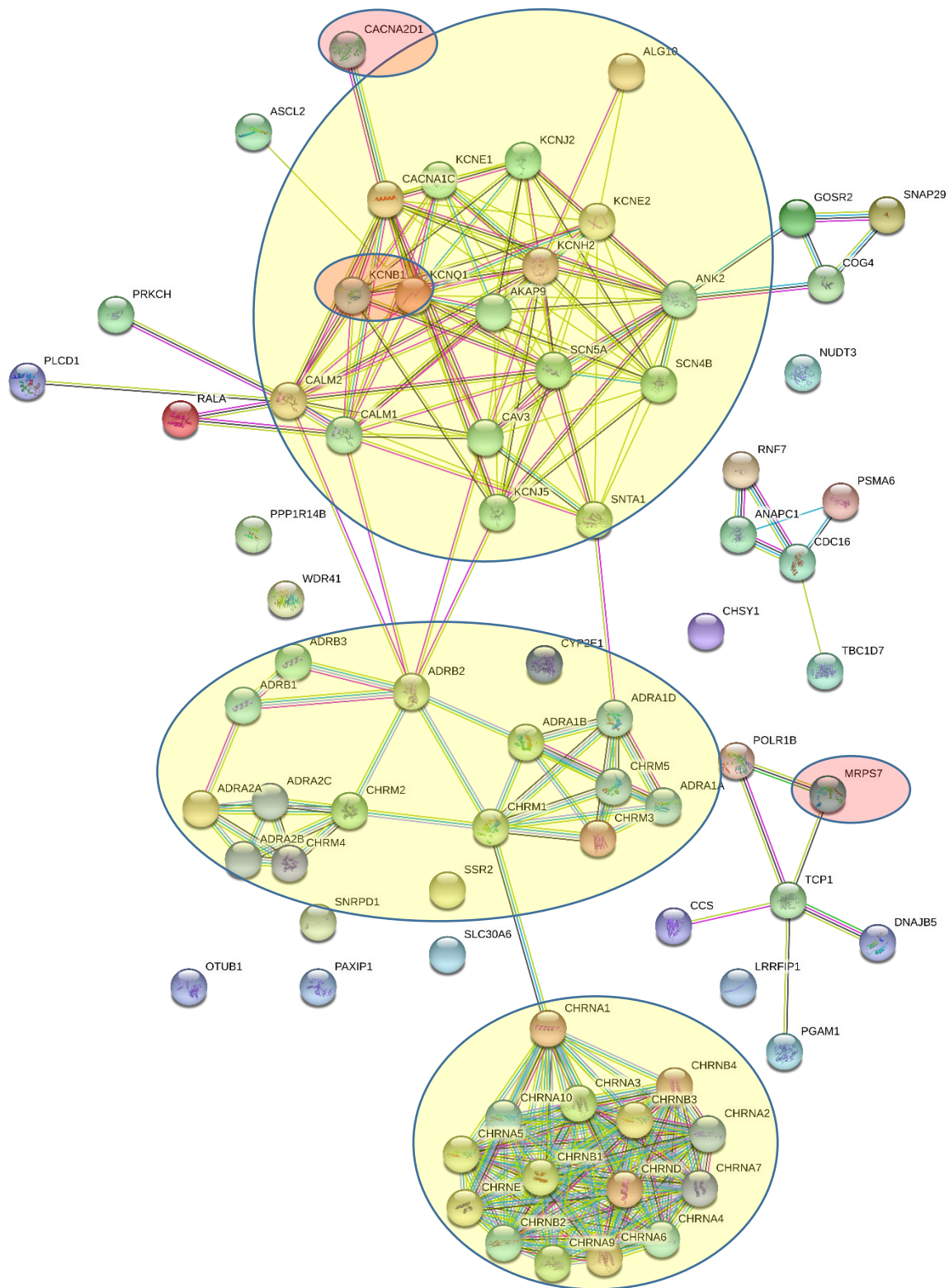
Section 3.3.72.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Sensory Organs

In Figure 84, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center right and bottom left.

CACNA2D1 is a Ca^{2+} ion channel involved with excitation-contraction coupling. Mean expression of CACNA2D1 was lower in the QT group compared to the NQT group.

KCNB1 is a K^+ ion channel. Mean expression of KCNB1 was lower in the QT group compared to the NQT group.

MRPS7 is a mitochondrial ribosomal proten. Mean expression of MRPS7 was lower in the QT group compared to the NQT group.

PRKCH is associated with apoptosis. Mean expression of PRKCH was lower in the QT group compared to the NQT group.

Section 3.3.73: Steroid Synthesis Inhibitors

Table LXXX: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Steroid Synthesis Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW862653_PROBE1	NUDT4	Nudix hydrolase 4
NM_012903_PROBE1	ANP32A	Acidic nuclear phosphoprotein 32 family member A
BF405883_PROBE1	DHX16	DEAH-box helicase 16
D70816_PROBE1	CPLX2	Complexin 2
NM_012545_PROBE1	DDC	Dopa decarboxylase
AW141873_PROBE1	MRPL14	Mitochondrial ribosomal protein L14
AF271156_PROBE1	CAMK2N1	Calcium/calmodulin dependent protein kinase II inhibitor 1
AI229833_PROBE1	SUMF2	Sulfatase modifying factor 2
BF556833_PROBE1	RNF2	Ring finger protein 2
NM_013027_PROBE1	SELENOW	Selenoprotein W
U73503_PROBE1	CAMK2G	Calcium/calmodulin dependent protein kinase II gamma
AF077000_PROBE1	PTPN23	Protein tyrosine phosphatase, non-receptor type 23
BE103543_PROBE1	RFC1	Replication factor C subunit 1
BF420628_PROBE1	UNK	Unkempt family zinc finger
BF557396_PROBE1	FUT8	Fucosyltransferase 8
NM_017285_PROBE1	PSMB3	Proteasome subunit beta 3
X83231_PROBE1	ITIH3	Inter-alpha-trypsin inhibitor heavy chain 3
AI103106_PROBE1	LMNB1	Lamin B1
AW916201_PROBE1	SCCPDH	Saccharopine dehydrogenase (putative)
D85035_PROBE1	DPYD	Dihydropyrimidine dehydrogenase
AJ003004_PROBE1	ABCB6	ATP binding cassette subfamily B member 6 (Langereis blood group)
AI171632_PROBE1	TRIM11	Tripartite motif containing 11
AW523642_PROBE1	KMT5B	Lysine methyltransferase 5B
BE113064_PROBE1	KPNA6	Karyopherin subunit alpha 6
BF407916_PROBE1	GDF11	Growth differentiation factor 11
BF392344_PROBE1	MTMR7	Myotubularin related protein 7

Figure 85: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Steroid Synthesis Inhibitors

Permanent Link: http://bit.ly/2wa0efr
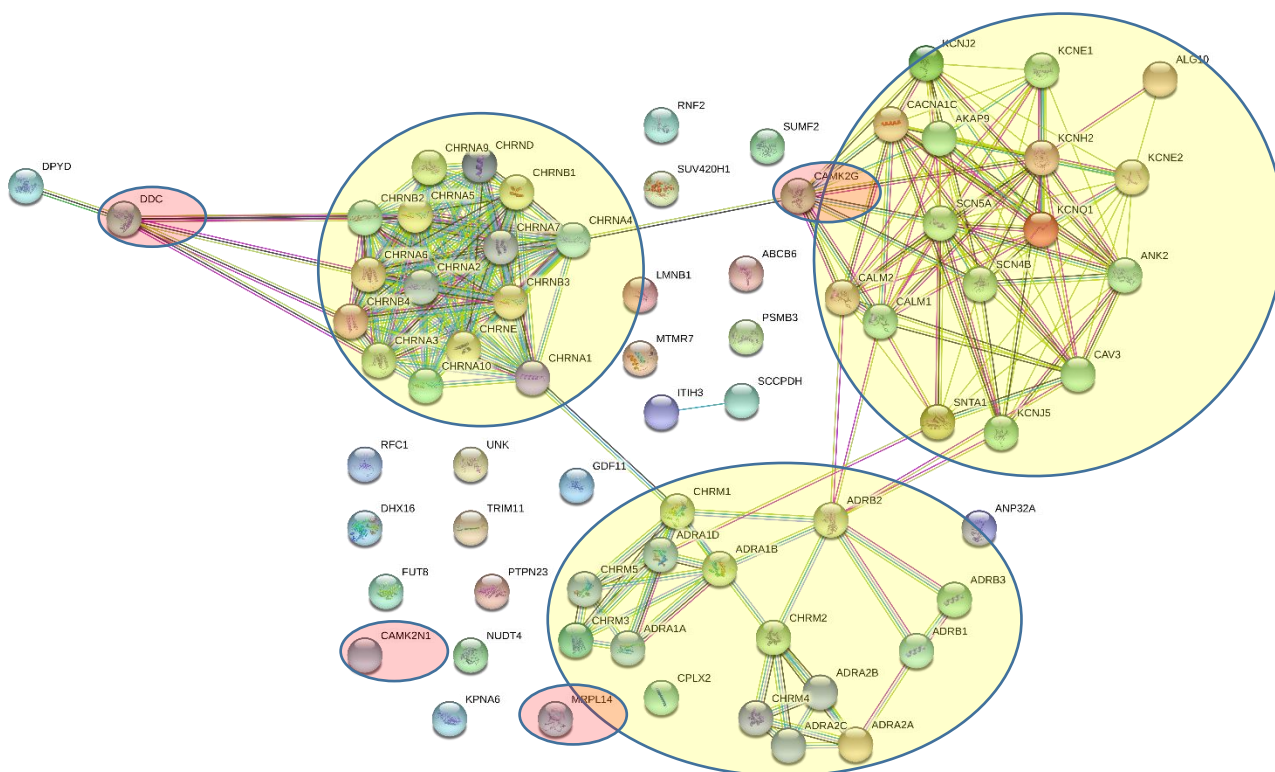
Section 3.3.73.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Steroid Synthesis Inhibitors

In Figure 85, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the bottom center and top left.

DDC is associated with catecholamine biosynthesis. Mean expression of DDC was lower in the QT group compared to the NQT group.

MRPL14 is a mitochondrial ribosomal protein. Mean expression of MRPL14 was lower in the QT group compared to the NQT group.

CAMK2N1 and **CAMK2G** are associated with cytoplasmic Ca^{2+} regulation. Mean expression of both was lower in the QT group compared to the same probes in the NQT group.

Section 3.3.74: Sulfonamides

Table LXXXI: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Sulfonamides

Probe ID	Gene Symbol	Human Equivalent Gene Name
U86635_PROBE1	GSTM5	Glutathione S-transferase mu 5
AW251213_PROBE1	IPO7	Importin 7
U94709_PROBE1	PTGER4	Prostaglandin E receptor 4
AI454418_PROBE1	IGSF1	Immunoglobulin superfamily member 1
AW253367_PROBE1	RNF10	Ring finger protein 10
AI137569_PROBE1	UCK1	Uridine-cytidine kinase 1
NM_017284_PROBE1	PSMB2	Proteasome subunit beta 2
NM_017049_PROBE1	SLC4A3	Solute carrier family 4 member 3
U94856_PROBE1	PON1	Paraoxonase 1
AF220760_PROBE1	TXNRD1	Thioredoxin reductase 1
Y00047_PROBE1	PCNA	Proliferating cell nuclear antigen
AA799550_PROBE1	MRFAP1	Morf4 family associated protein 1
NM_012833_PROBE1	ABCC2	ATP binding cassette subfamily C member 2
J05181_PROBE1	GCLC	Glutamate-cysteine ligase catalytic subunit
NM_012687_PROBE1	TBXAS1	Thromboxane A synthase 1
J00750_PROBE1	EMC3	ER membrane protein complex subunit 3
AI113104_PROBE1	PRC1	Protein regulator of cytokinesis 1
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
M30596_PROBE1	ME1	Malic enzyme 1
M22642_PROBE1	TK1	thymidine kinase 1
U53512_PROBE1	MRPL17	Mitochondrial ribosomal protein L17
AA800803_PROBE1	DCAKD	Dephospho-CoA kinase domain containing
AI102009_PROBE1	PRKRA	Protein activator of interferon induced protein kinase EIF2AK2
AF081582_PROBE1	PLEKHB1	Pleckstrin homology domain containing B1
BE113020_PROBE1	FBXW5	F-box and WD repeat domain containing 5
M26125_PROBE1	EPHX1	Epoxide hydrolase 1

Figure 86: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Sulfonamides

Permanent Link: http://bit.ly/2xpakHO
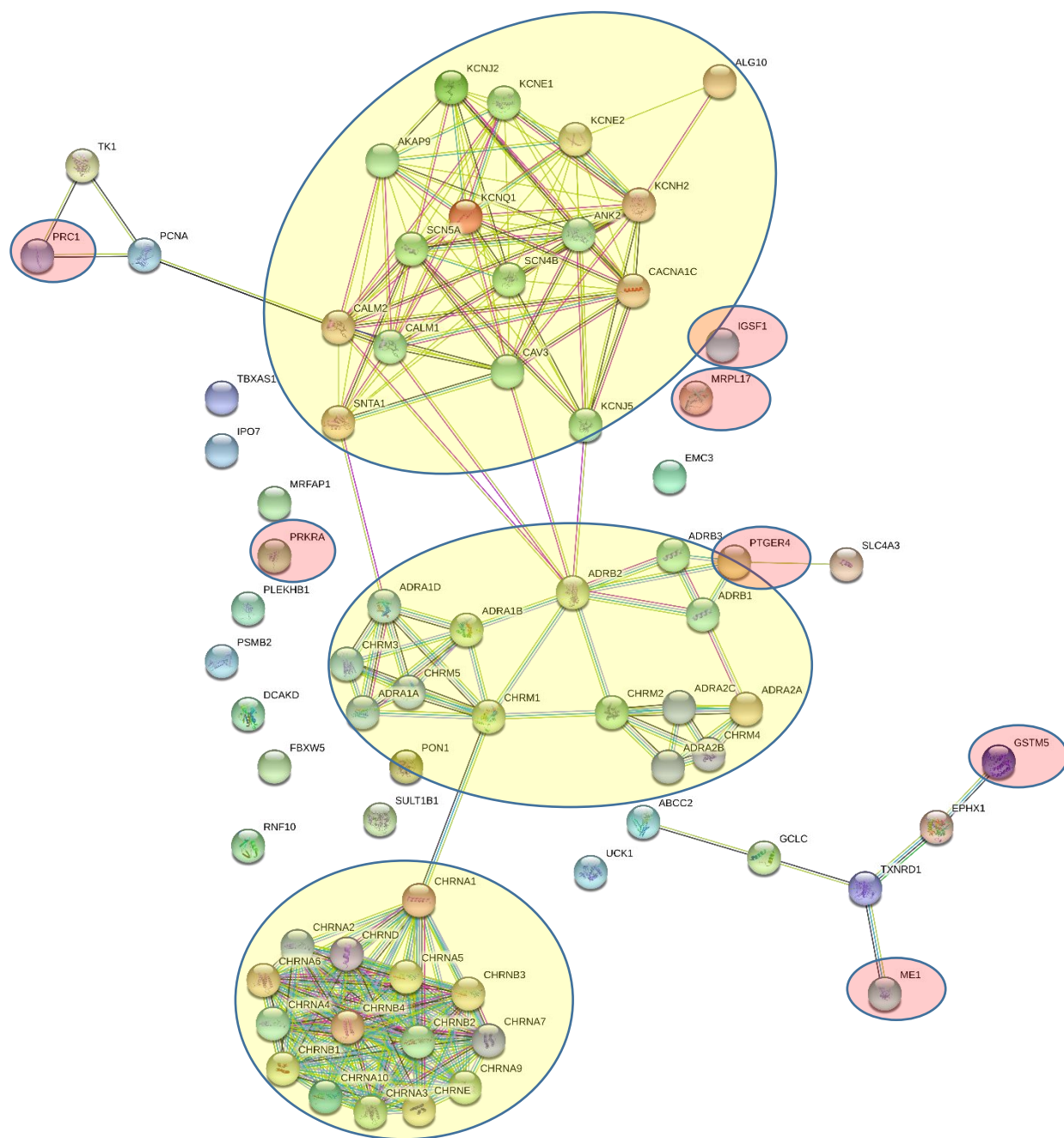
Section 3.3.74.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Sulfonamides

In Figure 86, genes associated with cLQTS are highlighted in yellow at the top right. Genes associated with the ANS are connected and highlighted yellow at the bottom center and top left.

IGSF1, **PRC1**, and **PRKRA** are associated with immune responses and apoptosis. Mean expression of all of these was lower in the QT group compared to the same probes in the NQT group.

PTGER4 is associated with G protein activity. Mean expression of PTGER4 was lower in the QT group compared to the NQT group.

GSTM5 is associated with glutathione. Mean expression of GTSM5 was lower in the QT group compared to the NQT group.

ME1 is associated with fatty acid metabolism. Mean expression of ME1 was lower in the QT group compared to the NQT group.

MRPL17 is a mitochondrial ribosomal protein. Mean expression of MRPL17 was lower in the QT group compared to the NQT group.

Section 3.3.75: Sulfones

Table LXXXIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Sulfones

Probe ID	Gene Symbol	Human Equivalent Gene Name
U86635_PROBE1	GSTM5	Glutathione S-transferase mu 5
NM_017049_PROBE1	SLC4A3	Solute carrier family 4 member 3
U94856_PROBE1	PON1	Paraoxonase 1
AA800803_PROBE1	DCAKD	Dephospho-CoA kinase domain containing
M22642_PROBE1	TK1	Thymidine kinase 1
AW253367_PROBE1	RNF10	Ring finger protein 10
AI454418_PROBE1	IGSF1	Immunoglobulin superfamily member 1
U94709_PROBE1	PTGER4	Prostaglandin E receptor 4

Figure 87: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Sulfones

Permanent Link: http://bit.ly/2xoDTsZ
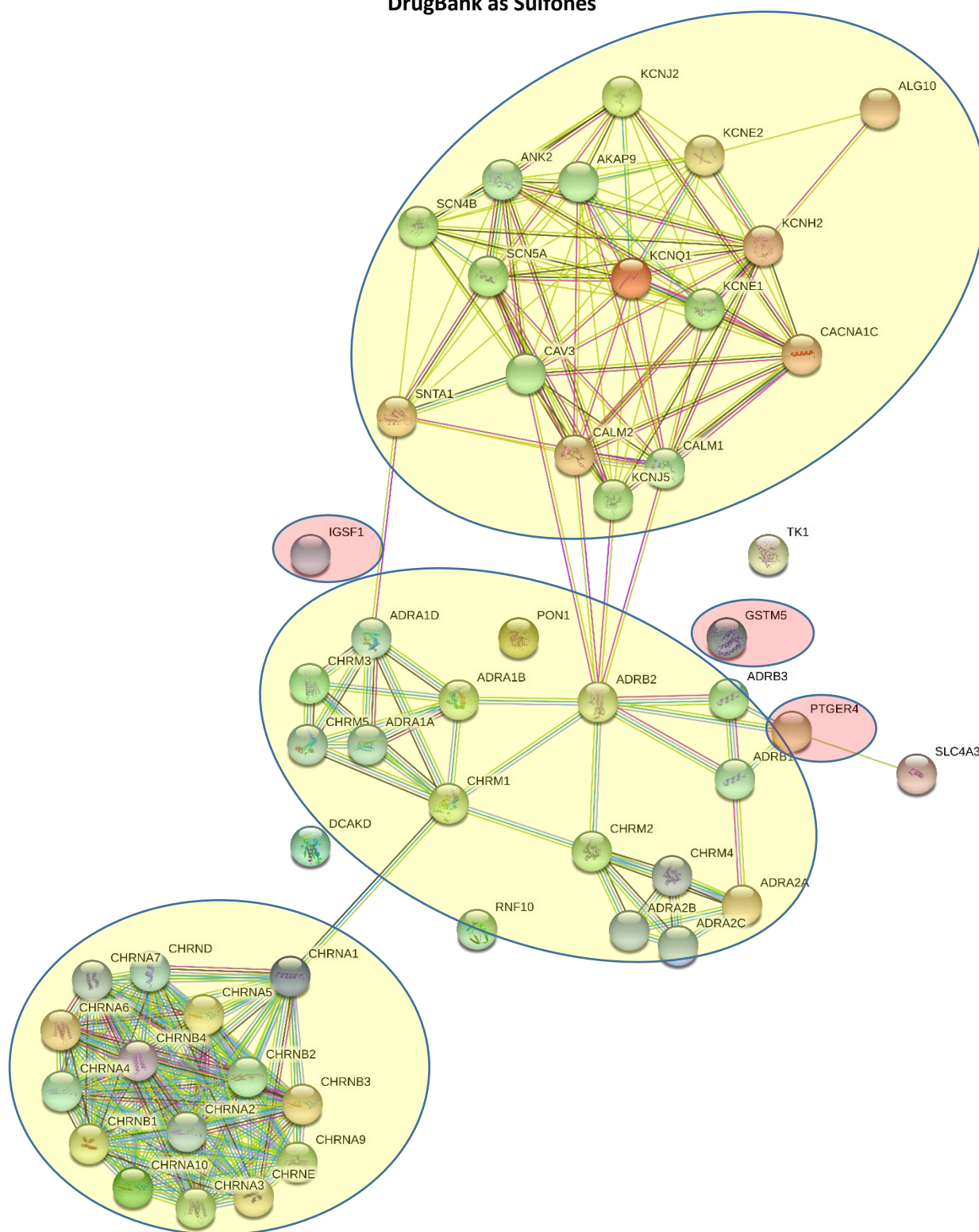
Section 3.3.75.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Sulfones

In Figure 87, genes associated with cLQTS are highlighted in yellow at the top. Genes associated with the ANS are connected and highlighted yellow at the center and bottom left.

GSTM5 is associated with glutathione. Mean expression of GSTM5 was lower in the QT group compared to the NQT group.

IGSF1 is associated with immune responses. Mean expression of IGSF1 was lower in the QT group compared to the NQT group.

PTGER4 is associated with G protein activity. Mean expression of PTGER4 was lower in the QT group compared to the NQT group.

Section 3.3.76: Sulfur Compounds

Table LXXXIII: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Sulfur Compounds

Probe ID	Gene Symbol	Human Equivalent Gene Name
D89375_PROBE1	SULT1B1	Sulfotransferase family 1B member 1
NM_017187_PROBE1	HMGB2	High mobility group box 2
M18467_PROBE1	GOT2	Glutamic-oxaloacetic transaminase 2
AB033418_PROBE1	SLC2A8	Solute carrier family 2 member 8
BE115417_PROBE1	MTA2	Metastasis associated 1 family member 2
BF398680_PROBE1	MAP4K4	Mitogen-activated protein kinase kinase kinase kinase 4
D10233_PROBE1	RENBP	Renin binding protein
D63834_PROBE1	SLC16A1	Solute carrier family 16 member 1
L04684_PROBE1	CACNA1S	Calcium voltage-gated channel subunit alpha1 S
BE113076_PROBE1	NFATC4	Nuclear factor of activated T-cells 4
L09653_PROBE1	TGFBR2	Transforming growth factor beta receptor 2
BF281149_PROBE1	DLGAP5	DLG associated protein 5
AA850509_PROBE1	TRIP13	Thyroid hormone receptor interactor 13
AW253880_PROBE1	KIFC1	Kinesin family member C1
AI233916_PROBE1	HLTF	Helicase like transcription factor
NM_019179_PROBE1	TYMS	Thymidylate synthetase
M69246_PROBE1	SERPINH1	Serpin family H member 1
U45986_PROBE1	MXD3	MAX dimerization protein 3
AF335281_PROBE1	STEAP3	STEAP3 metalloreductase
AA892918_PROBE1	TJP1	Tight junction protein 1
AI101475_PROBE1	DCTPP1	dCTP pyrophosphatase 1
M22323_PROBE1	ACTA2	Actin, alpha 2, smooth muscle, aorta
U69550_PROBE1	PLD1	Phospholipase D1
U89282_PROBE1	TEP1	Telomerase associated protein 1
X97831_PROBE1	SLC25A20	Solute carrier family 25 member 20
AI603128_PROBE1	CCNA2	Cyclin A2
BF281184_PROBE1	MYBL2	MYB proto-oncogene like 2
U10894_PROBE1	AIF1	Allograft inflammatory factor 1
AF072124_PROBE1	CASP7	Caspase 7
D13126_PROBE1	HPCAL1	Hippocalcin like 1
AI228249_PROBE1	LARP4B	La ribonucleoprotein domain family member 4B
BF566580_PROBE1	FANCD2	Fanconi anemia complementation group D2
M64300_PROBE1	MAPK1	Mitogen-activated protein kinase 1
AI598467_PROBE1	CDCA8	Cell division cycle associated 8
AW914045_PROBE1	EPS8L2	EPS8 like 2
AF276774_PROBE1	LIG1	DNA ligase 1
AW251612_PROBE1	TARS2	Threonyl-tRNA synthetase 2, mitochondrial (putative)
AF220760_PROBE1	TXNRD1	Thioredoxin reductase 1
L18889_PROBE1	CANX	Calnexin

Figure 88: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Sulfur Compounds

Permanent Link (Short link not provided by String): https://version-10-5.string-
db.org/cgi/network.pl?all_channels_on=1&block_structure_pics_in_bubbles=0&direct_neighbor=1&hide_disconnected_nodes
=0&hide_node_labels=0&limit=0&network_display_mode=svg&network_flavor=evidence&targetmode=proteins&identifiers=9
606.ENSP00000296503%250D9606.ENSP00000258385%250D9606.ENSP00000217381%250D9606.ENSP00000349467%250D96
06.ENSP00000320828%250D9606.ENSP00000343782%250D9606.ENSP00000310749%250D9606.ENSP00000261007%250D960
6.ENSP00000401867%250D9606.ENSP00000304290%250D9606.ENSP00000312663%250D9606.ENSP00000351905%250D9606
.ENSP00000365227%250D9606.ENSP00000250699%250D9606.ENSP00000355192%250D9606.ENSP00000155840%250D9606.
ENSP00000289957%250D9606.ENSP00000247461%250D9606.ENSP00000287647%250D9606.ENSP00000166345%250D9606.E
NSP00000393963%250D9606.ENSP00000358060%250D9606.ENSP00000274026%250D9606.ENSP00000306490%250D9606.EN
SP00000266376%250D9606.ENSP00000434516%250D9606.ENSP00000362469%250D9606.ENSP00000276410%250D9606.ENS
P00000328968%250D9606.ENSP00000385026%250D9606.ENSP00000263274%250D9606.ENSP00000359285%250D9606.ENSP
00000305372%250D9606.ENSP00000266483%250D9606.ENSP00000386069%250D9606.ENSP00000376822%250D9606.ENSP0
0000224784%250D9606.ENSP00000314363%250D9606.ENSP00000319984%250D9606.ENSP00000215832%250D9606.ENSP00
000358327%250D9606.ENSP00000261751%250D9606.ENSP00000281537%250D9606.ENSP00000308770%250D9606.ENSP000
00349588%250D9606.ENSP00000350894%250D9606.ENSP00000368766%250D9606.ENSP00000290310%250D9606.ENSP0000
0326128%250D9606.ENSP00000409378%250D9606.ENSP00000245206%250D9606.ENSP00000357461%250D9606.ENSP00000
262715%250D9606.ENSP00000315644%250D9606.ENSP00000387281%250D9606.ENSP00000339960%250D9606.ENSP000003
22524%250D9606.ENSP00000315602%250D9606.ENSP00000217026%250D9606.ENSP00000372750%250D9606.ENSP0000040
7546%250D9606.ENSP00000272298%250D9606.ENSP00000369960%250D9606.ENSP00000322460%250D9606.ENSP00000358
301%250D9606.ENSP00000243457%250D9606.ENSP00000388910%250D9606.ENSP00000341940%250D9606.ENSP000003263
05%250D9606.ENSP00000342793%250D9606.ENSP00000337255%250D9606.ENSP00000316121%250D9606.ENSP0000026218
6%250D9606.ENSP00000255380%250D9606.ENSP00000358640%250D9606.ENSP00000377303%250D9606.ENSP00000280155
%250D9606.ENSP00000299565%250D9606.ENSP00000308944%250D9606.ENSP00000278823%250D9606.ENSP00000293780%
250D9606.ENSP00000247191%250D9606.ENSP00000306662%250D9606.ENSP00000348573

Section 3.3.76.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Sulfur Compounds

In Figure 88, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the bottom left and bottom right.

MAP4K4 and **MAPK1** are part of the MAPK family. Mean expression for both was lower in the QT group compared to the same probes in the NQT group.

CACNA1S is a Ca^{2+} ion channel. Mean expression of CACNA1S was lower in the QT group compared to the NQT group.

CANX and **NFATC4** are associated with immune responses. Mean expression of both was lower in the QT group compared to the same probes in the NQT group.

GOT2 is associated with metabolite exchange between mitochondria and the cytosol, and it is also involved with fatty acid metabolism. Mean expression of GOT2 was lower in the QT group compared to the NQT group.

TYMS is involved with mitochondrial metabolism. Mean expression of TYMS was lower in the QT group compared to the NQT group.

SLC2A8 is an insulin-mediated glucose transporter, which might suggest a link to diabetes. Mean expression of SLC2A8 was lower in the QT group compared to the NQT group.

Section 3.3.77: Topoisomerase II Inhibitors

Table LXXXIV: Differentially Expressed Genes Used as Input from Drugs Classified in DrugBank as Topoisomerase II Inhibitors

Probe ID	Gene Symbol	Human Equivalent Gene Name
AW915580_PROBE1	PCF11	PCF11 cleavage and polyadenylation factor subunit
NM_017034_PROBE1	PIM1	Pim-1 proto-oncogene, serine/threonine kinase
AF044264_PROBE1	NPY5R	Neuropeptide Y receptor Y5
AI009197_PROBE1	VKORC1	Vitamin K epoxide reductase complex subunit 1
L04535_PROBE1	SSTR5	Somatostatin receptor 5
AI009820_PROBE1	SLC35F5	Solute carrier family 35 member F5
AI555457_PROBE1	CTNNAL1	Catenin alpha like 1
AJ000347_PROBE1	BPNT1	3'(2'), 5'-bisphosphate nucleotidase 1
NM_012818_PROBE1	AANAT	Aralkylamine N-acetyltransferase
AI012235_PROBE1	CXCL11	C-X-C motif chemokine ligand 11
AI407464_PROBE1	SIPA1L2	Signal induced proliferation associated 1 like 2
AF069306_PROBE1	TALDO1	Transaldolase 1
NM_012747_PROBE1	STAT3	Signal transducer and activator of transcription 3
D85760_PROBE1	GNA12	G protein subunit alpha 12
U19614_PROBE1	TOR1AIP1	Torsin 1A interacting protein 1
D00833_PROBE1	GLRA1	Glycine receptor alpha 1
NM_012670_PROBE1	TCP1	T-complex 1
NM_017022_PROBE1	ITGB1	Integrin subunit beta 1
AA819488_PROBE1	PDCD6	Programmed cell death 6
AW143093_PROBE1	GGT7	Gamma-glutamyltransferase 7
AW916347_PROBE1	SMPD1	Sphingomyelin phosphodiesterase 1
NM_012705_PROBE1	CD4	CD4 molecule
NM_019326_PROBE1	NEUROD2	Neuronal differentiation 2

Figure 89: String Database Results for Top Differentially Expressed Genes using Drugs Classified in DrugBank as Topoisomerase II Inhibitors

Permanent Link: http://bit.ly/2xoFnmY
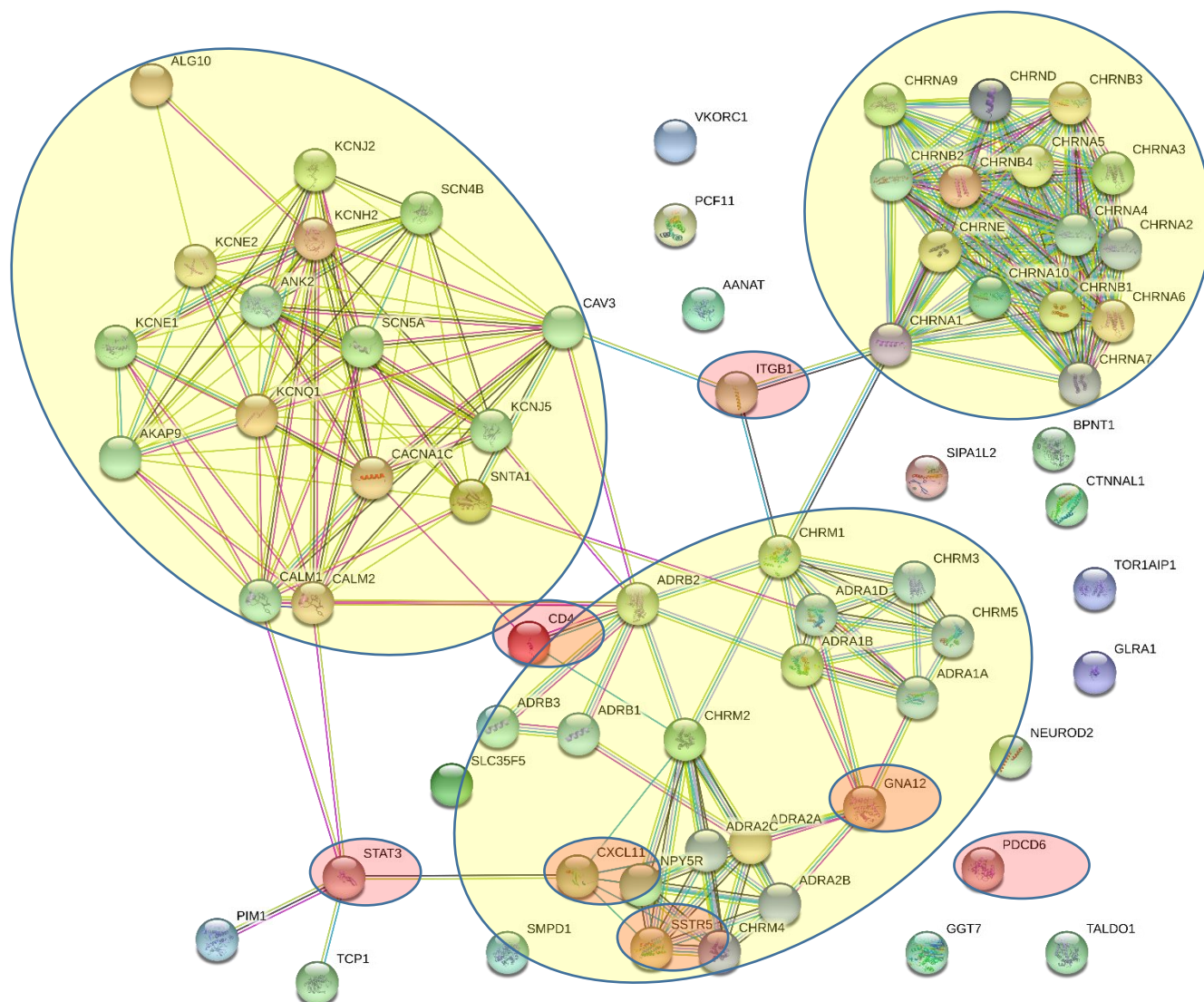
Section 3.3.77.1: Observations from String and Proposed Mechanisms using Drugs Classified in DrugBank as Topoisomerase II Inhibitors

In Figure 89, genes associated with cLQTS are highlighted in yellow at the top left. Genes associated with the ANS are connected and highlighted yellow at the bottom center and top right.

CD4, **CXCL11**, **STAT3**, and **PDCD6** are associated with immune responses and apoptosis. Mean expression of CXCL11 and STAT3 was lower in the QT group compared to the same probes in the NQT group. Mean expression of CD4 and PDCD6 was higher in the QT group compared to the same probes in the NQT group.
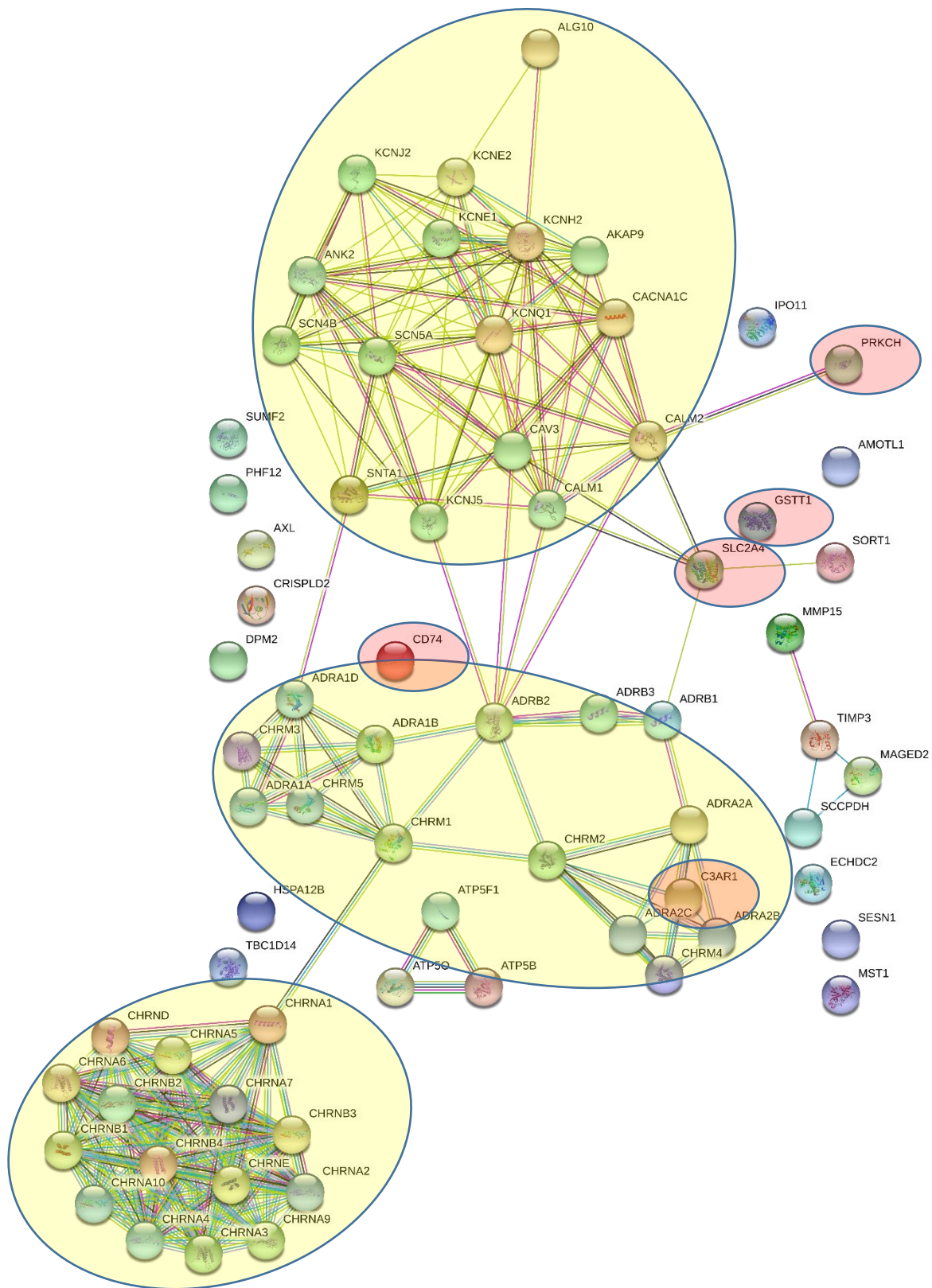
GNA12 and **SSTR5** are associated with G protein activity. Mean expression of GNA12 was higher in the QT group compared to the NQT group. Mean expression of SSTR5 was lower in the QT group compared to the NQT group.

CHAPTER 4: CONCLUSIONS

Prolongation of the QT interval on the electrocardiogram is acknowledged to be an imperfect cardiac safety biomarker and current patch clamp prediction methods leave room for improvement in terms of sensitivity and specificity. This study was intended to demonstrate a procedural proof of concept and to suggest a starting point for future studies. Being able to make more informed choices about which chemical entities to further pursue can help expedite the time to market while reducing the associated costs and ultimately provide ways to introduce safer and more effective new drugs, and to find ways to safely expand the use of existing drugs for novel indications.

The ICH E14 guideline currently considers a QT prolongation of greater than 10 milliseconds in humans to be clinically significant. Given the differences in animal species, and the fact that it is a guidance rather than a requirement, ICH S7B does not provide similar pre-clinical threshold requirements, although the investigator should be able to justify the model and any thresholds used in pre-clinical studies. Current ICH guidances also currently do not include or suggest the use of machine learning models. The results of this investigation suggest that machine learning tools might be considered as an addition to the guidances. The CiPA initiative, while suggesting the need for better methods, does not suggest the use of multi-gene expression signatures as defined in this investigation. At the time of this writing, the authors are not aware of a similar associative study using a large number of pre-clinical expression profiles related to drug exposure to directly predict QT liability in humans, thus we believe this represents a novel proposal.

The primary question being addressed in this investigation is whether or not the available open-source *in vivo* rat liver RNA expression data can be used to derive an expression profile which can be used as a biomarker and as input to *in silico* machine learning-based predictions of QT prolongation in humans to augment the currently evolving CiPA paradigm. The results of this investigation suggest machine learning classification algorithms may be used to predict QT prolongation liability and augment

286

pre-clinical cardiac safety testing in the drug development process. While the phenomenon of drug-induced QT prolongation does occur in rats, this investigation is not intended to predict QT prolongation in the rat model since it is not relevant to the primary endpoint and electrophysiological differences are known to exist between rats and humans, nor is it intended to imply that one or more genes are directly responsible for prolongation of the QT interval in rats or in humans. While the association of the expression of some protein or combination of proteins in rat liver may not necessarily suggest a mechanistic link to prolongation of the QT interval in humans, the expression signature could be used as both a biomarker during the drug development process and as guide to suggest further studies to elucidate novel physiological pathways.

The SVMs trained in this investigation consistently performed better than recently reported patch clamp sensitivities and specificities. Given the limitations of machine learning, this does not suggest that machine learning should be a replacement for patch clamp testing; however, the SVM sensitivity and specificity results from this study suggest that the available dataset may be suitable to augment the existing pre-clinical toolset for QT prolongation predictions in humans. By comparison to the 64-82% sensitivity and 75-88% specificity reported from patch clamp predictions of QT prolongation in humans, using all datasets as input to an SVM (i.e. a general, nonspecific dataset only classified as QT or NQT), sensitivity was found to be approximately 3-21% higher and the specificity was approximately 2-15% higher than patch clamp models. On sub-classified (i.e. more targeted) models, sensitivities were on average approximately 10-28% higher and specificities were approximately 6-19% higher than existing patch clamp models. With additional microarray probes designed specifically for testing QT prolongation liability from heart tissue, machine learning classification models may be a promising addition to the existing tools used for pre-clinical and clinical QT liability evaluations. By extension, such analyses could potentially contribute to the increased safety of drugs being developed as well as for

drugs currently on the market. Such modeling information could also contribute to the drug development process when making decisions about continuing development of a new drug.

Clustering showed that drugs may cluster together to 1) predict QT prolongation for drugs currently not classified to do so, 2) help clarify and narrow potential mechanisms associated with QT prolongation which are gene expression-based, 3) suggest novel uses for existing drugs, and 4) serve as a validity check of the model, assuming QT prolonging drugs cluster together, which in this study was the case. Clustering results may be further used to consider potential alternative uses for drugs within the same cluster, such as one drug in the cluster that is known to prolong QT while another does not, the NQT drug might be considered as a safer alternative for clinical therapy. Further tuning of the clustering process may help to identify additional "cluster specific" expression signatures that may be associated with QT prolongation and which may be used to suggest further in vitro or in vivo studies and perhaps contribute to an individualized medicine approach based on gene expression or variants thereof.

Regarding the limitations of this investigation, the public domain dataset used is expansive, but the probe set was designed to explore and classify drugs based on a hepatotoxicity profile and the experimental data is derived from rat liver tissue in only male rats. From the perspective of human cardiac physiology, the rat liver data used in this study is from a surrogate tissue so the extent of expression conservation or differences between rat liver and human cardiomyocytes is unclear. The microarray chips used in this study may not contain an optimal probe set to target and evaluate human cardiotoxicity. The dataset also does not contain a consistent number of microarray experiments for each drug. An additional limitation is that some drugs had data for multiple doses while others only had one dose, and some drugs had varying numbers of exposure durations, all of which contribute to a bias in the datasets which could impact the training of machine learning models and the clustering results. For example, amiodarone in the QT drug group had microarray datasets for one dose (147mg), and that one dose was tested at three durations (1 day, 3 days, and 5 days). All three dose-durations had 3

microarray datasets available (i.e. triplicate tests for all dose-durations). By comparison in the NQT drug group, indomethacin had microarray datasets from six doses with the number of duration groups ranging from 1-4 and the number of experiments at each dose-duration group ranging from 2-3. All available microarray experiments for all of the drugs tested were included to avoid selection bias in the choice of datasets, although it is acknowledged that the imbalance in the number of datasets for each drug introduces a different type of bias. Furthermore, the list of drugs available in this investigation only contain a small subset (less than 13%) of the drugs currently classified in CredibleMeds as having the potential to prolong the QT interval in humans. The extent to which a particular drug/dose/duration prolonged the QT interval in the rat model was not available, nor was the absorption, distribution, metabolism, and excretion (ADME) data from the original experiment available, and therefore not taken into consideration when building the SVM models.

Networks connections from String had several connections to the genes associated with cLQTS and the autonomic nervous system which are described in more detail in each of the applicable drug classes. Since autorhythmic cardiomyocytes can be influenced by autonomic inputs, drugs which influence the autonomic nervous system may indirectly impact the electrophysiology of the heart by way of the autonomic innervation of the autorhythmic cardiomyocytes.

In this project, there were 4 drug classes associated with the nervous system used in this project. Heart rate variability (HRV) and the QT interval are known to be influenced by the autonomic nervous system. Heart rate variability can be broken in to two broad categories: 1) acute HRV, and 2) diurnal HRV. Differential expression of genes related to the ANS resulting from pharmaceuticals may have different effects depending on acute and diurnal autonomic states and drug exposure in terms of concentration and duration. Further investigation would be required to determine what impact, if any, direct or indirect autonomic changes related to pharmaceutical use might have on the QT interval and subsequently the liability to potentially life-threatening cardiac arrhythmias.

While it is acknowledged that the phenomenon of direct ion channel blockade exists, expression of proteins directly connected to cLQTS or ANS proteins had six prevailing association patterns across the 77 groupings, which are presented here alphabetically which may be considered for further study as potential biomarkers, even if the associated processes do not directly impact cardiac electrophysiology:

1) Fatty acid metabolism
2) G proteins
3) Glutathione
4) Immune responses and apoptosis
5) Mitochondrial activity and electron transport
6) Mitogen activated protein kinases (MAPKs)

While it is widely accepted that association does not imply a cause, differential expression of certain genes may be used as a predictive biomarker. Experiments could also be performed to confirm an existing known pathway or elucidate new mechanistic pathways.

The degree to which fatty acid β-oxidation contributes to overall oxidative energy metabolism in cardiac cells can range from almost 100% of the total energy requirement of the heart, to only making a minor contribution [32]. Marfella, et al. [33] suggests that elevated plasma fatty acid may stimulate the sympathetic NS and affect ventricular repolarization at least in part due to increased catecholamines, which in turn, can prolong the QT interval. Inhibition of fatty acid metabolism through a downregulation of the proteins associated with the process may be a possible way to increase circulating fatty acid and by extension prolong the QT interval. This could be experimentally confirmed by inhibiting genes which encode proteins associated with fatty acid metabolism and measuring circulating fatty acids and catecholamines.

G proteins are involved in a constellation of intracellular physiological processes. Increased or decreased expression of genes involved with these processes extends beyond the scope of this discussion and could be multiple separate projects. While it would need to be confirmed experimentally, it is possible that intracellular processes may competitively use intracellular ions or change intracellular ion concentrations, modify the allosteric conformation of membrane bound ion

channel proteins, or generate a metabolite which might block ion channels from the cytoplasmic side of the plasma membrane. The HTR7 (serotonin) receptor is mediated by G proteins and is associated with cytokines. The activity of this receptor is mediated by G proteins that stimulate adenylate cyclase. The appearance of adverse cardiac events, including cardiac arrhythmias (torsade de pointes and QT prolongation), syncope, increased systolic and diastolic right ventricular volume, and the production of pro-inflammatory cytokines leading atherosclerosis development, has also been expected with the chronic use of some types of selective serotonin re-uptake inhibitors (SSRIs) [34].

Glutathione is an antioxidant which prevents cellular damage by acting as an electron donor and is subsequently reduced enzymatically using NADPH as an electron donor. It is not clear how downregulation of this might directly or indirectly impact cardiac electrophysiology, but givent the link to oxidative metabolism, there may be a functional link with mitochondrial activity and electron transport changes also identified in this study which were also downregulated. Ayden, et al. [35] suggest that glutamine is the precursor of glutathione which is an antioxidant and has been demonstrated to improve outcome after several critical illnesses. Ayden further suggests that recent studies have shown that several special amino acids, such as glutamine, glycine, arginine and taurine, exhibit cytoprotective effect on the cardiomyocyte, and have established the cardioprotective properties of glutamine. Ayden demonstrated the protective role of glutamine against cardiotoxic effects of a pesticide in rats. This protective effect was confirmed by showing both tissue level improvement in oxidative stress markers and improvement in prolonged QT interval.

Immune responses and apoptosis involve numerous proteins and gene expression sequences and cascades. Whether there is a direct link between genes associated with immune responses found in this study and QT prolongation would need to be experimentally determined; however, links have been shown between increased levels of interleukins, TNFα, and other cytokines associated with immune responses, apoptosis, and prolongation of the QT interval in addition to the production of pro-

inflammatory cytokines leading atherosclerosis development as described in the section related to G

proteins above. Lazzerini, et al. [36] and Sordillo, et al. [37] have suggested an immune component link

to QT prolongation. Spence, et al. [38] suggested a link between apoptosis and QT prolongation. Bronte,

et al. [39] have suggested a link between RAS activity and QT prolongation. Furthermore, differentially

expressed genes related to glucagon and glucose metabolism might suggest a potential link to diabetes.,

there are known associations between diabetes and prolongation of the QT interval have been proposed

by Dimitropoulos, et al. [9] and Kobayashi, et al. [40].

Oxidative metabolism involves the transfer of electrons between chemical entities. Oxidative

metabolism of fatty acids is one example, and the electron transport chain associated with oxidative

phosphorylation which takes place in mitochondria is another example. In this investigation, several

mitochondrial ribosomal proteins were differentially expressed and downregulated in the QT group

compared to the corresponding NQT group. Baik, et al. [41] found prolongation of the QT interval to be

associated with mitochondrial disease in children.

Mitogen activated protein kinases (MAPKs) are a family of proteins that communicate signals

from cell surface receptors to the nucleus to control DNA as part of the cell replication cycle.

Malfunctions in MAPKs are commonly associated with the uncontrolled cell replication cycle associated

with cancer. Schrader, et al. [42] demonstrated that MAPKs can regulate potassium channels by direct

phosphorylation in neurons. The impact of changes in expression of one or more differentially expressed

MAPKs found in this study on potassium and other ion channels and the cardiac action potential would

require further investigation.

Considering current state and future directions, the Natsoulis study was designed to evaluate

heptatotoxicity and did not include ECG measurements since it was not an endpoint for that study. To

make the type of *in silico* assessment proposed here more robust, future studies should consider the

development of an expression library by testing all available compounds known to prolong the QT

interval in humans pre-clinically both *in vivo* and *in vitro* using multiple animal models. The study design

for each drug would include the use of untreated animals, animals treated with the drug vehicle alone,

positive control substances, and reference compounds to demonstrate responsiveness of *in vitro*

preparations and to evaluate assay sensitivity for *in vivo* studies. Inclusion of ECG monitoring such as

telemetry during the course of drug treatment would be helpful to track the magnitude and duration of

interval changes associated with drug treatment, and the establishment of gene expression profiles for

ECG changes above/below the established thresholds. Categorization of QT prolongation changes into

categories such as small, moderate, large or a quantitative equivalent may help with the assessment of

expression differences as well as the doses at which these changes occur for each drug.

For electrophysiological testing, ICH S7B suggests the use of other animal models such as

monkey, dog, swine, rabbit, ferret, and Guinea pig because of their similarity to human

electrophysiology. ICH S7B also states that the primary cardiac ion currents in rats and mice are

different from humans so electrophysiological testing in rats and mice is not considered appropriate,

thus the aforementioned animal models would be better for experiments which would integrate gene

expression and electrophysiological testing. Surrogate animal models are widely used in the drug

development process; however, gene expression differences between species might be considered

limitations for these models, although the extent of that limitation is not currently clear. Knowing that

QT interval differences related to gender exist, inclusion of both male and female species would be

required to test for gender differences. Furthermore, collection of different organ tissues from the

same experiment might help to elucidate previously unknown organ-organ interactions such as a heart-

liver interaction that might address the question of QT prolongation in cirrhosis or similar interactions. A

broader tissue base would also allow for GWAS studies. While experimentation in humans would

represent the most robust results for predictions in humans, the technical and ethical considerations

make the limitations of such testing self-evident. Given alternate splicing and single nucleotide

polymorphisms (SNPs), consideration should be given to more than just RNA probes and should include DNA and protein assays. The expression of microRNAs should also be considered. Collection of gene expression data during a sustained episode of an arrhythmia such as TdP would be technically difficult to collect but might reveal pathological changes related to genetic expression in both naturally occurring scenarios such as cLQTS and diLQTS. Confounding factors for *in vivo* experiments include effects on heart rate or autonomic tone introduced by a particular test-substance, and toxicities such as emesis, tremors, or convulsions should also be considered when developing *in vivo* models.

It is also possible that a metabolite produced by the breakdown of a drug can prolong the QT interval while the parent compound does not, thus considerations should be made for expression changes that may be caused by a metabolite rather than the parent compound. Future experiments should also consider Absorption Distribution Metabolism and Excretion (ADME) profiles and both intracellular and extracellular ion concentrations.

A better understanding of gene expression profiles associated with drug-induced QT prolongation may help to confirm existing mechanisms and elucidate novel molecular pathways such as ion concentration changes associated with these genetic expression changes that might prolong the QT interval and may serve as a novel biomarker for cardiotoxicity.

While an association between rat liver RNA expression profiles and QT prolongation in human heart tissue does not imply that a specific gene expression profile is responsible for the QT prolongation in a direct way, the results of this investigation suggest that gene expression profiles can be used to predict QT liability in pre-clinical testing. Further development and use of machine learning methods may augment the current process of testing ion channel activities as part of pre-clinical cardiac safety assessment of drugs during the discovery and development process and may lead to a better mechanistic understanding of off-target effects which might contribute to new indications for new drugs, and introducing safer new drugs to market more quickly and at a reduced cost.

CITED LITERATURE

1. Isbister, GK, Page, CB. *Drug Induced QT Prolongation: The Measurement and Assessment of the QT Interval in Clinical Practice.* British Journal of Clinical Pharmacology. 2013 Jul; 76(1): 48-57.

2. Nachimuthu, S, Assar, MD, Schussler, JM. *Drug-Induced QT Interval Prolongation: Mechanisms and Clinical Management.* Therapeutic Advances in Drug Safety. 2012 Oct; 3(5): 241-253.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline E14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrythmic Drugs. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

4. Vincent, GM. *The Long QT Syndrome.* Indian Pacing Electrophysiol Journal. 2002 Oct; 2(4): 127-142.

5. Newton-Cheh C, Larson MG, Corey DC, Benjamin EJ, Herbert AG, Levy D, D'Agostino RB, O'Donnell CJ. *QT Interval is a Heritable Quantitative Trait with Evidence of Linkage to Chromosome 3 in a Genome-Wide Linkage Analysis: The Framingham Heart Study.* Heart Rhythm. 2005; 2: 277–284.

6. Newton-Cheh C, Eijgelsheim M, Rice KM, de Bakker PI, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JC, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BH. *Common Variants at Ten Loci Influence QT Interval Duration in the QTGEN Study.* Nature Genetics. 2009; 41: 399–406.

7. Silverman, E. *What Does It Cost to Develop a New Drug? Latest Study Says $2.6 Billion.* Wall Street Journal (20 November 2014).

8. Parekh, A, Buckman-Garner S, McCune S, ONeill R, Geanacopoulos M, Amur S, Clingman C, Barratt R, Rocca M, Hills I, Woodcock J. *Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities.* Clinical Pharmacology and Therapeutics. Volume 97, Issue 3, March 2015: 221-233.

9. Dimitropoulos, G, Tahrani, AA, and Stevens, MJ. *Cardiac Autonomic Neuropathy in Patients with Diabetes Mellitus.* World Journal of Diabetes. 2014 Feb15; 5(1): 17–39.

10. Fossa, AA. *The Impact of Varying Autonomic States on the Dynamic Beat-to-Beat QT–RR and QT–TQ Interval Relationships.* British Journal of Pharmacology. 2008 Aug; 154(7): 1508–1515.

11. Fouad, YM, and Yehia, R. *Hepato-Cardiac Disorders.* World Journal of Hepatology. 2014 Jan 27; 6(1): 41–54.

12. Mozos, I. *Arrhythmia Risk in Liver Cirrhosis.* World Journal of Hepatology. 2015 Apr 8; 7(4): 662–672.

13. Shi RQ, Lee JK, Hayashi Y, Takeuchi Y, Kambe F, Futaki S, Seo H, Murata Y, Kodama I. *Long-Term Amiodarone Treatment Causes Cardioselective Hypothyroid-Like Alteration in Gene Expression Profile.* European Journal of Pharmacology. 2008 Jan 14; 578(2-3): 270-8.

CITED LITERATURE (continued)

14. Vicente J, Johannesen L, Mason JW, Crumb WJ, Pueyo E, Stockbridge N, and Strauss DG, *Comprehensive T wave morphology assessment in a randomized clinical study of dofetilide, quinidine, ranolazine, and verapamil.* Journal of the American Heart Association. (2015) Apr; 4(4): e001615.

15. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. The Non-Clinical Evaluation of the Potential for Delayed Venetricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

16. Babcock JJ, Du F, Xu K, Wheelan SJ, Li M. *Integrated Analysis of Drug-Induced Gene Expression Profiles Predicst Novel hERG Inhibitors.* PLoS One. 2013 Jul 23; 8(7): e69513.

17. Gintant G, Sager PT, Stockbridge N. *Evolution of Strategies to Improve Preclinical Cardiac Safety Testing.* Nature Reviews Drug Discovery. 2016 Jul; 15(7): 457-71.

18. https://www.yourgenome.org/facts/how-are-drugs-designed-and-developed

19. https://lifeinthefastlane.com/ecg-library/basics/qt_interval/

20. Sintra Grilo L, Carrupt PA and Abriel H. *Stereoselective inhibition of the hERG1 potassium channel.* Frontiers in Pharmacology. 2010; 1: 137.

21. Claret B, Claret M, and Mazet JL. *Ion transport and membrane potential of rat liver cells in normal and low-chloride solutions*. Journal of Physiology. 1973; 230: 87-101.

22. Natsoulis G, Pearson CI, Gollub J, Eynon BP, Ferng J, Nair R, Idury R, Lee MD, Fielden MR, Brennan RJ, Roter AH, Jarnagin K. *The Liver Pharmacological and Xenobiotic Gene Response Repertoire.* Molecular Systems Biology. 2008; 4: 175.

23. Domingos P. *A Few Useful Things to Know about Machine Learning*. Communications of the ACM. 2012; 55 (10): 78-87.

24. http://www.holehouse.org/mlclass/10_Advice_for_applying_machine_learning.html

25. Cortes C, and Vapnik V. *Support-Vector Networks*. Machine Learning. 1995; 20: 273-297.

26. Gillani Z, Akash MSH, Rahaman MDM, and Chen M. *Compare SVM: Supervised Support Vector Machine (SVM) Inference of Gene Regularity Networks*. BMC Bioinformatics. 2014; 15(1): 395.

27. https://www.researchgate.net/figure/260283043_fig13_Figure-A15-The-non-linear-SVM-classifier-with-the-kernel-trick

28. https://www.quora.com/What-are-C-and-gamma-with-regards-to-a-support-vector-machine

CITED LITERATURE (continued)

29. Meyer D, Dimitriadou E, Hornik K, Weingessel A, and Leisch F (2015). *e1071: Misc Functions of the Department of Statistics, Probability Theory Group (Formerly: E1071).* TU Wein. R Package Version 1.6-7. http://CRAN.R-project.org/package=e1071

30. Dal Pozzolo A, Caelen O, and Bontempi G (2015). *unbalanced: Racing for Unbalanced Methods Selection.* R package version 2.0. https://CRAN.Rproject.org/package=unbalanced

31. Bodenhofer U, Kothmeier A, and Hochreiter S. *APCluster: An R Package for Affinity Propagation Clustering.* Bioinformatics 2011; 27: 2463-2464.

32. Lopashuk GD, Ussher JR, Folmes CDL, Jaswal JS, and Stanley WC. *Myocardial Fatty Acid Metabolism in Health and Disease.* Physiology Reviews. 2010; 90: 207-258.

33. Marfella R, De Angels L, Nappo F, Manzella D, Siniscalchi M, Paolisso G, Guigliano D. *Elevated Fatty Acid Concentrations Prolong Cardiac Repolarization in Healthy Subjects*. The American Journal of Clinical Nutrition. 2001; 73: 27-30.

34. Nezafati MH, Eshraghi A, Vojdanparast M, Abtahi S, Nezafati P. *Selective Serotonin Reuptake Inhibitors and Cardiovascular Events: A Systematic Review*. Journal of Research in Medical Sciences. 2016; 21: 66.

35. Aydin M, Yildiz A, Ibiloglu I, Ekinci A, Ulger BV, Yuksel M, Bilik MZ, Ozaydogdu N, Ekinci C, Yazgan UC. *The Protective Role of Glutamine against Acute Toxicity in Rats*. Toxicology Mechanisms and Methods. 2015; 25(4): 296-301.

36. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A, Selvi E, Bacarelli MR, Finizola F, Vanni F, Lazaro D, Aromolaran A, El Sherif N, Boutjdir M, Capecchi PL. *Systemic Inflammation as a Novel Q-T Prolonging Risk Factor in Patients with Torsade de Pointes*. Heart. 2017 Nov; 103(22): 1821-1829.

37. Sordillo PP, Sordillo DC, Helson L. *Review: The Prolonged QT Interval: Role of Pro-Inflammatory Cytokines, Reactive Oxygen Species and the Ceramide and Sphingosine-1 Phosphate Pathways*. In Vivo. 2015 Nov-Dec; 29(6): 619-36.

38. Spence S, Deurinck M, Ju H, Traebert M, McLean L, Marlowe J, Emotte C, Tritto E, Tseng M, Shultz M, Friedrichs GS. *Histone Deacetylase Inhibitors Prolong Cardiac Repolarization through Transcriptional Mechanisms*. Toxicological Sciences. 2016; 153(1): 39–54.

39. Bronte E, Bronte G, Novo G, Bronte F, Bavetta MG, Lo Re G, Brancatelli G, Bazan V, Natoli C, Novo S, Russo A. *What Links BRAF to the Heart Function? New Insights from the Cardiotoxicity of BRAF Inhibitors in Cancer Treatment*. Oncotarget. 2015 Nov 3; 6(34): 35589-601.

40. Kobayashi S, Nagao M, Asai A, Fukuda I, Oikawa S, Sugihara H. *Severity and Multiplicity of Microvasuclar Complications are Associated with QT Interval Prolongation in Patients with Type 2 Diabetes*. Journal of Diabetes Investigation. 2017 Nov 2; 1-6.

41. Baik R, Yu R, Lee YM, Kang HC, Lee JS, Kim HD. *Early Cardiac Evaluation in Children with Non-Specific Mitochondrial Disease with Isolated Mitochondrial Respiratory Chain Complex I Defect*. <u>Journal of Pediatrics and Child Health</u>. 2012 Nov; 48(11): 1016-20.

42. Schrader LA, Birnbaum SG, Nadin BM, Ren Y, Bui D, Anderson AE, and Sweatt JD. *ERT/MAPK Regulates the Kv4.2 Potassium Channel by Direct Phosphorylation of the Pore-Forming Subunit*. <u>American Journal of Physiology-Cell Physiology</u>. 2006; 290: C852-C861.

APPENDICES

Support Vector Machine Results for Individual Models and Corresponding Receiver Operating Characteristic Curves

Table LXXXV: Support Vector Classifier Results – All Classes

DrugBank Classification	Sensitivity	Specificity	MCC
All Drugs	0.8546	0.9001	0.8102
Alimentary Tract and Metabolism	0.9927	0.9668	0.9286
Amides	0.9600	0.9338	0.8837
Antifungal Agents	0.9023	0.9421	0.8361
Antifungals Dermatological	0.8881	0.9381	0.8735
AntiInfective Agents	0.8928	0.9113	0.8683
Antiinfectives for Systemic Use	0.9175	0.9752	0.9016
Antineoplastic Agents	0.9400	0.9337	0.9064
Azoles	0.9433	0.9789	0.9420
BCRP/ABCG2 Substrates	1.0000	1.0000	1.0000
Benzimidazoles	1.0000	1.0000	1.0000
Cardiovascular Agents	0.8651	0.9331	0.8136
Cardiovascular System	0.9685	0.9091	0.9009
Central Nervous System Agents	0.9335	0.9177	0.8642
Central Nervous System Depressants	0.9238	0.9414	0.8522
Chemically Induced Disorders	0.9051	0.9490	0.8765
Combined Inducers of CYP3A4 and P-Glycoprotein	0.9978	0.9668	0.8987
Combined Inhibitors of CYP3A4 and P-Glycoprotein	0.8019	0.8784	0.6358
CYP2D6 Inhibitors (Weak)	0.8603	0.9666	0.8519
CYP3A4 Inhibitors (Weak)	0.9442	0.9431	0.9817
Cytochrome P450 CYP1A2 Inhibitors	0.8437	0.9005	0.7837
Cytochrome P450 CYP1A2 Inhibitors (Moderate)	1.0000	0.9835	1.0000
Cytochrome P450 CYP1A2 Inhibitors (Weak)	0.8356	0.9103	0.7309
Cytochrome P450 CYP1A2 Substrates	0.9031	0.9111	0.8707
Cytochrome P450 CYP2A6 Inhibitors	0.9157	0.9545	0.8632
Cytochrome P450 CYP2A6 Substrates	0.9891	0.9640	0.9313
Cytochrome P450 CYP2B6 Substrates	0.9509	0.9806	0.9490
Cytochrome P450 CYP2C8 Inhibitors	0.8914	0.8955	0.8590
Cytochrome P450 CYP2C8 Substrates	0.9500	0.9527	0.9680
Cytochrome P450 CYP2C9 Inhibitors	0.8194	0.8856	0.7924
Cytochrome P450 CYP2C9 Substrates	0.9111	0.9232	0.7406
Cytochrome P450 CYP2C19 Inhibitors	0.8747	0.9039	0.7719

Table LXXXV: Support Vector Classifier Results – All Classes (continued)

DrugBank Classification	Sensitivity	Specificity	MCC
Cytochrome P450 CYP2C19 Substrates	0.8997	0.9225	0.8347
Cytochrome P450 CYP2D6 Inhibitors	0.8387	0.9117	0.7566
Cytochrome P450 CYP2D6 Substrates	0.9067	0.9338	0.8936
Cytochrome P450 CYP2E1 Inhibitors	0.9632	0.9743	0.7214
Cytochrome P450 CYP2E1 Substrates	0.8870	0.9024	0.8390
Cytochrome P450 CYP3A4 Substrates	0.8896	0.9262	0.8637
Cytochrome P450 CYP3A Inducers	0.9863	0.9785	0.9249
Cytochrome P450 CYP3A Inhibitors	0.7586	0.8709	0.6599
Cytochrome P450 Enzyme Inhibitors	0.9672	0.9788	0.9650
Dermatologicals	0.8280	0.9064	0.7223
Drugs for Acid Related Disorders	0.9631	0.9806	0.9428
Drugs for Peptic Ulcer and Gastro Oesophageal Reflux Disease (GORD)	0.9424	0.9575	0.8549
Enzyme Inhibitors	0.9011	0.9265	0.8230
Estrogen Antagonists	1.0000	0.9837	1.0000
Fluoroquinolones	0.9984	0.9721	1.0000
Gastrointestinal Agents	0.9628	0.9641	0.9658
Heterocyclic Compounds	0.7955	0.8654	0.6738
Heterocyclic Compounds – 1 Ring	0.8964	0.9334	0.8474
Heterocyclic Compounds – 2 Ring	0.8387	0.9300	0.8659
Hormone Antagonists	0.8870	0.9203	0.8515
Hormones, Hormone Substitutes, and Hormone Antagonists	0.8228	0.8383	0.7554
Hydrocarbons	0.9018	0.9524	0.9382
Hydrocarbons, Aromatic	0.9817	0.9723	1.0000
Hydrocarbons, Cyclic	0.9165	0.9494	0.9101
Hyperglycemia Associated Agents	1.0000	0.9716	1.0000
Hypotensive Agents	0.9739	0.9279	0.9234
Imidazole Derivatives	0.9440	0.9192	0.9201
Inorganic Chemicals	0.9262	0.9435	0.8923
Nervous System	0.9359	0.9293	0.9003
Neurotransmitter Agents	0.9078	0.9356	0.8221
Ophthalmologicals	0.9066	0.9445	0.9509
Peripheral Nervous System Agents	0.9319	0.9228	0.8905
P-Glycoprotein/ABCB1 Inducers	0.9705	0.9550	0.9322
P-Glycoprotein/ABCB1 Inhibitors	0.8549	0.8829	0.7510
P-Glycoprotein/ABCB1 Substrates	0.8658	0.9165	0.8038
Piperazines	1.0000	1.0000	1.0000
Polycyclic Compounds	0.8971	0.9369	0.8465
Psycholeptics	0.9383	0.9518	0.9221
Respiratory System	1.0000	1.0000	1.0000

Table LXXXV: Support Vector Classifier Results – All Classes (continued)

DrugBank Classification	Sensitivity	Specificity	MCC
Sensory Organs	0.9540	0.9350	0.8627
Steroid Synthesis Inhibitors	0.9192	0.9839	0.9360
Sulfonamides	0.9841	0.9874	0.9846
Sulfones	0.9500	0.9416	0.9696
Sulfur Compounds	0.9134	0.9384	0.8114
Topoisomerase II Inhibitors	0.9810	0.9722	0.8782
N	77	77	77
Median	0.9192	0.9384	0.8782
Median Absolute Deviation	0.0408	0.0267	0.0561
Mean	0.9203	0.9402	0.8765
Std Dev	0.0570	0.0342	0.0874
Min	0.7586	0.8383	0.6358
Max	1.0000	1.0000	1.0000

Receiver Operating Characteristic Curves by Classification

Figure 90: Receiver Operating Characteristic Curve for All Drug Classes (QT versus Non-QT)
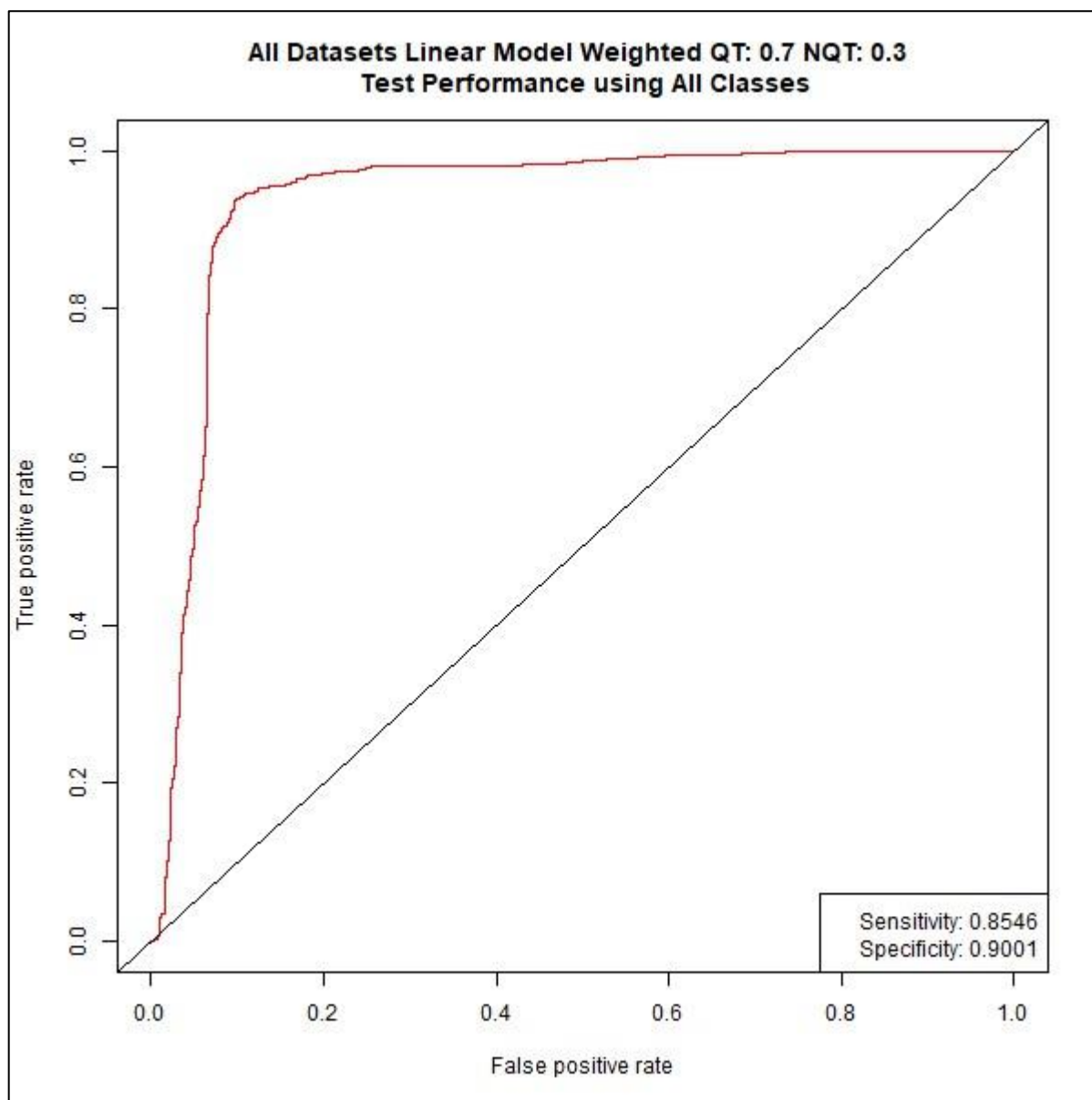
Figure 91: Receiver Operating Characteristic Curve for Alimentary Tract and Metabolism Class
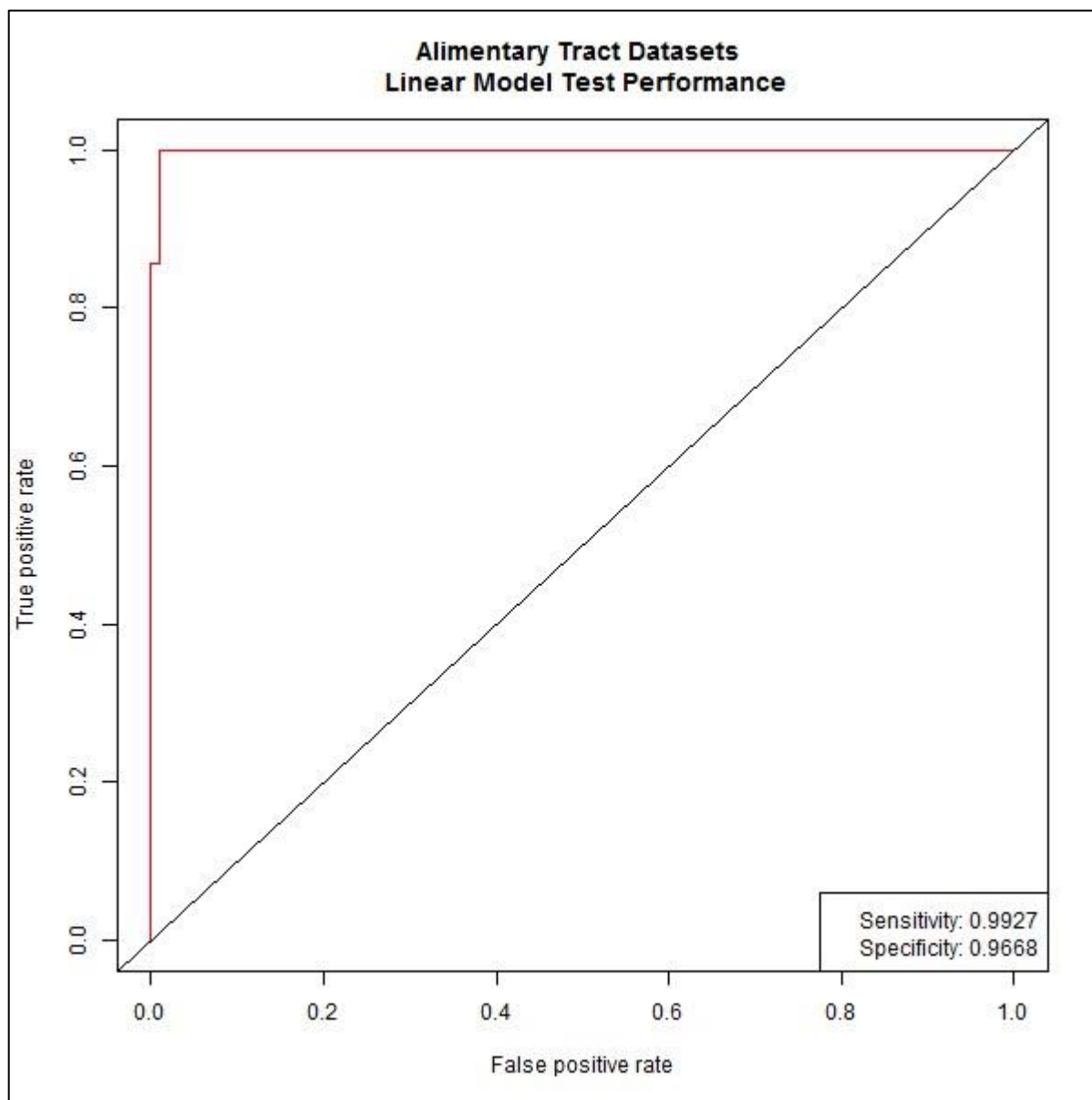
Figure 92: Receiver Operating Characteristic Curve for Amides Class
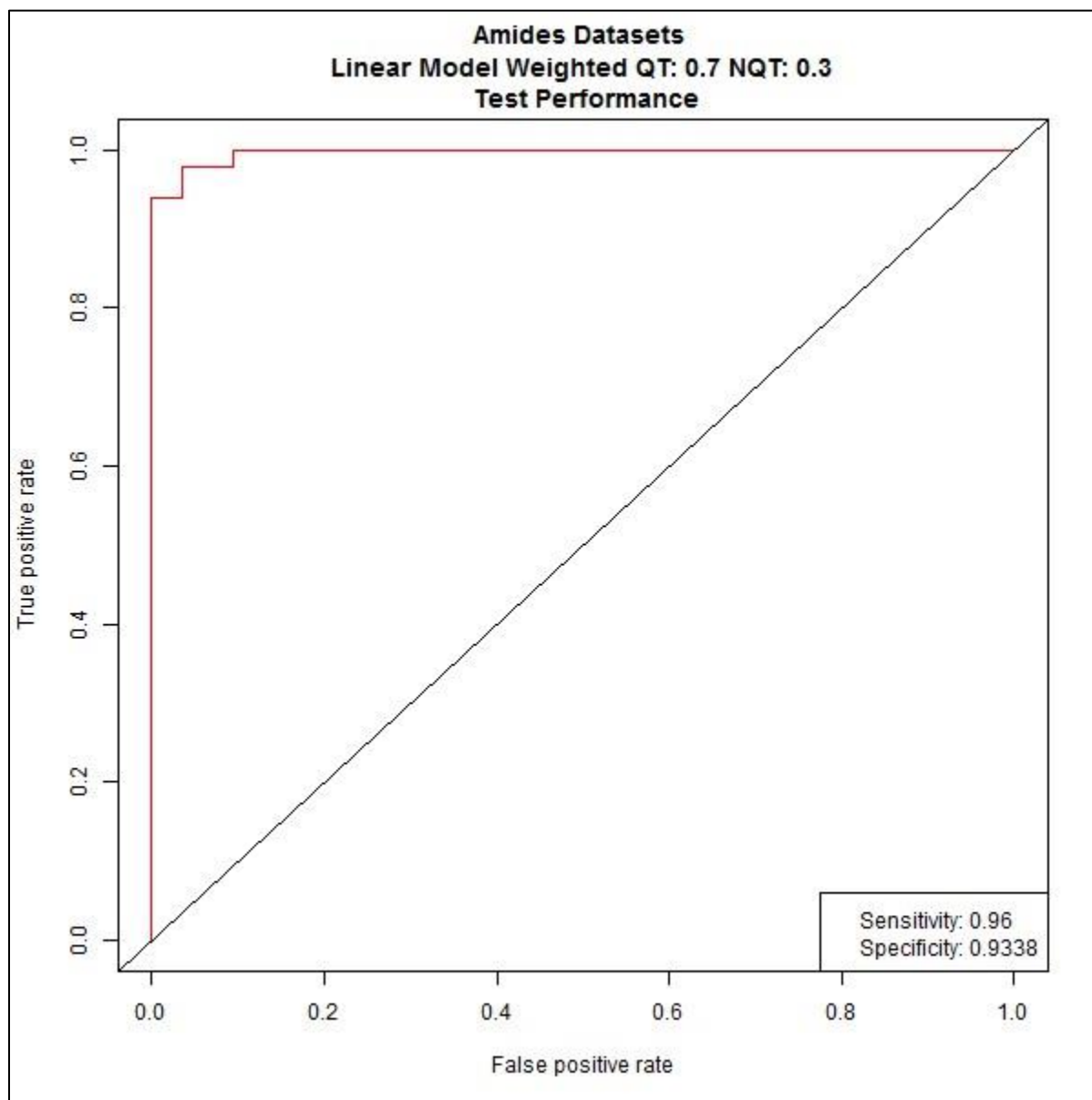
Figure 93: Receiver Operating Characteristic Curve for Antifungal Agents Class
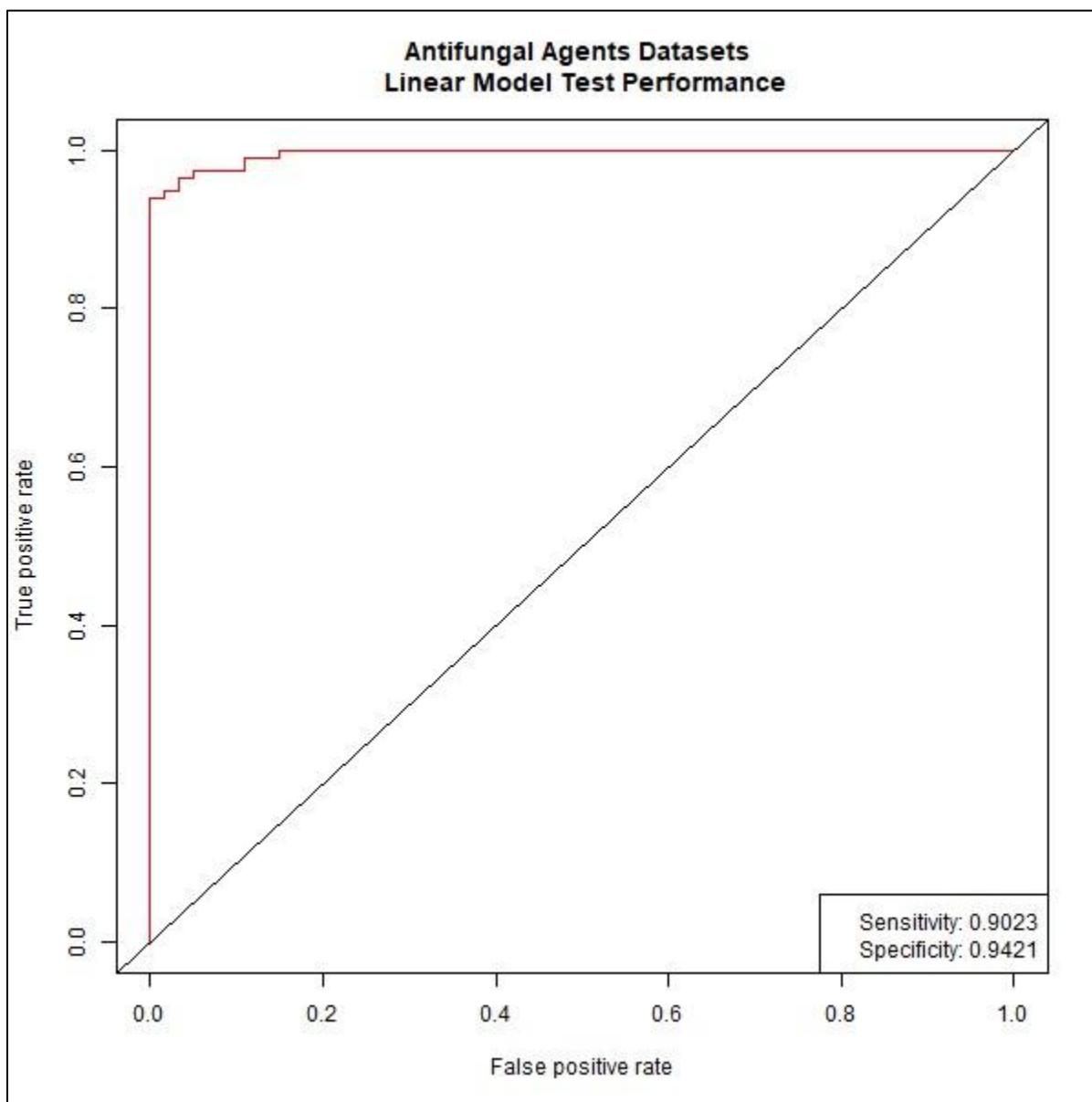
Figure 94: Receiver Operating Characteristic Curve for Antifungals for Dermatological Use Class

Antifungals-Dermatological Datasets
Linear Model Test Performance

Sensitivity: 0.8881
Specificity: 0.9381
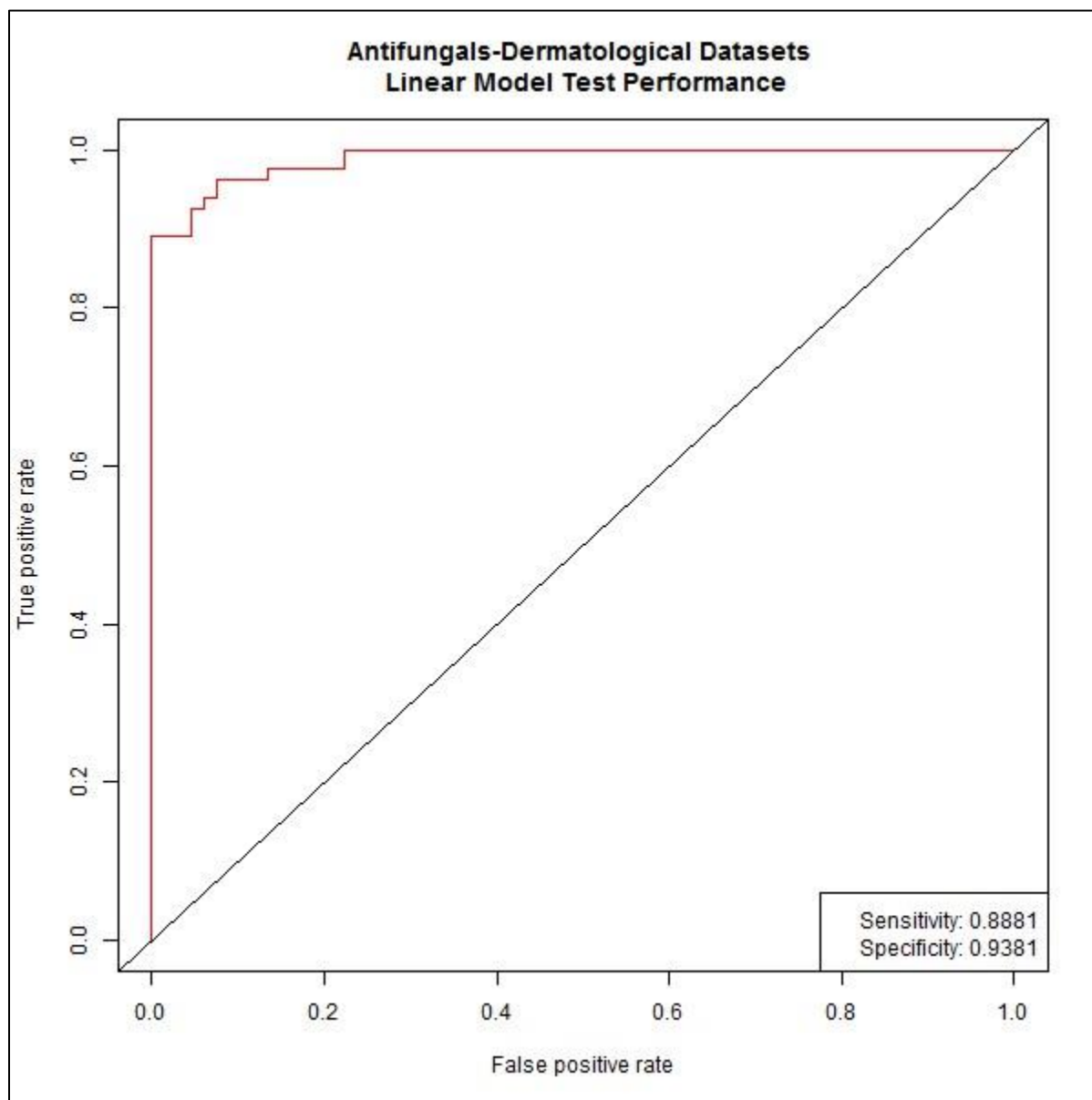
Figure 95: Receiver Operating Characteristic Curve for Anti-Infective Agents Class
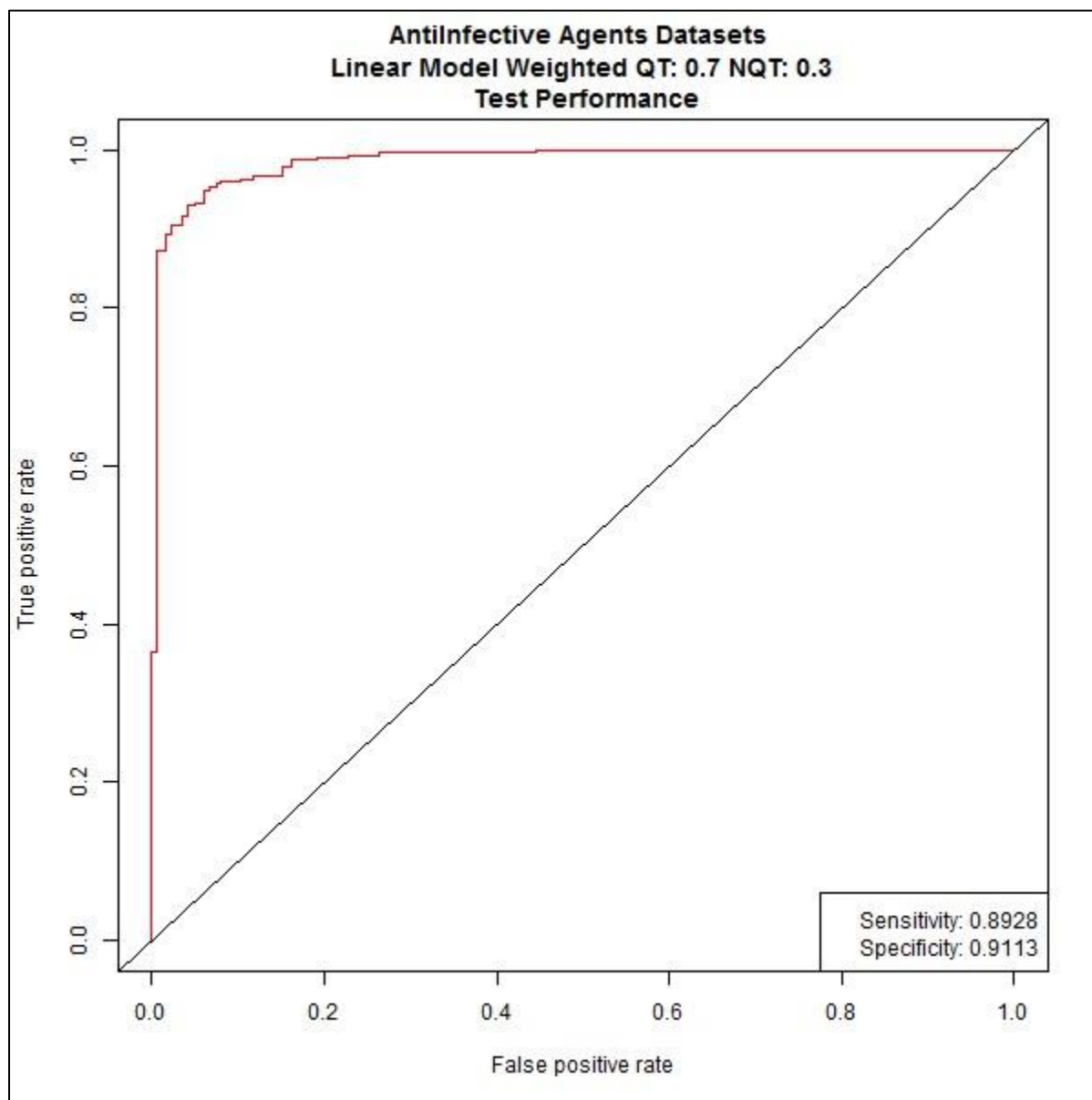
Figure 96: Receiver Operating Characteristic Curve for Antiinfectives for Systemic Use Class
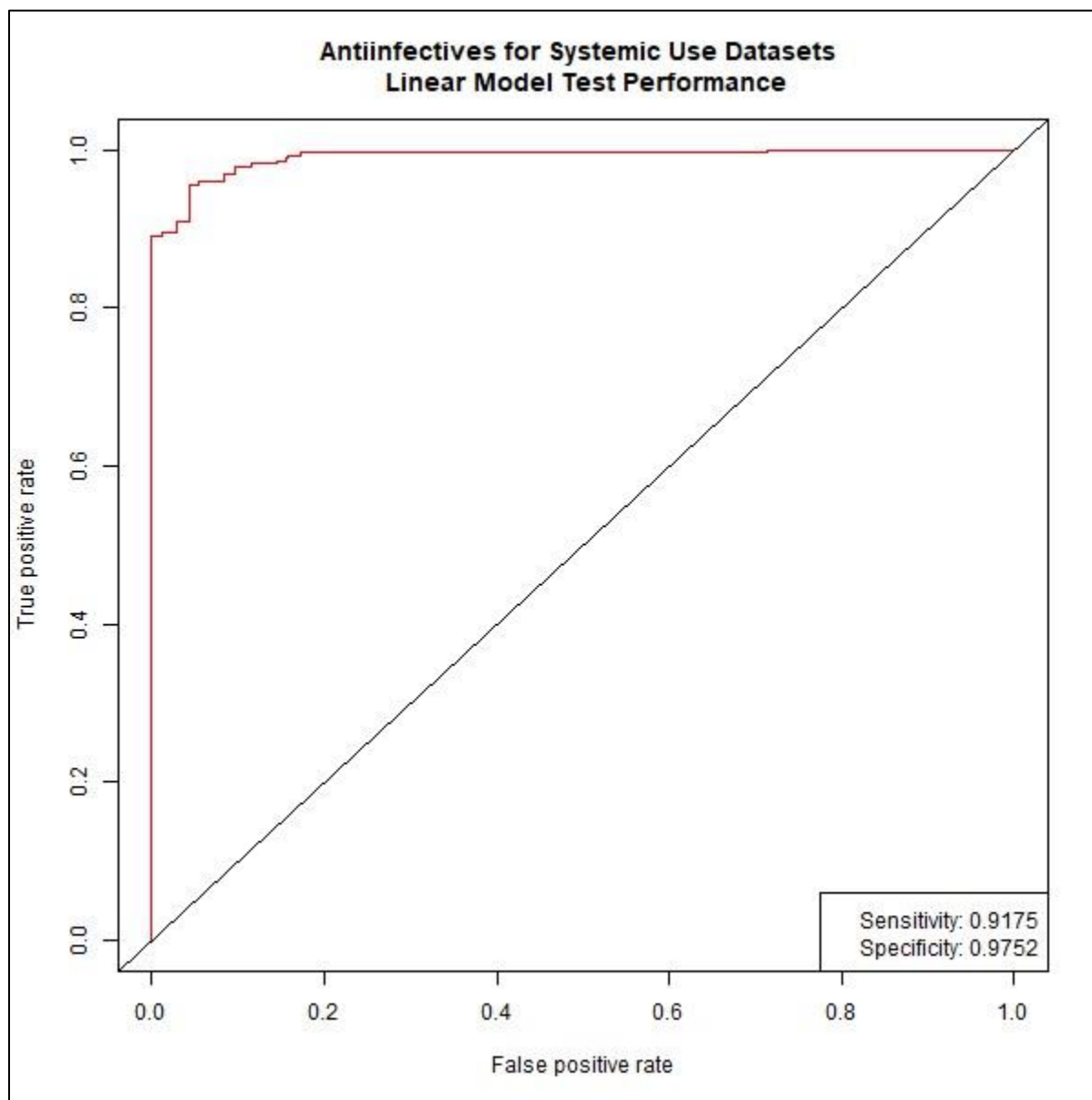
Figure 97: Receiver Operating Characteristic Curve for Antineoplastic Agents Class
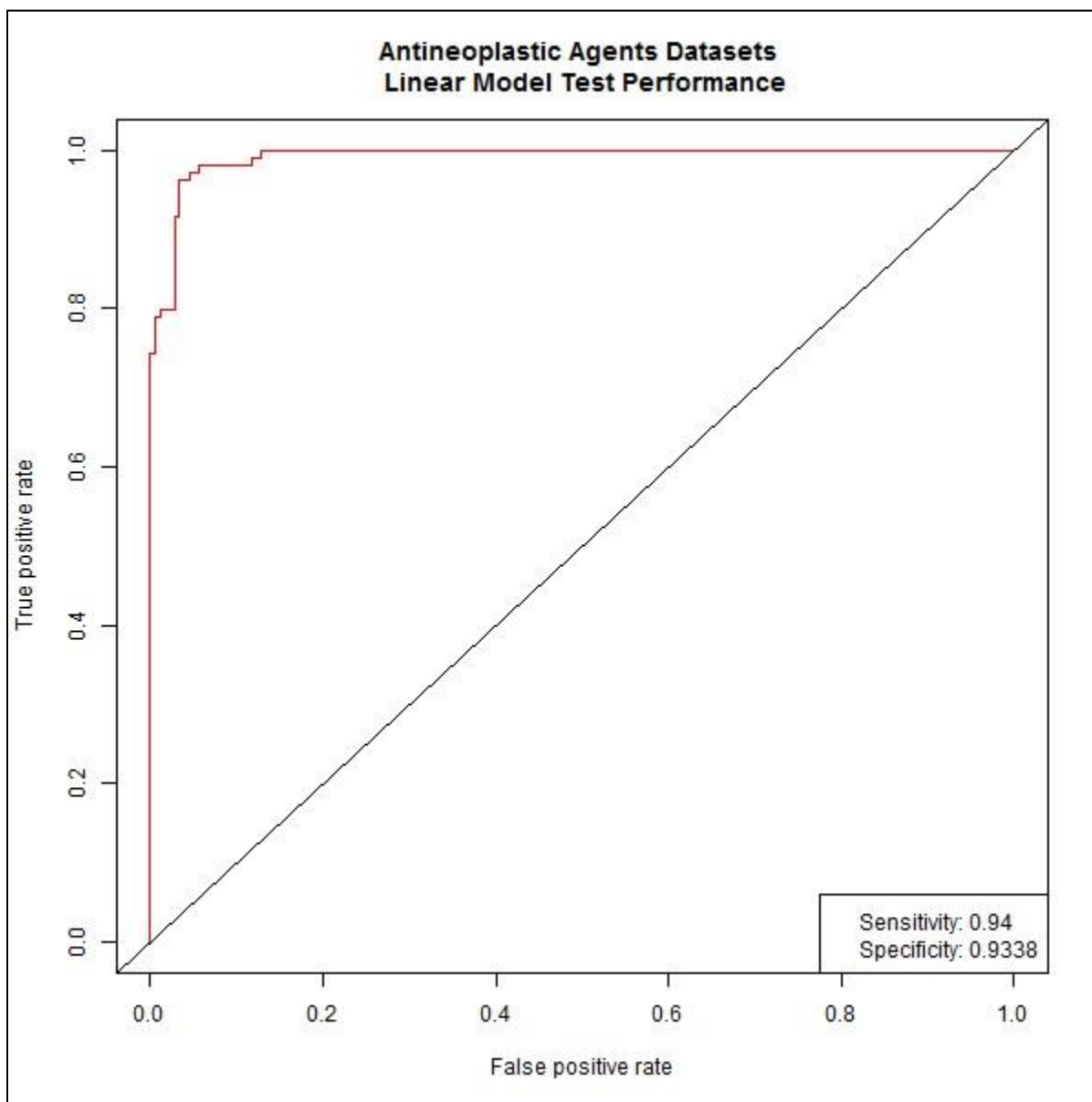
Figure 98: Receiver Operating Characteristic Curve for Azoles Class
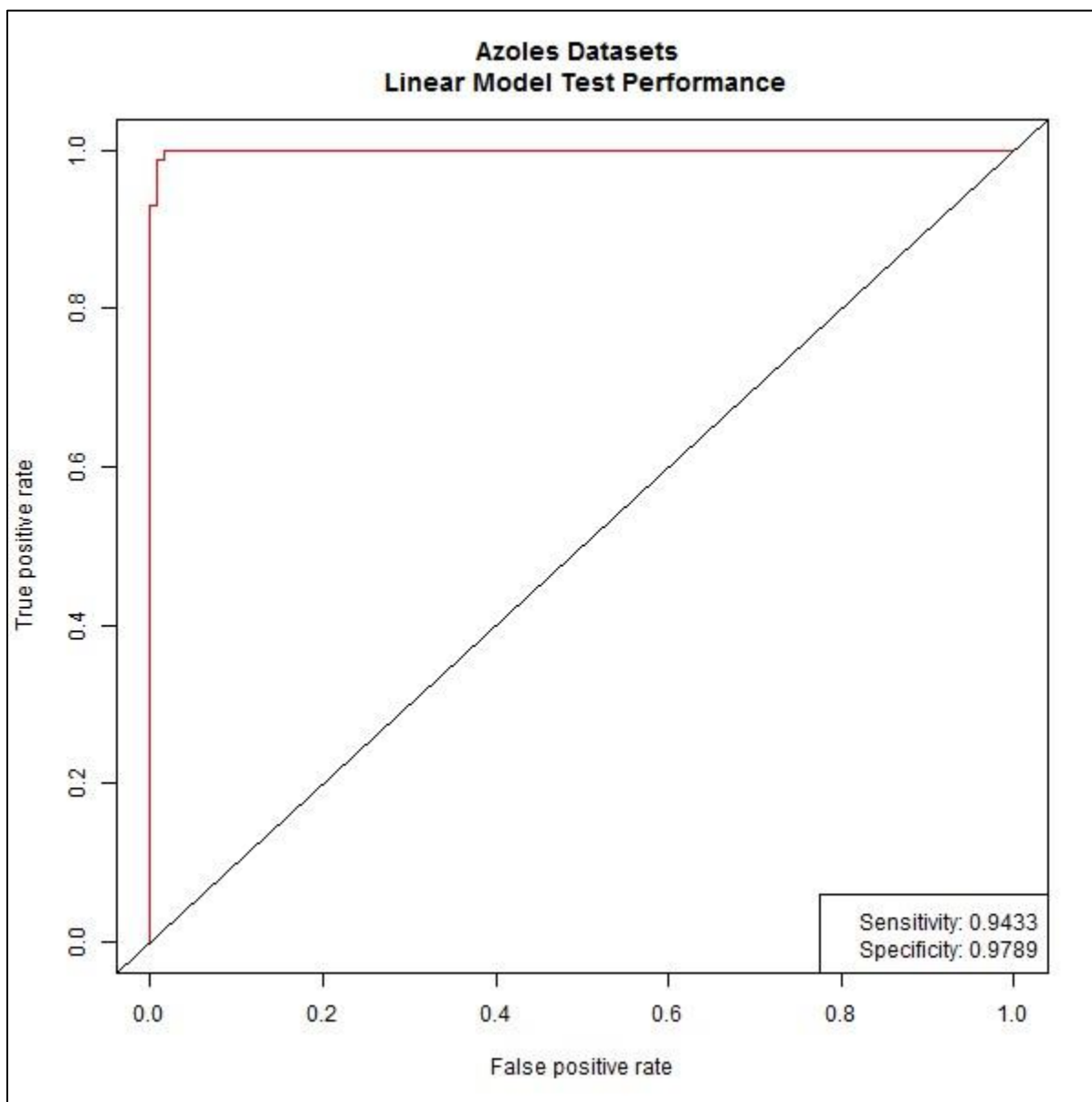
Figure 99: Receiver Operating Characteristic Curve for BCRP/ABCG2 Substrates Class
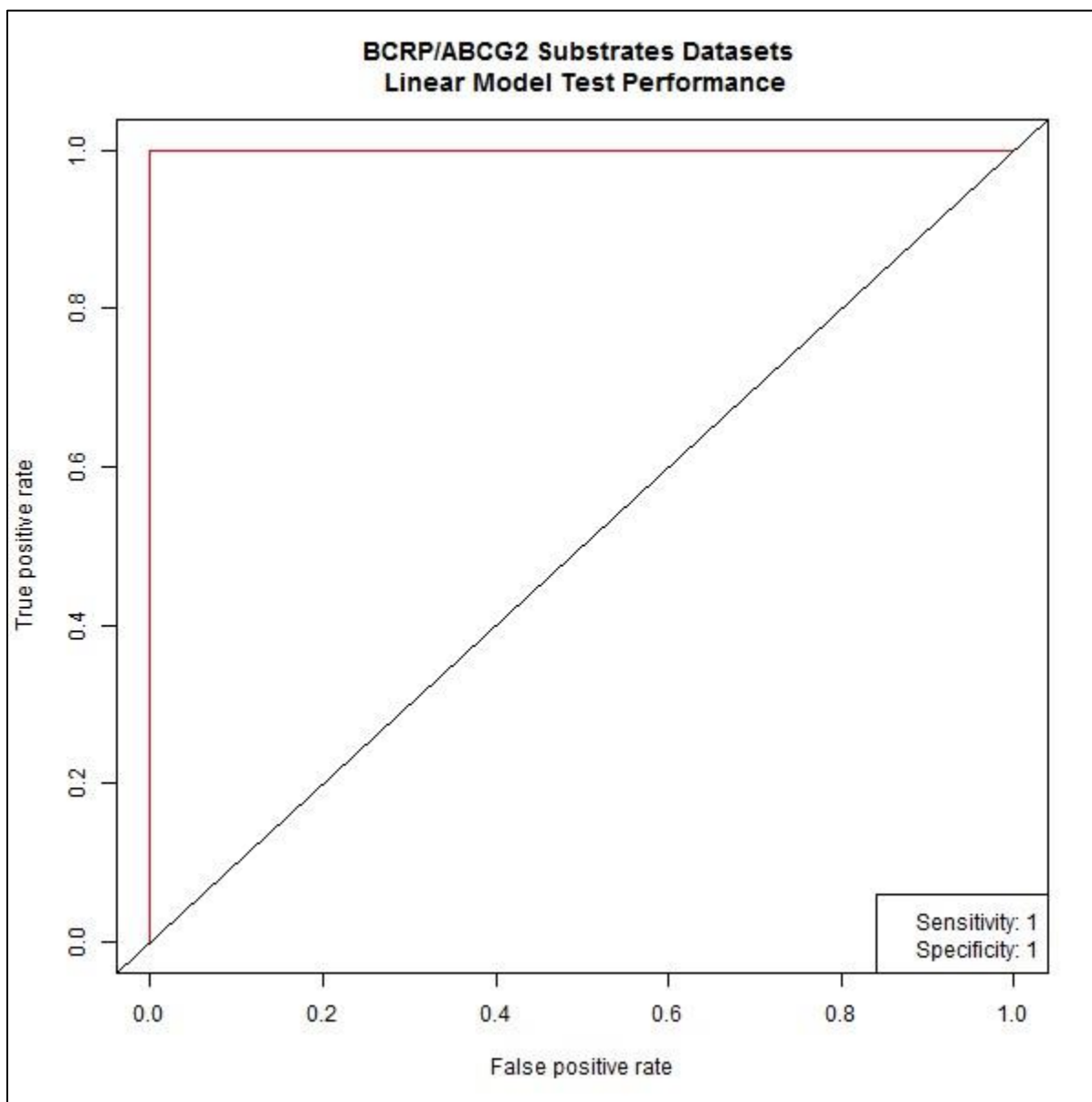
Figure 100: Receiver Operating Characteristic Curve for Benzamidazoles Class
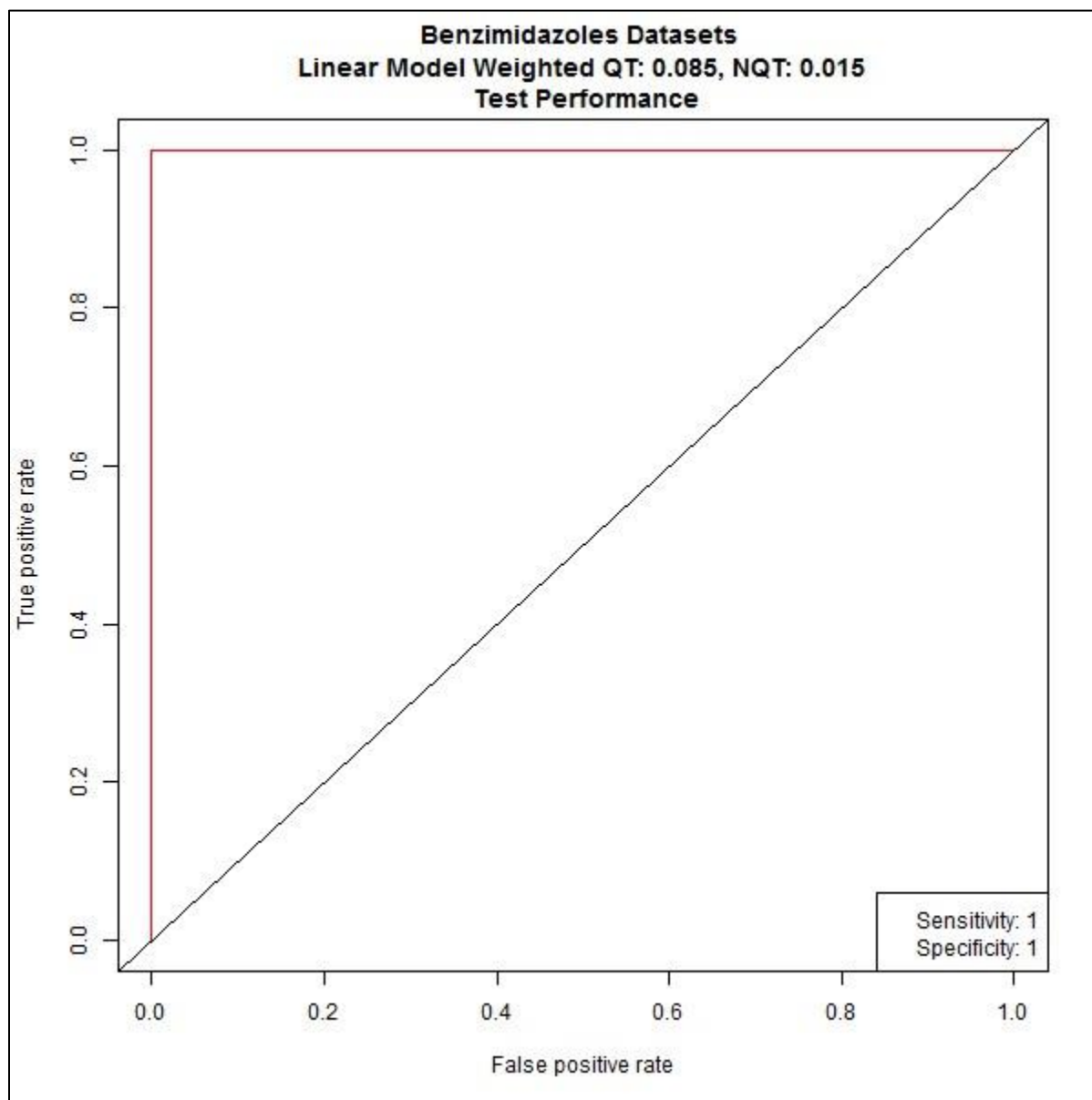
Figure 101: Receiver Operating Characteristic Curve for Cardiovascular Agents Class
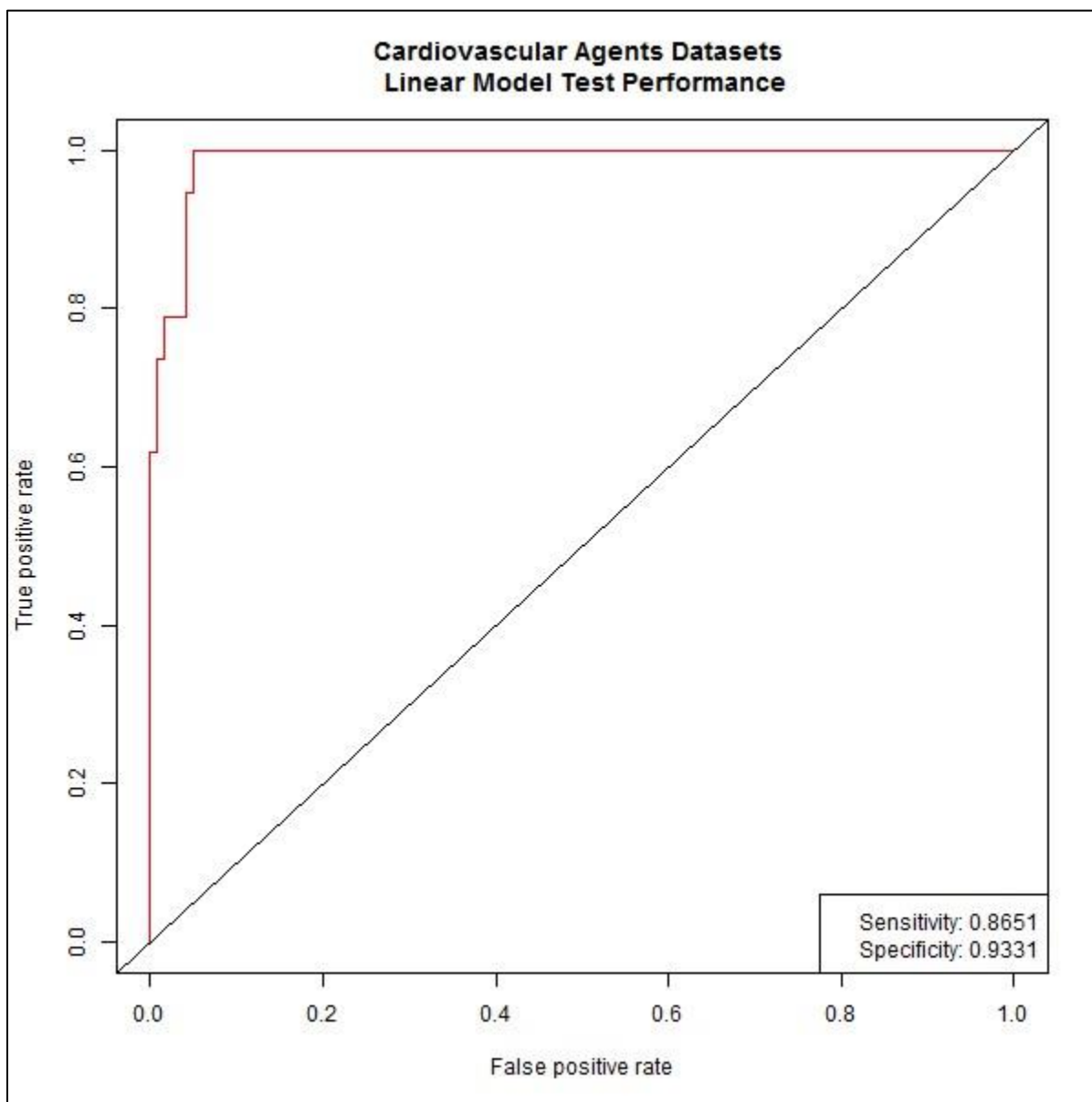
Figure 102: Receiver Operating Characteristic Curve for Cardiovascular System Class
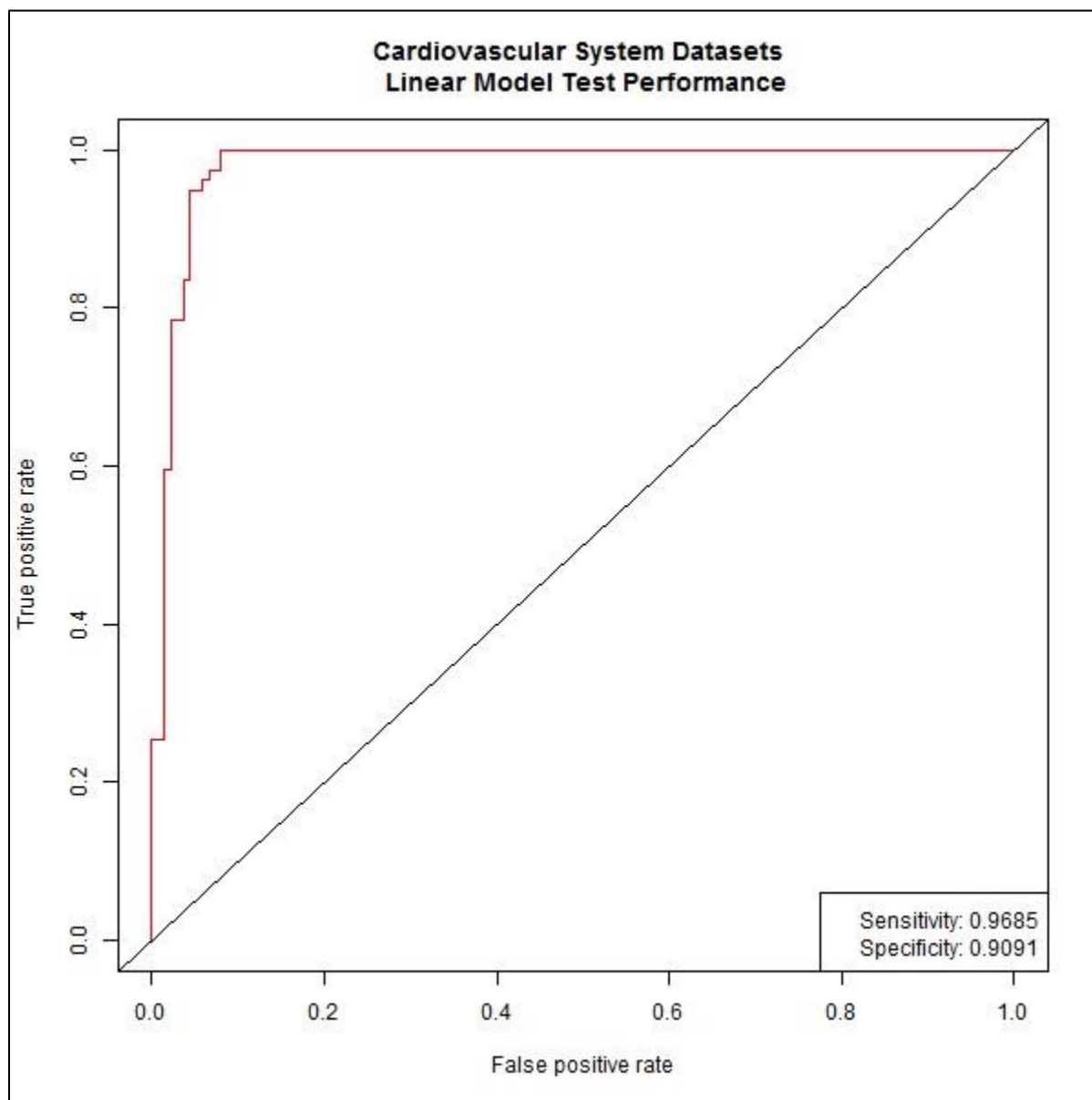
Figure 103: Receiver Operating Characteristic Curve for Central Nervous System Agents Class
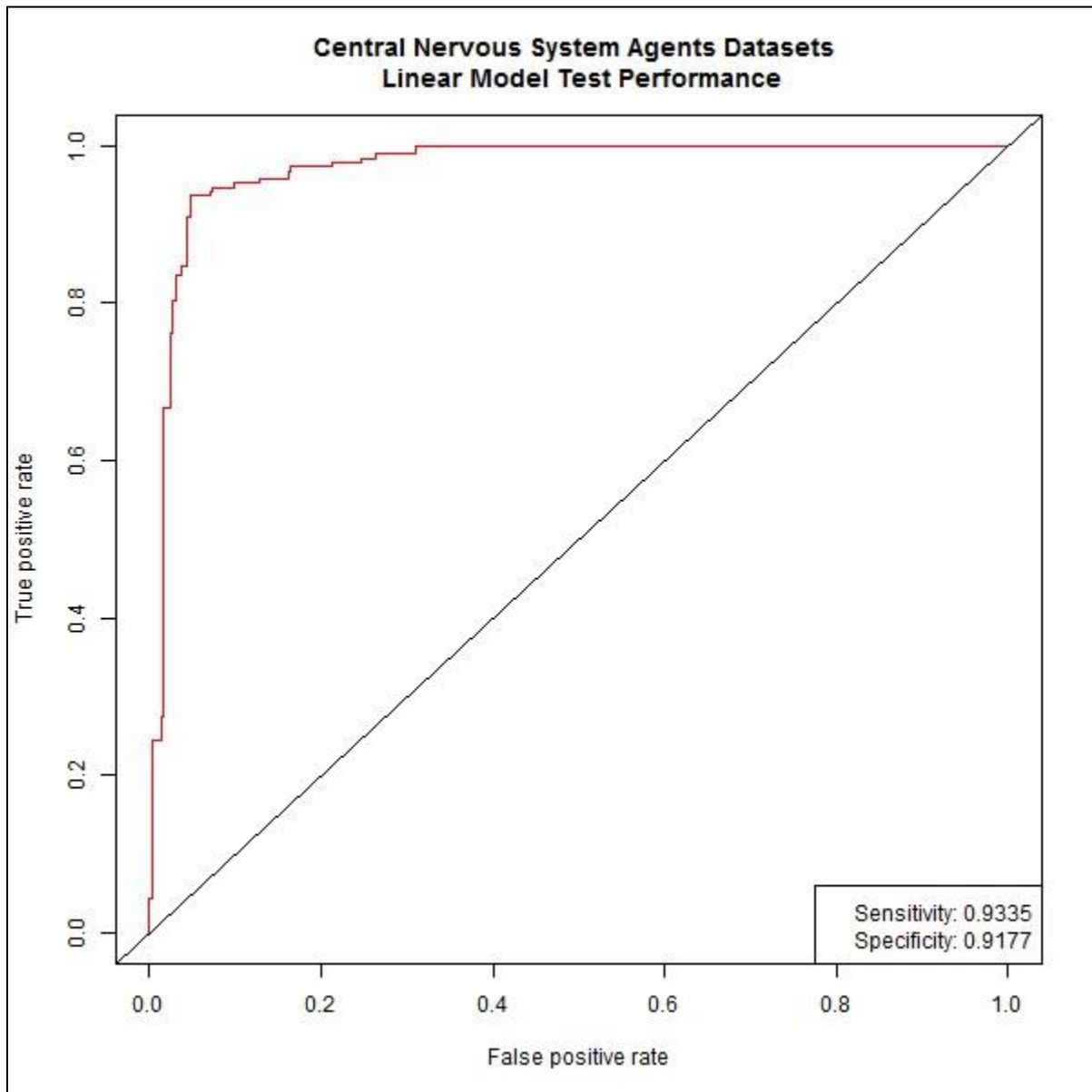
Figure 104: Receiver Operating Characteristic Curve for Central Nervous System Depressants Class
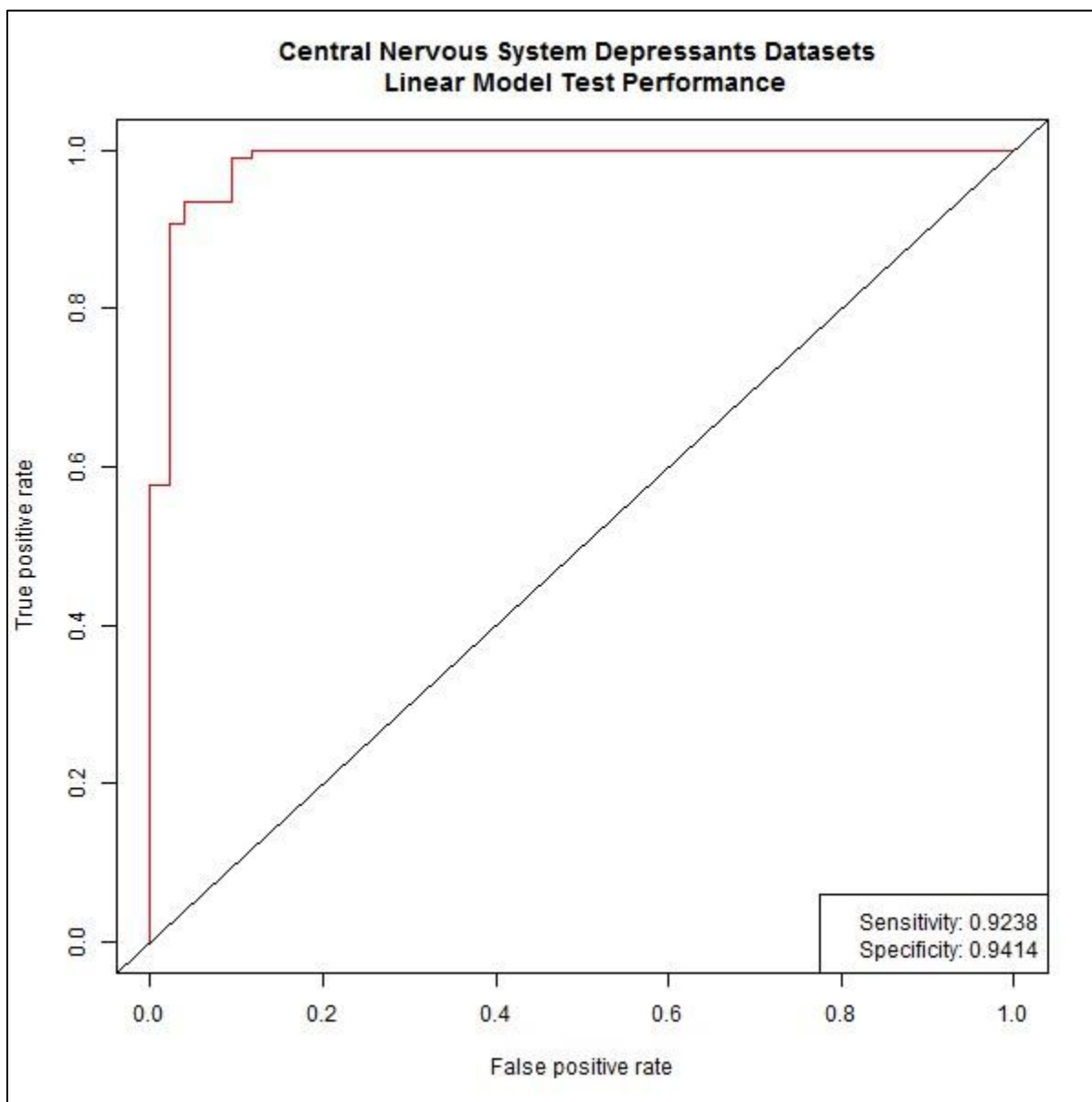
Figure 105: Receiver Operating Characteristic Curve for Chemically-Induced Disorders Class

Chemically Induced Disorders Datasets
Linear Model Test Performance

Sensitivity: 0.9051
Specificity: 0.949
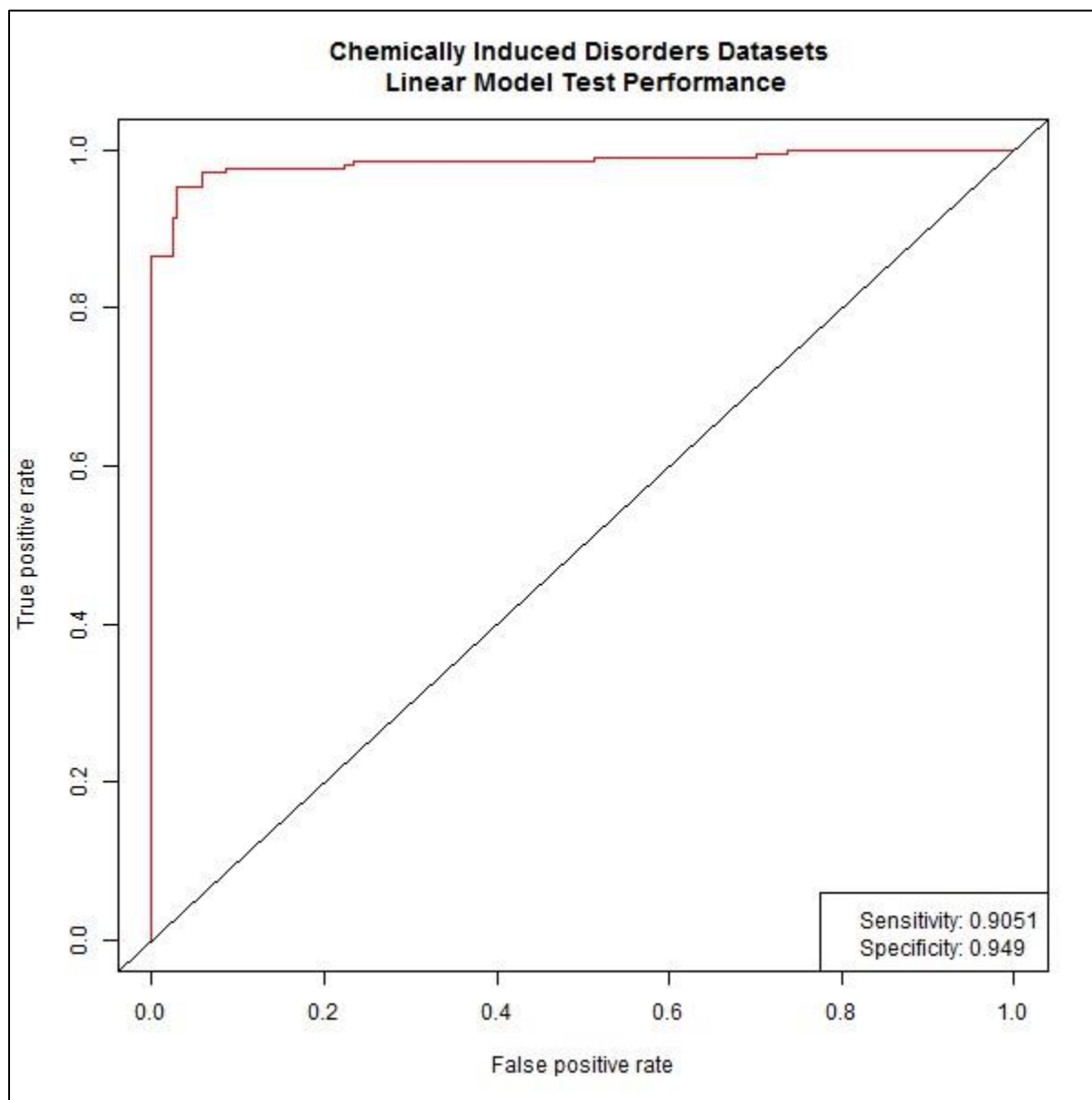
Figure 106: Receiver Operating Characteristic Curve for Combined Inducers of CYP3A4 and P-Glycoprotein Class
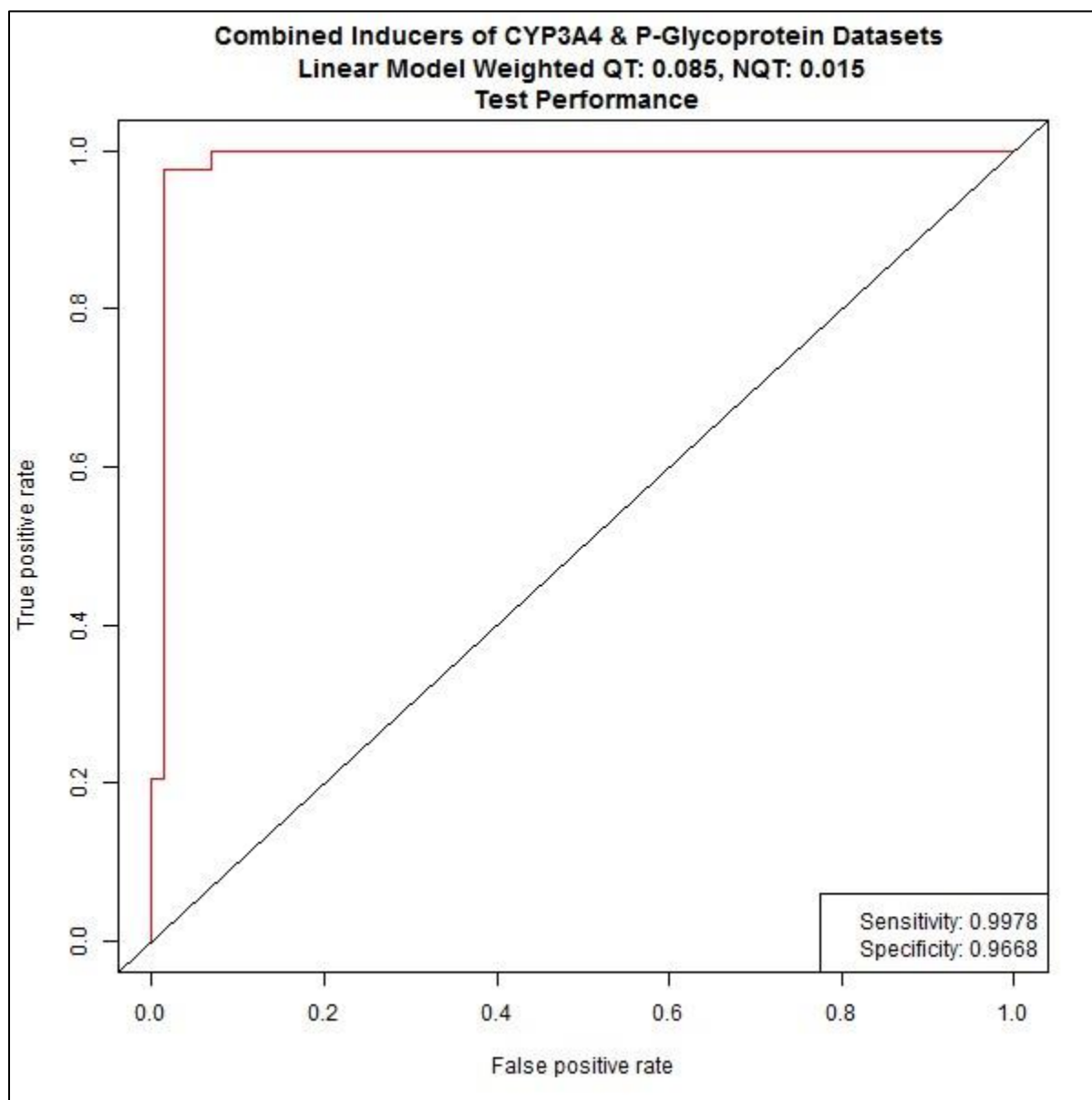
Figure 107: Receiver Operating Characteristic Curve for Combined Inhibitors of CYP3A4 and P-Glycoprotein Class
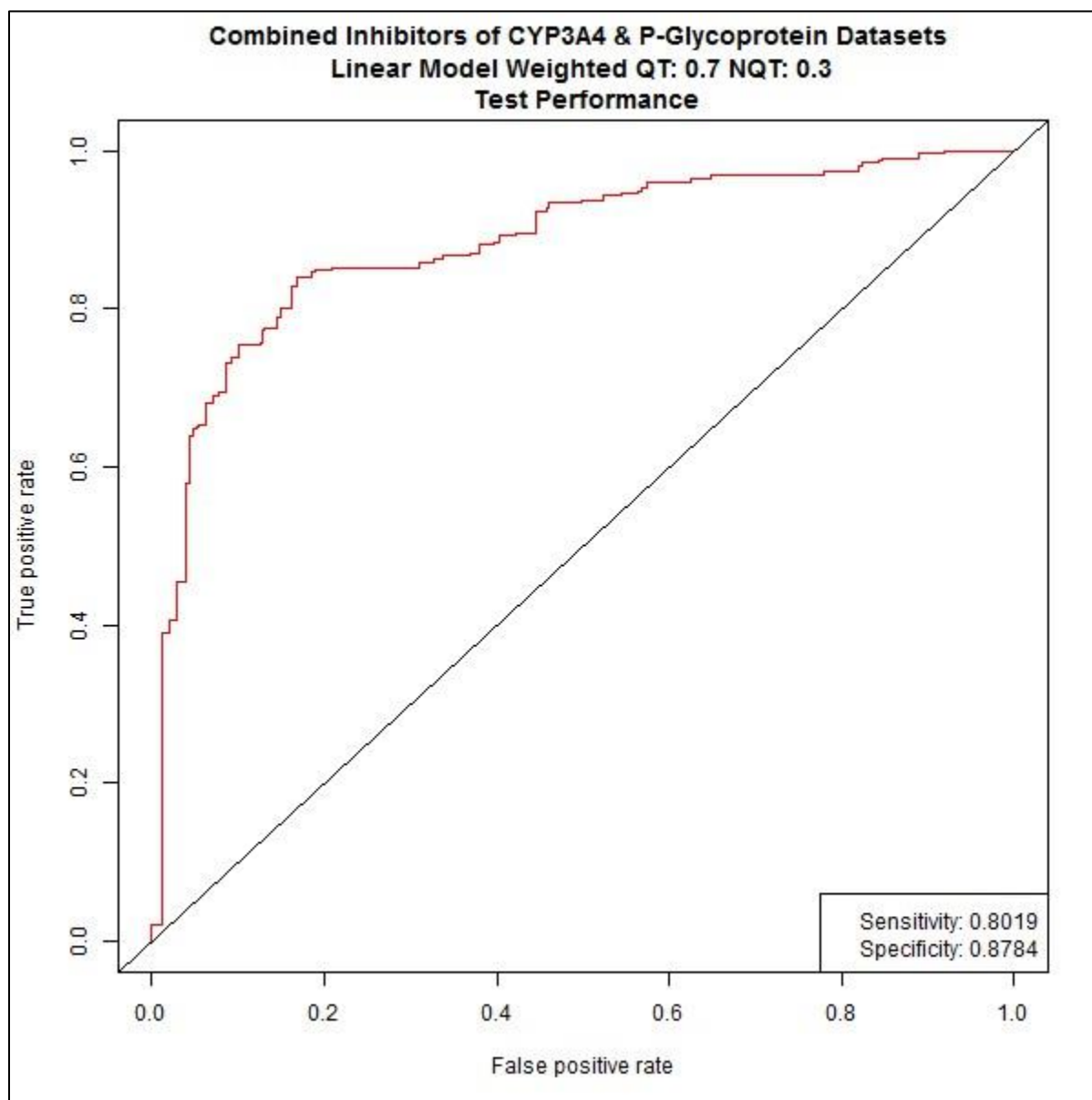
Figure 108: Receiver Operating Characteristic Curve for CYP2D6 Inhibitors (Weak) Class
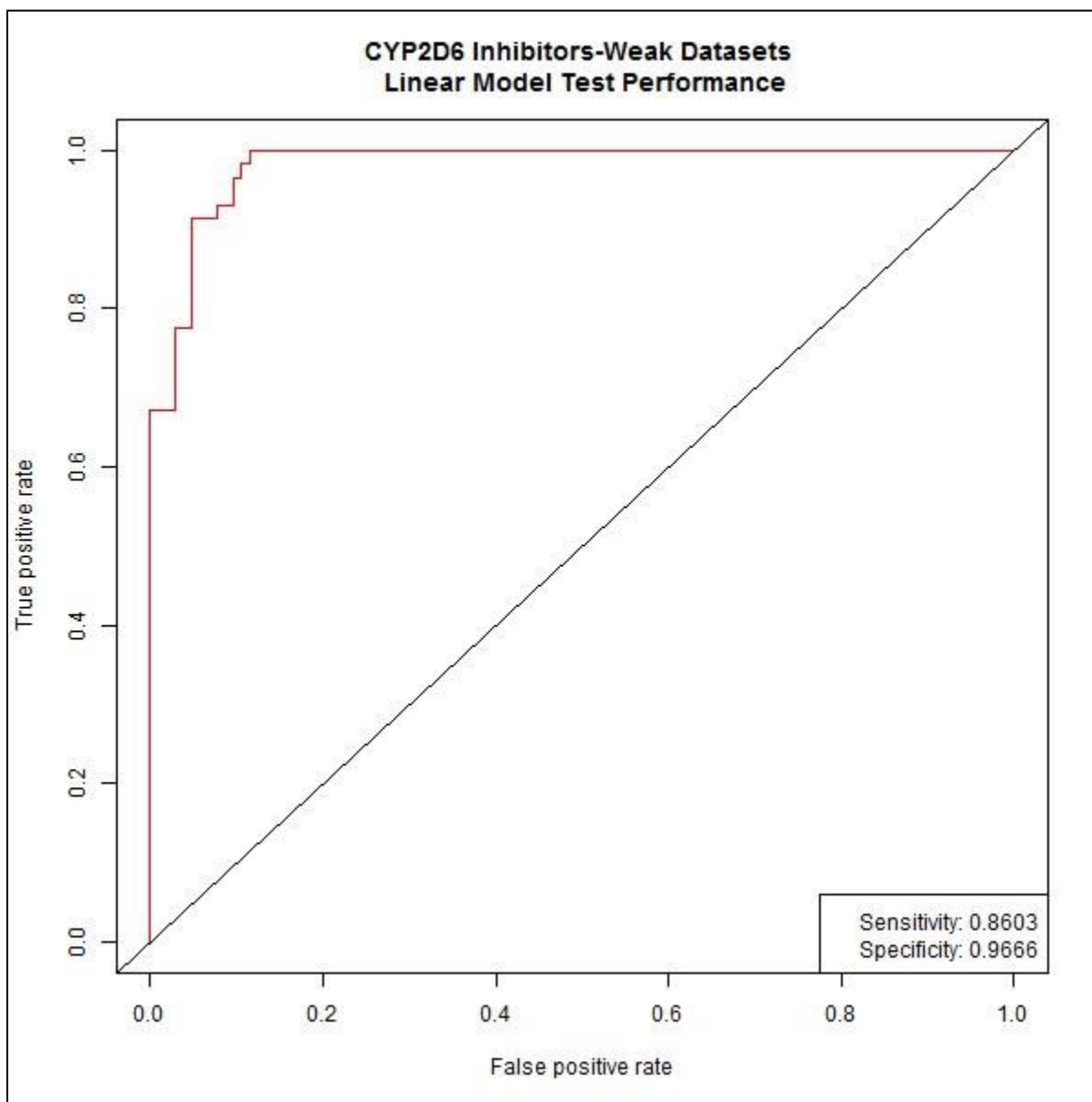
Figure 109: Receiver Operating Characteristic Curve for CYP3A4 Inhibitors (Weak) Class
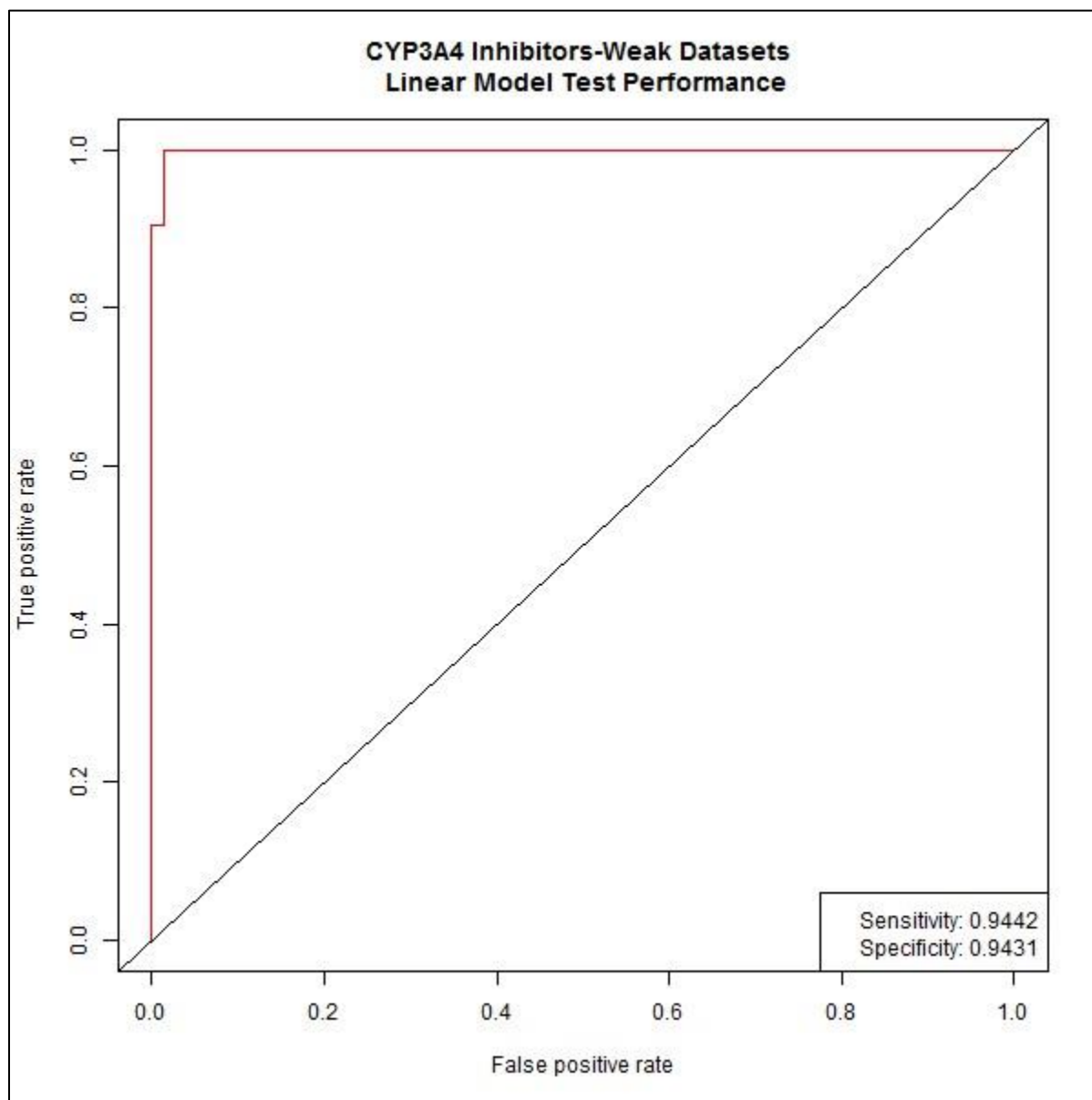
Figure 110: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP1A2 Inhibitors Class
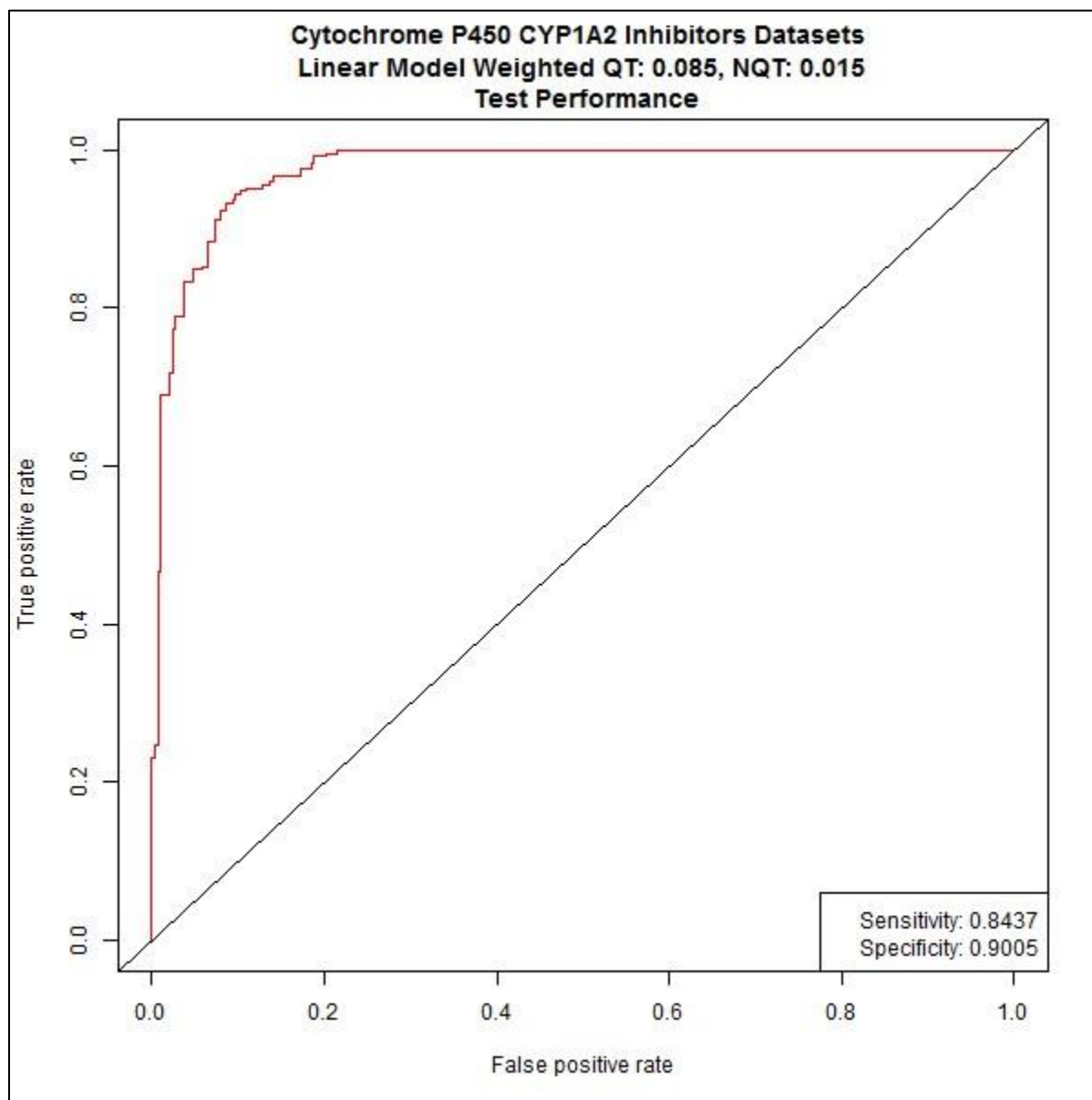
Figure 111: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP1A2 Inhibitors (Moderate) Class
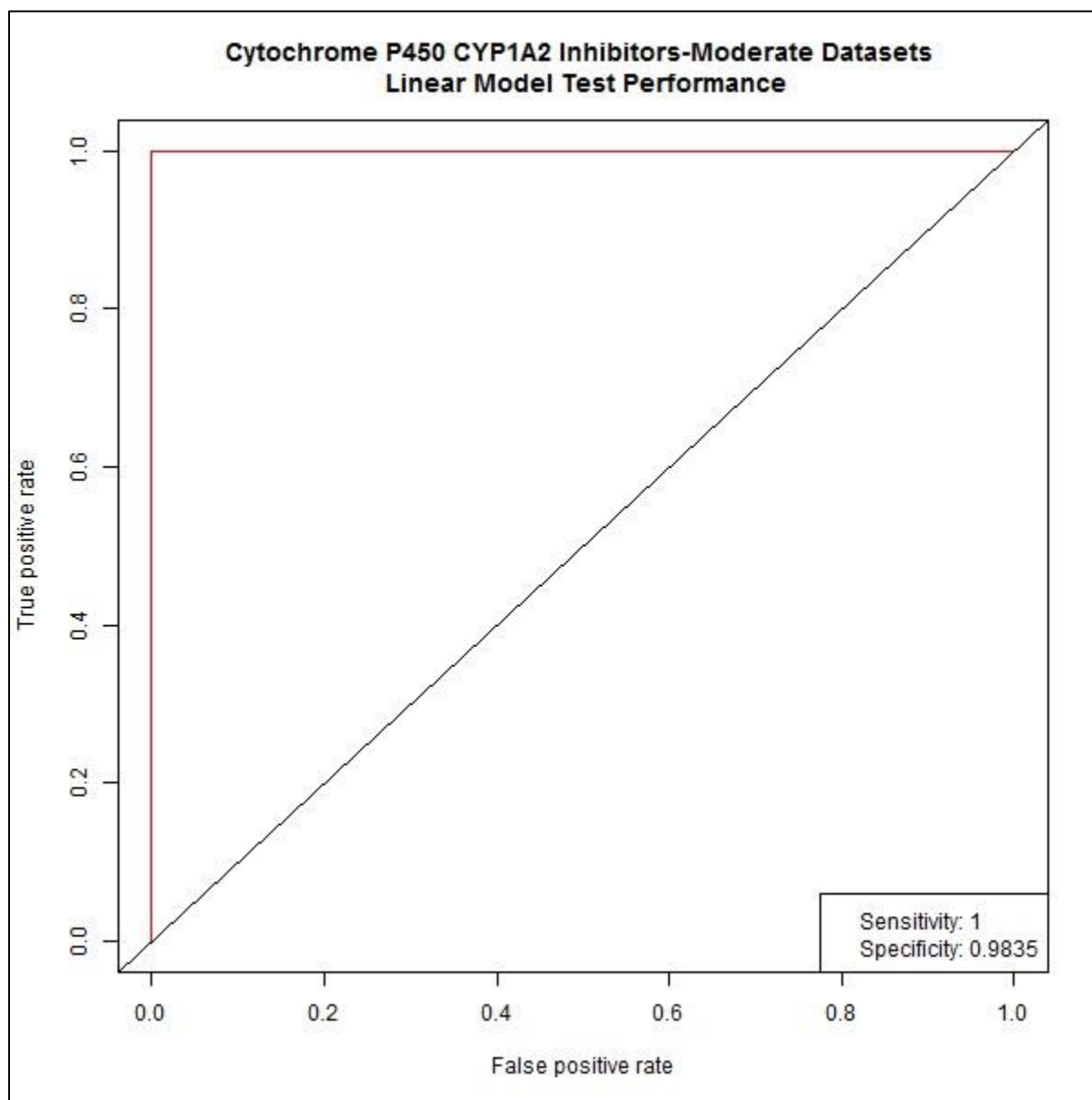
Figure 112: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP1A2 Inhibitors (Weak) Class
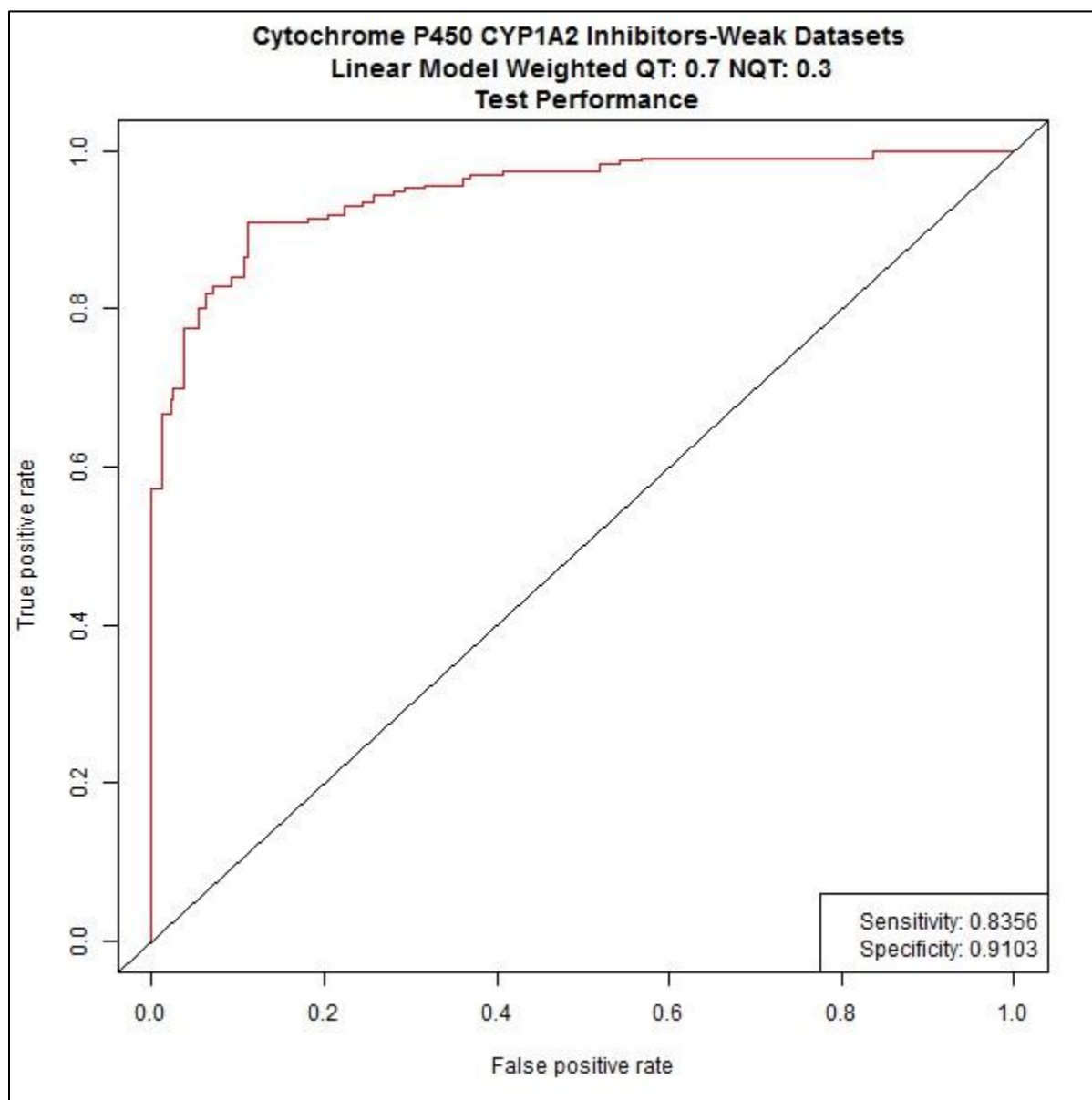
Figure 113: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP1A2 Substrates Class
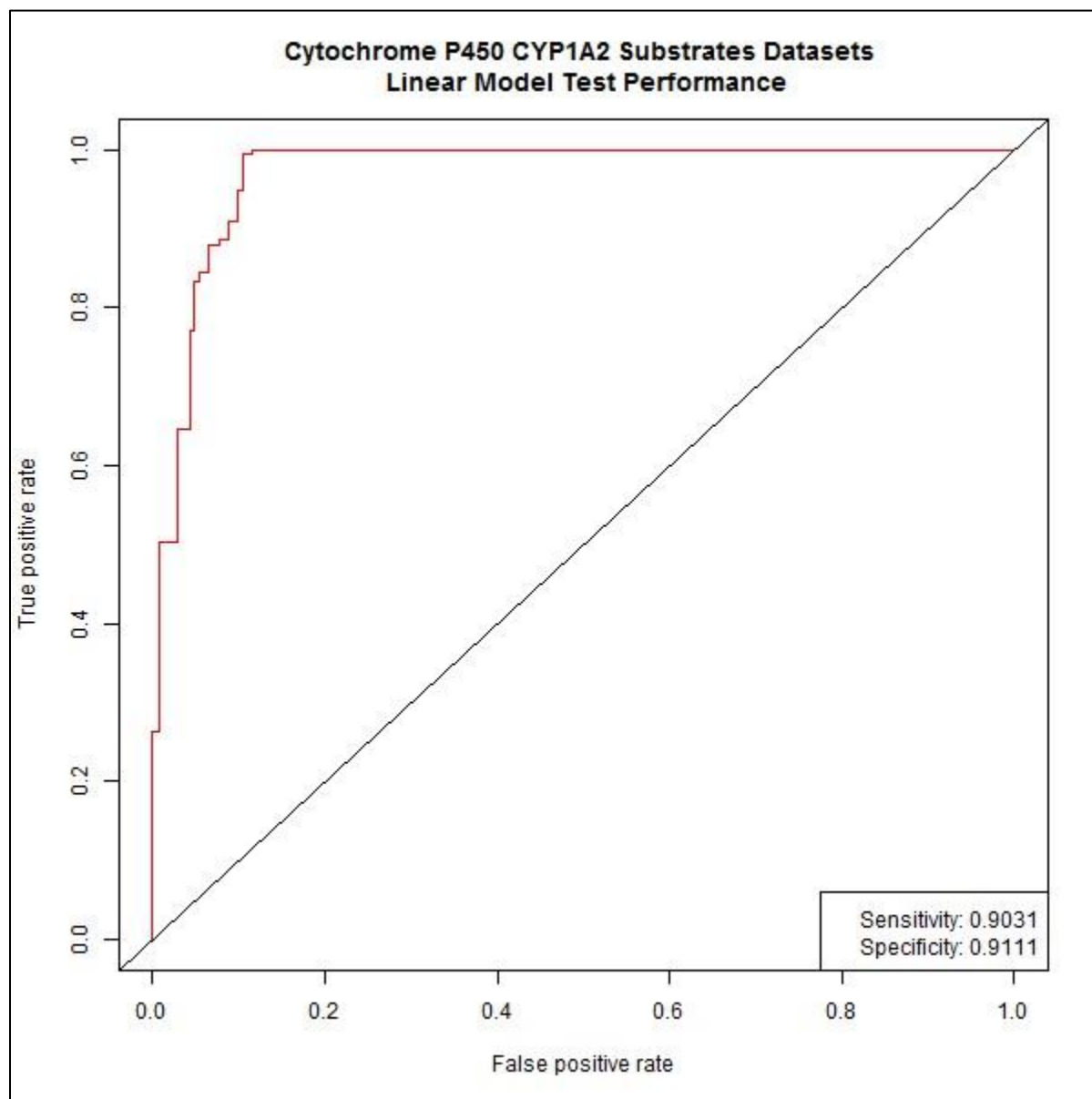
Figure 114: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2A6 Inhibitors Class
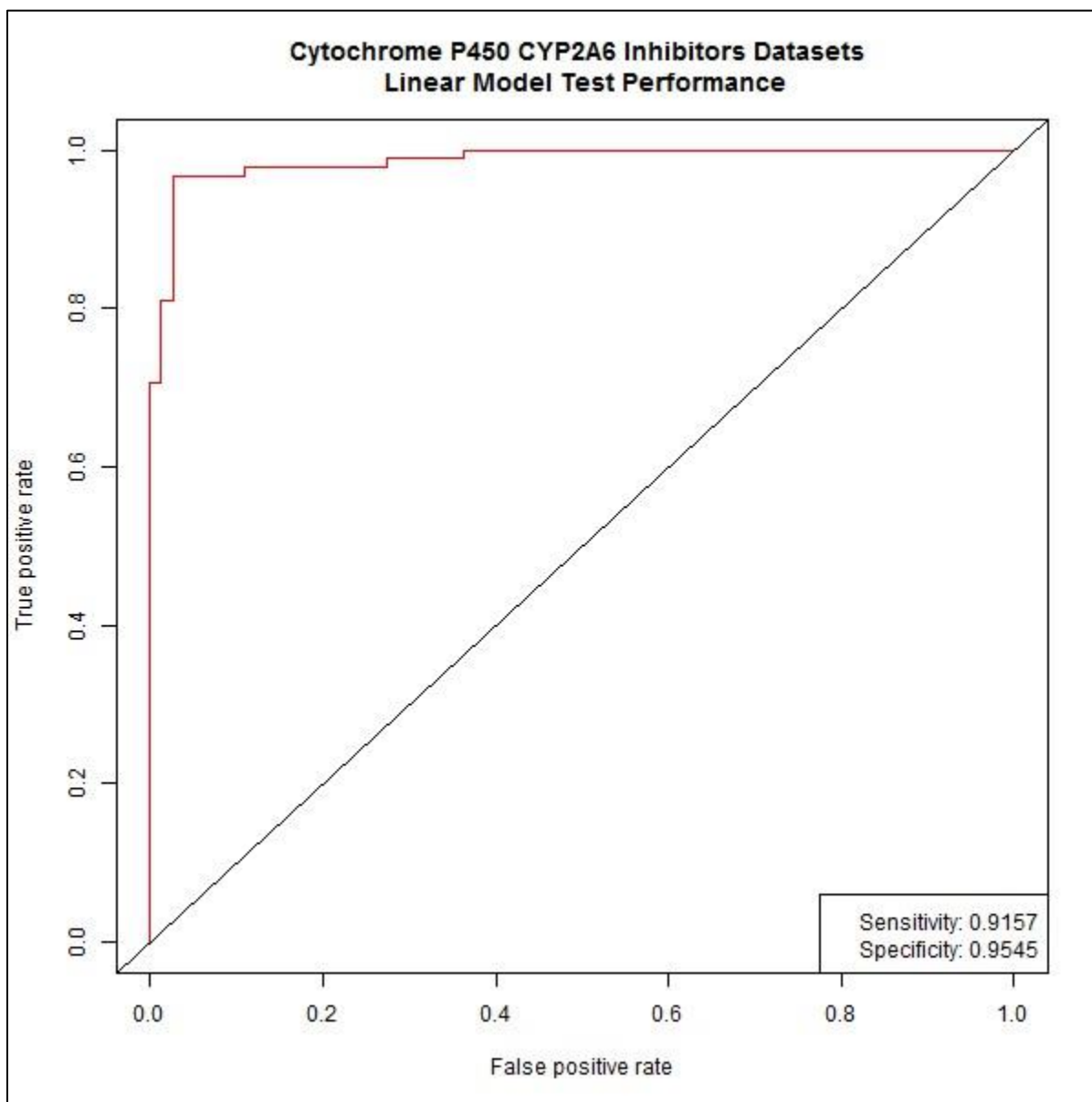
Figure 115: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2A6 Substrates Class
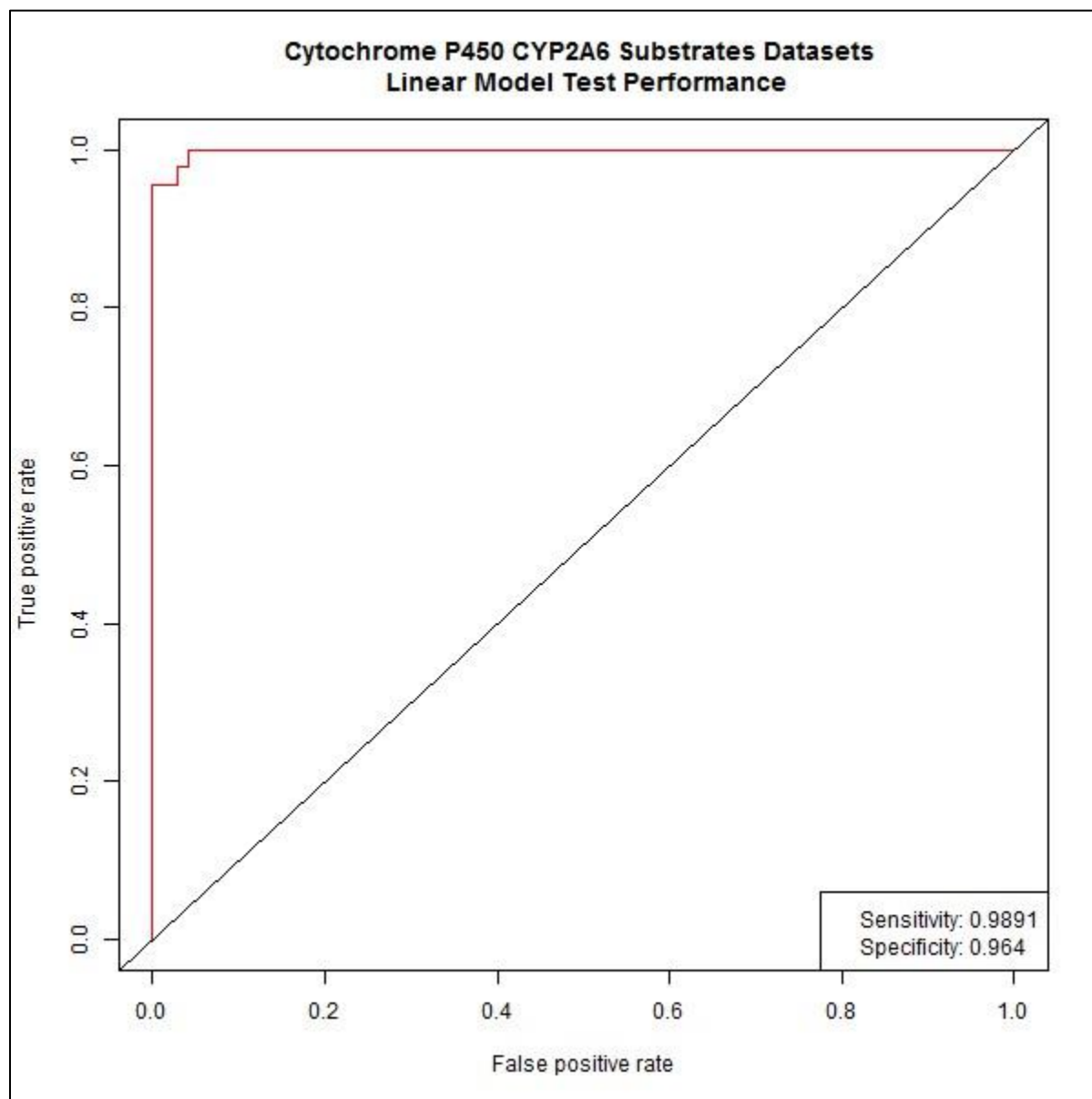
Figure 116: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2B6 Substrates Class
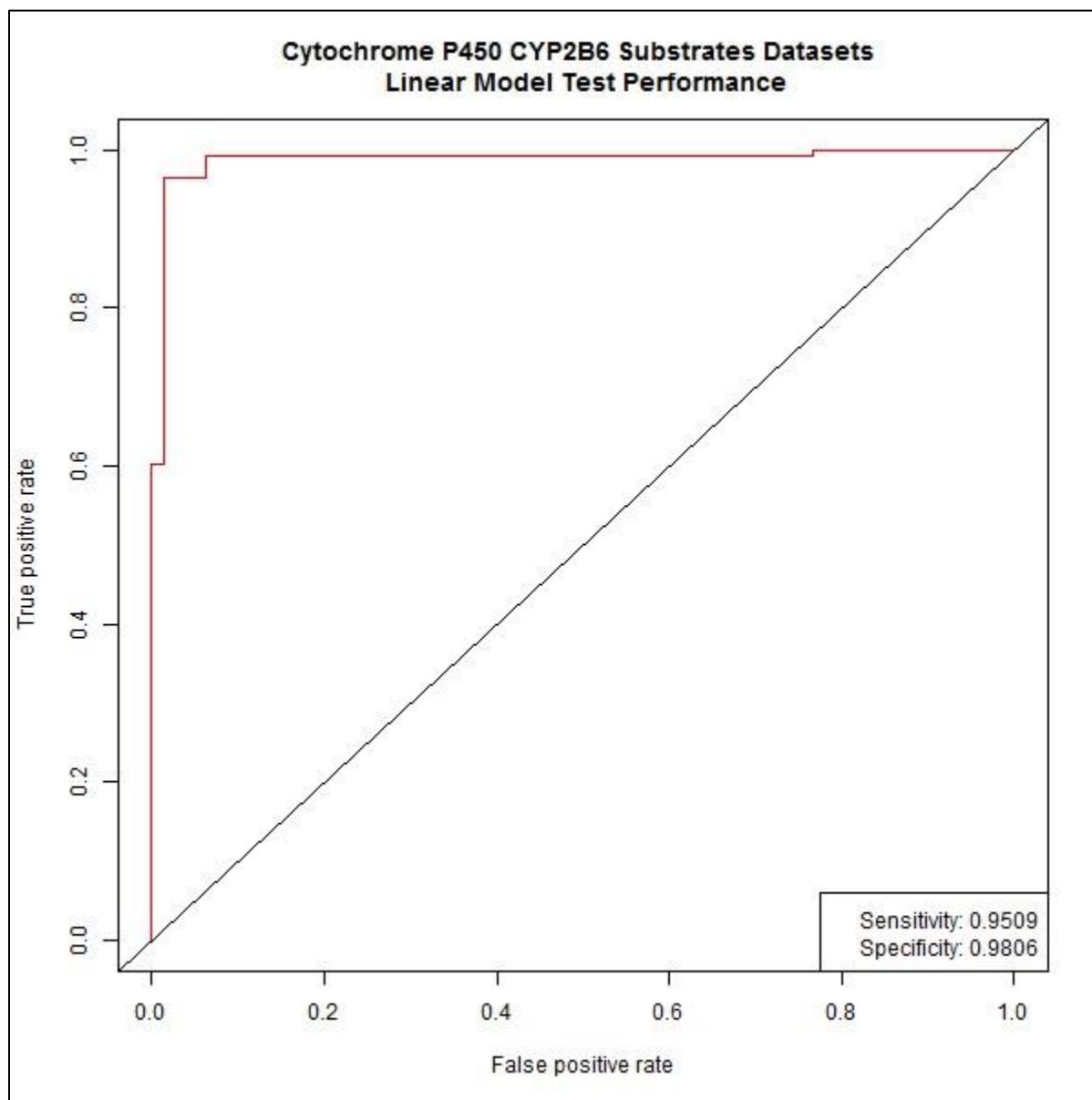
Figure 117: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C8 Inhibitors Class

Cytochrome P450 CYP2C8 Inhibitors Datasets
Linear Model Test Performance

Sensitivity: 0.8914
Specificity: 0.8955
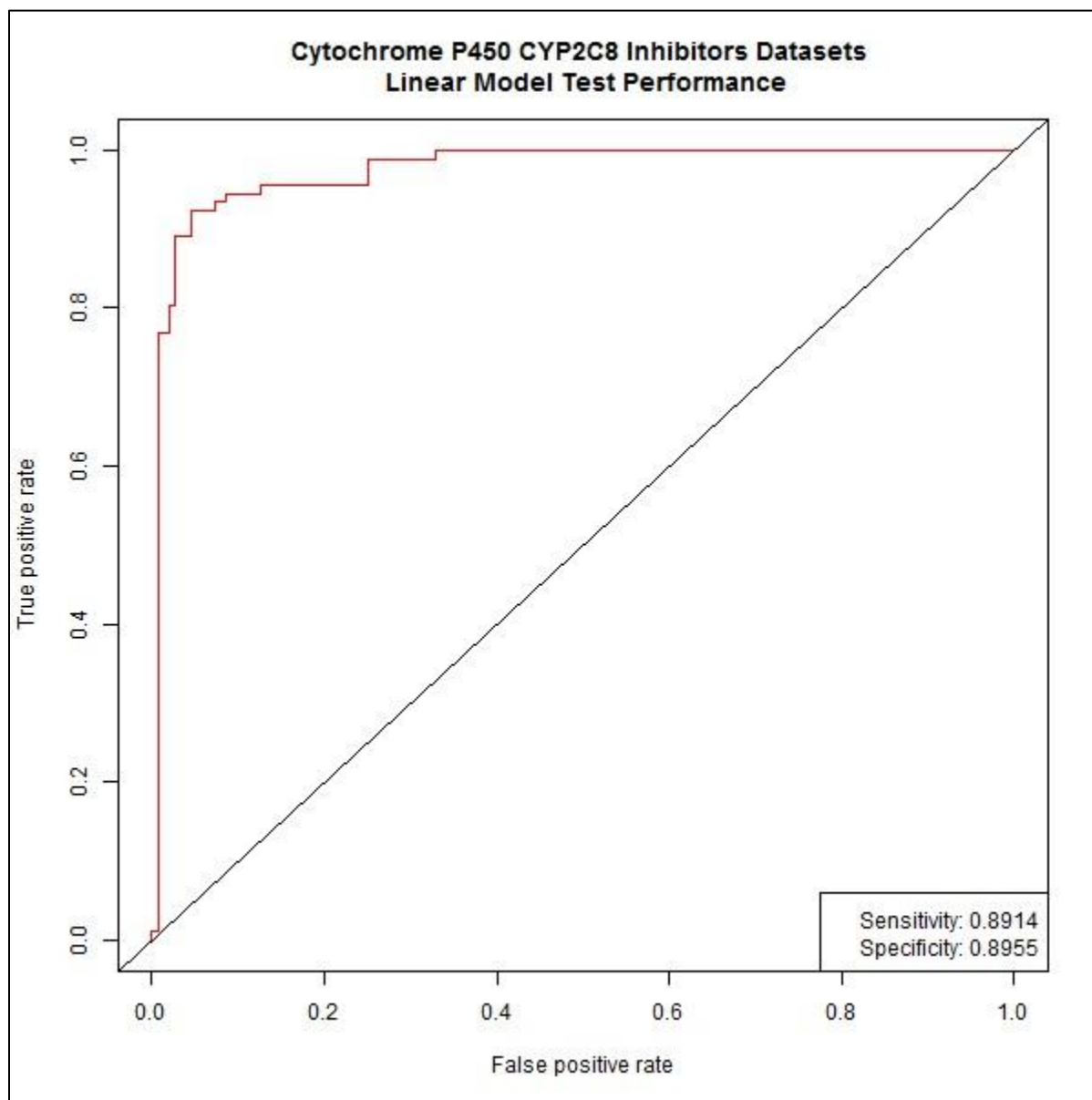
Figure 118: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C8 Substrates Class
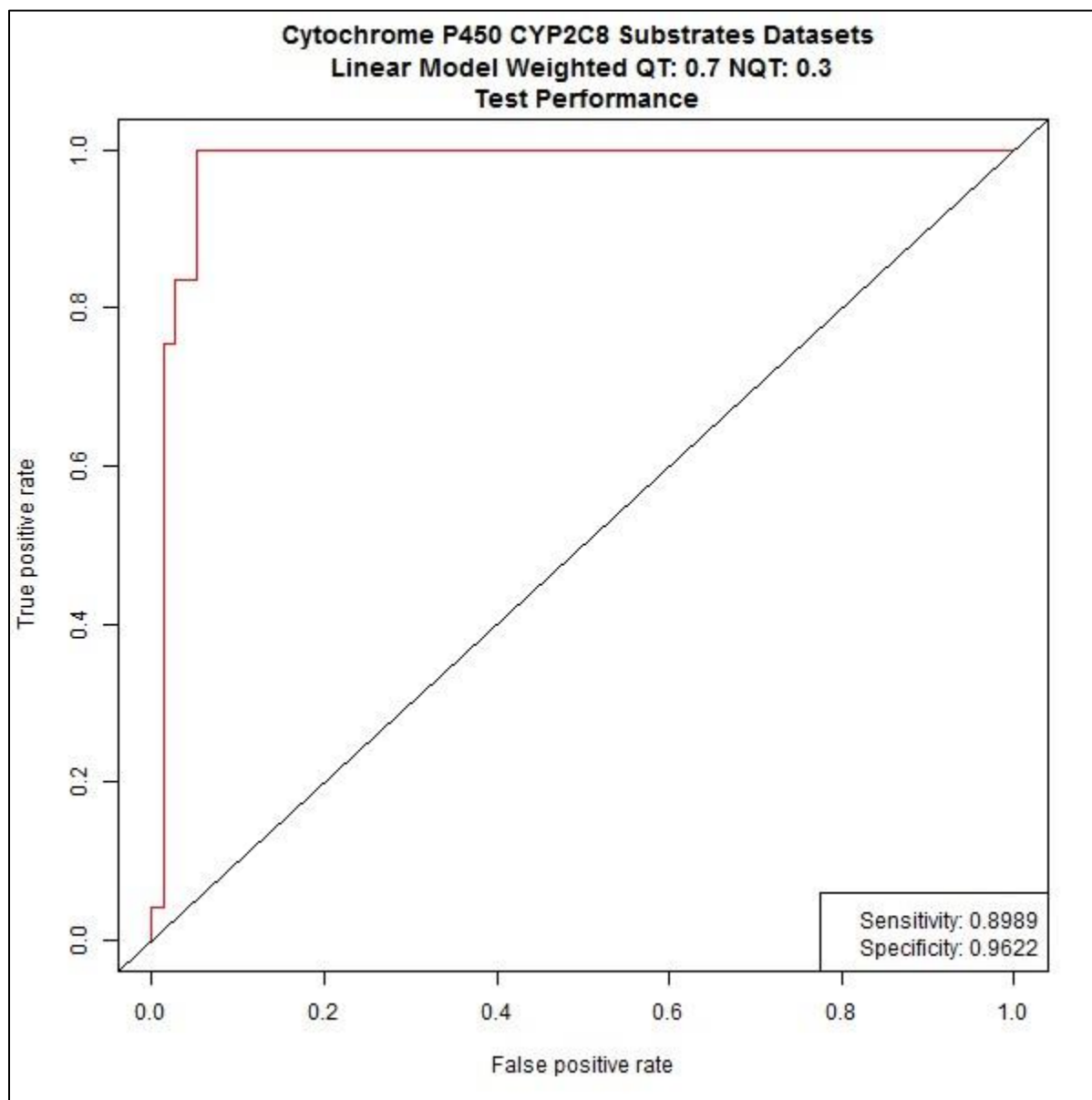
Figure 119: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C9 Inhibitors Class
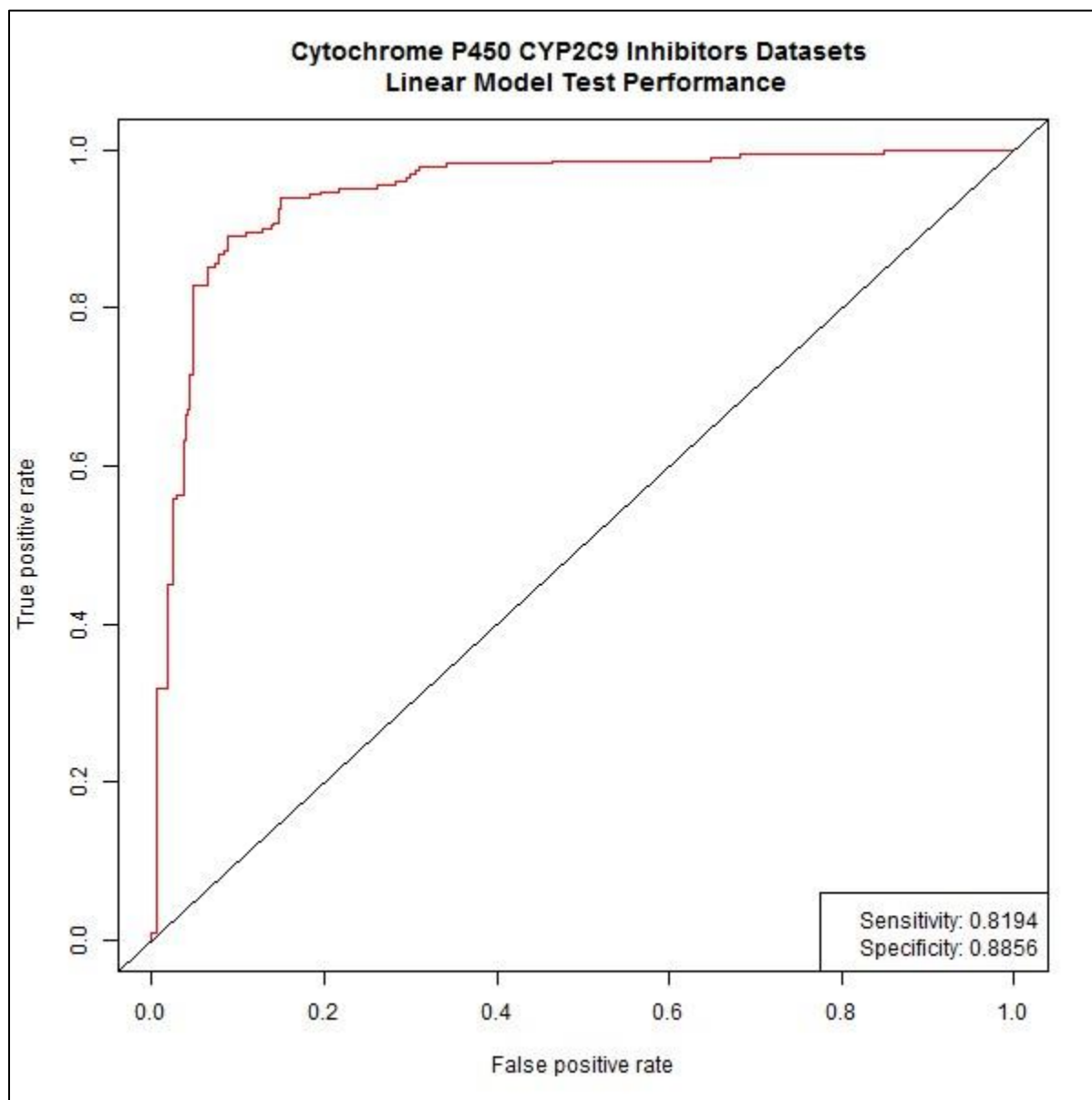
Figure 120: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C9 Substrates Class
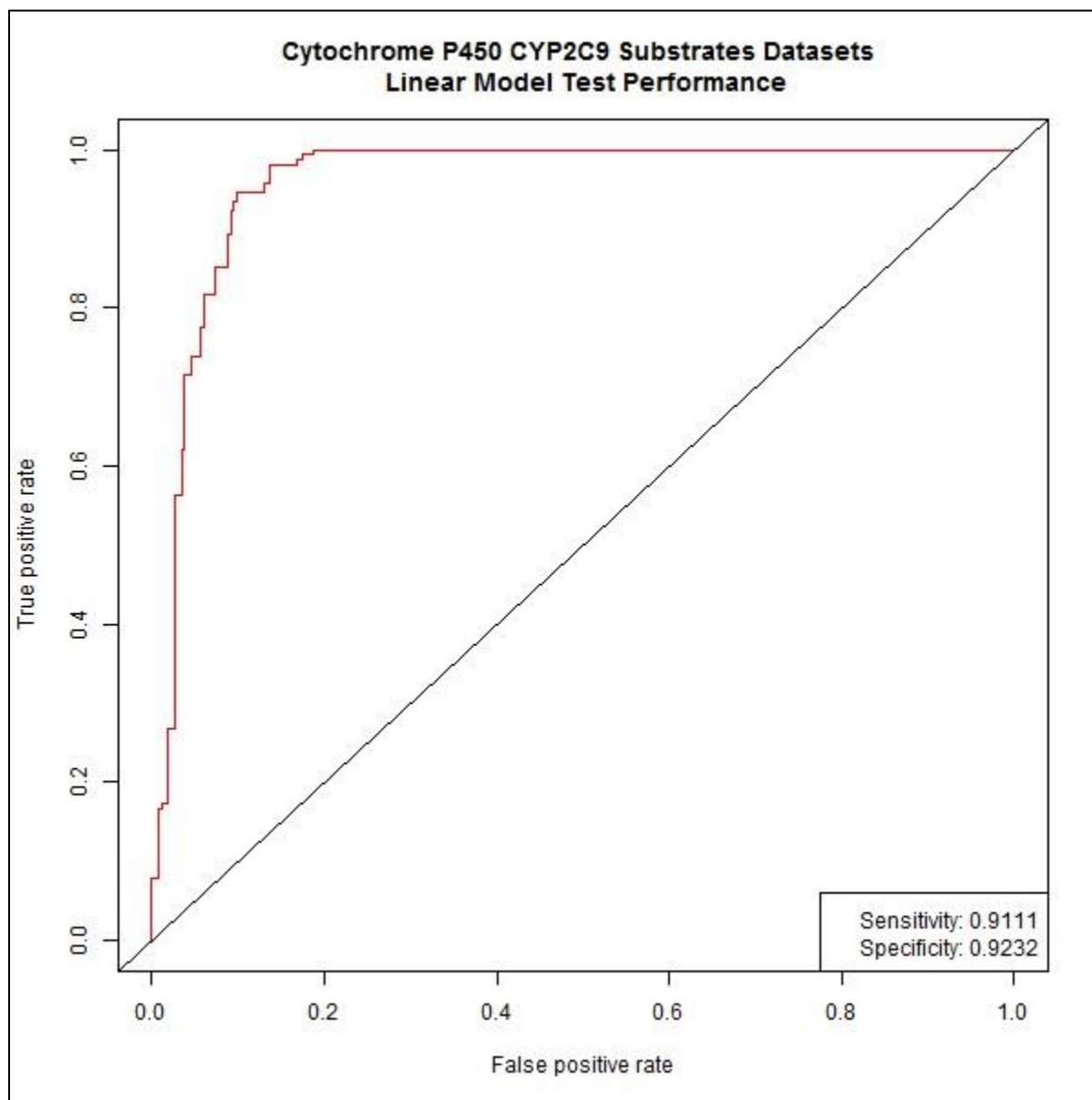
Figure 121: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C19 Inhibitors Class
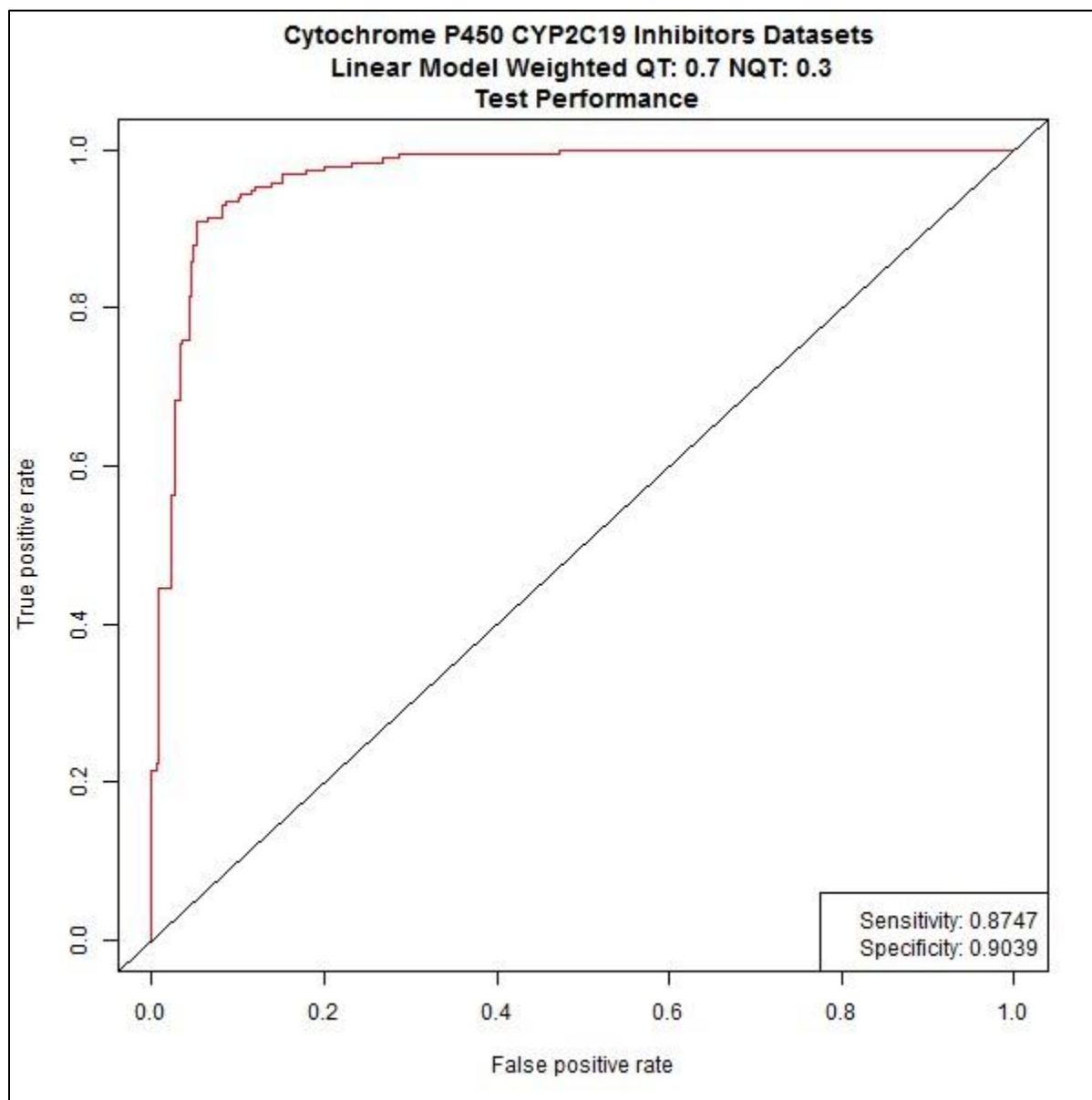
Figure 122: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2C19 Substrates Class
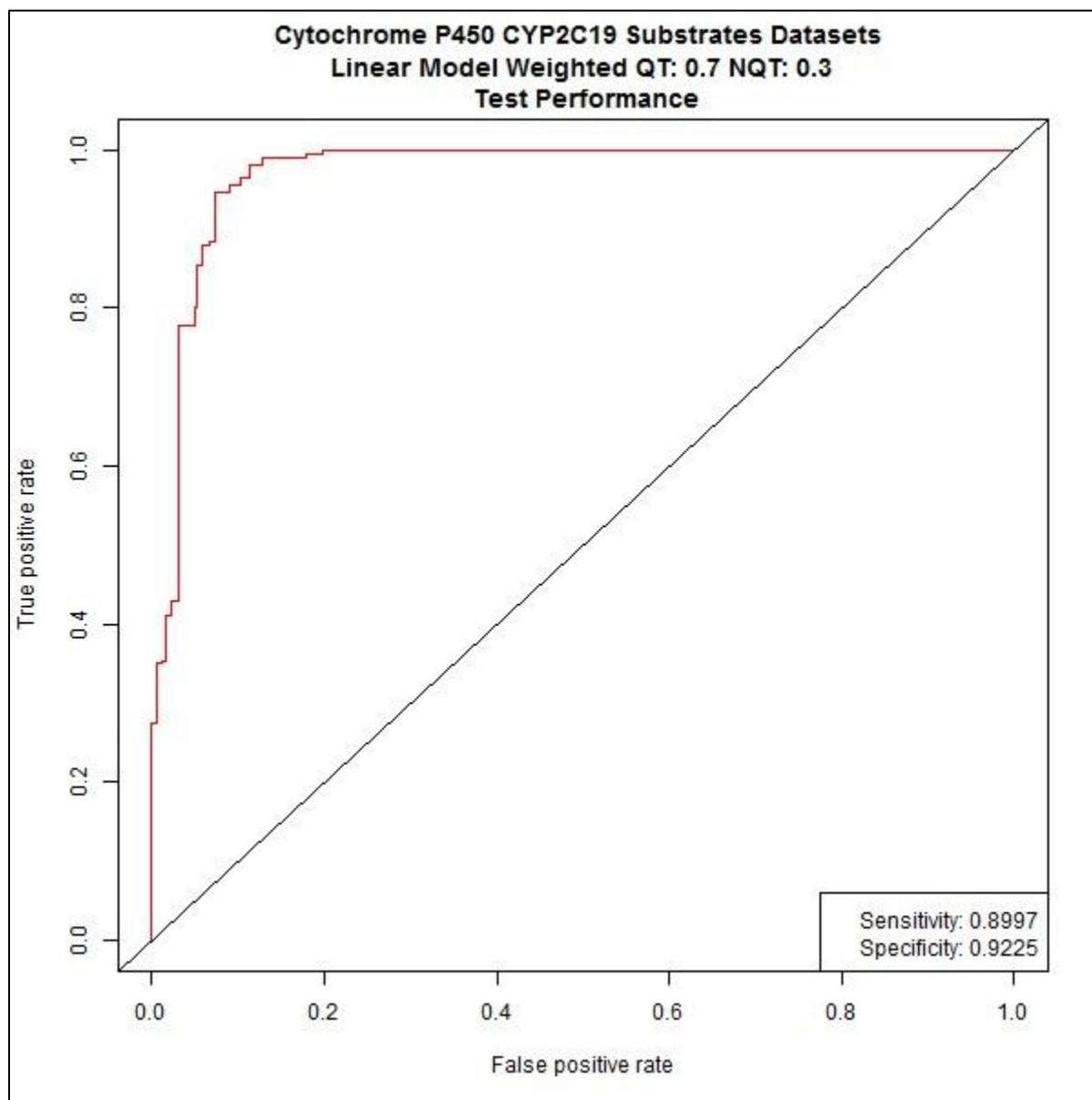
Figure 123: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2D6 Inhibitors Class
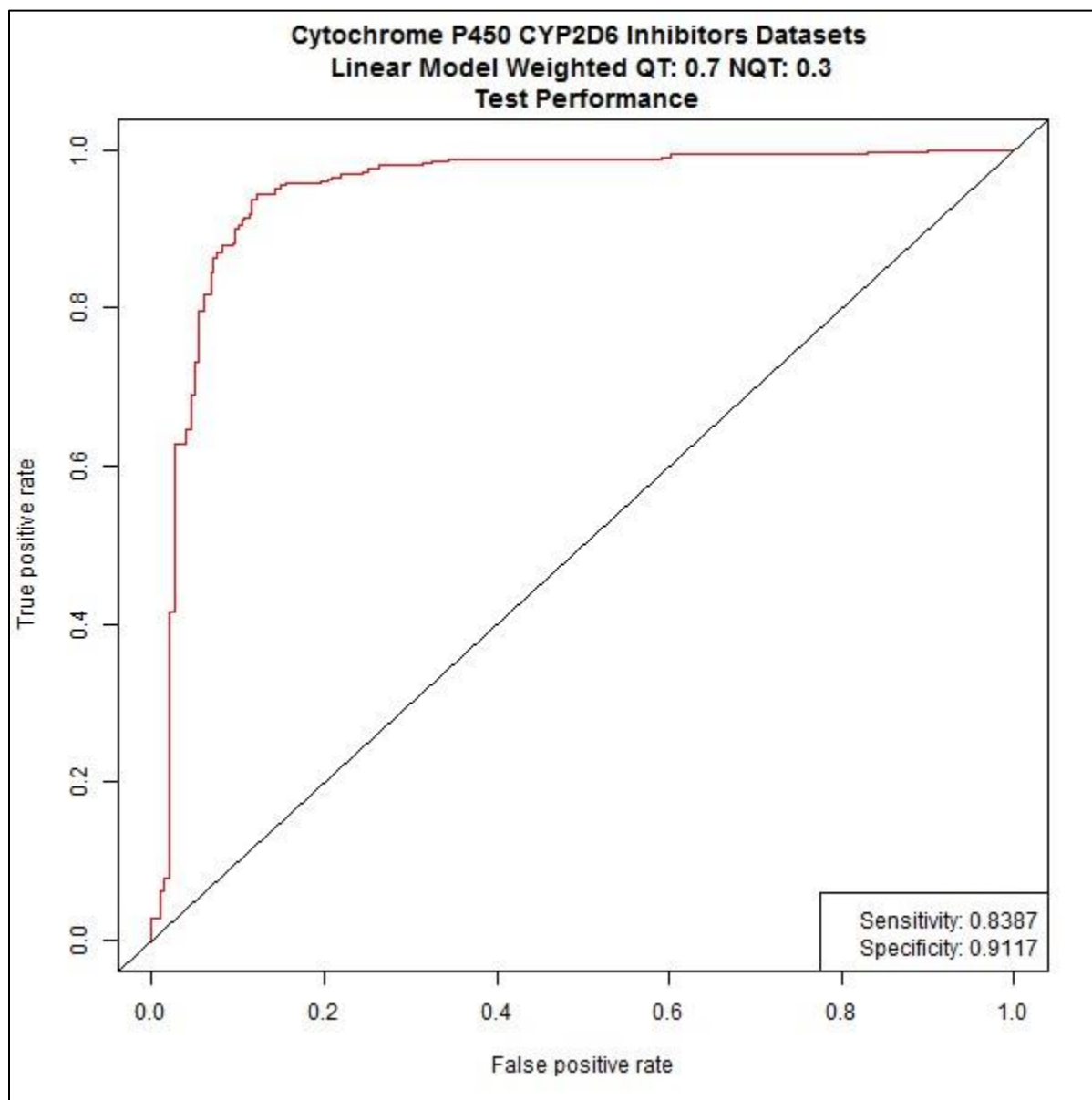
Figure 124: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2D6 Substrates Class
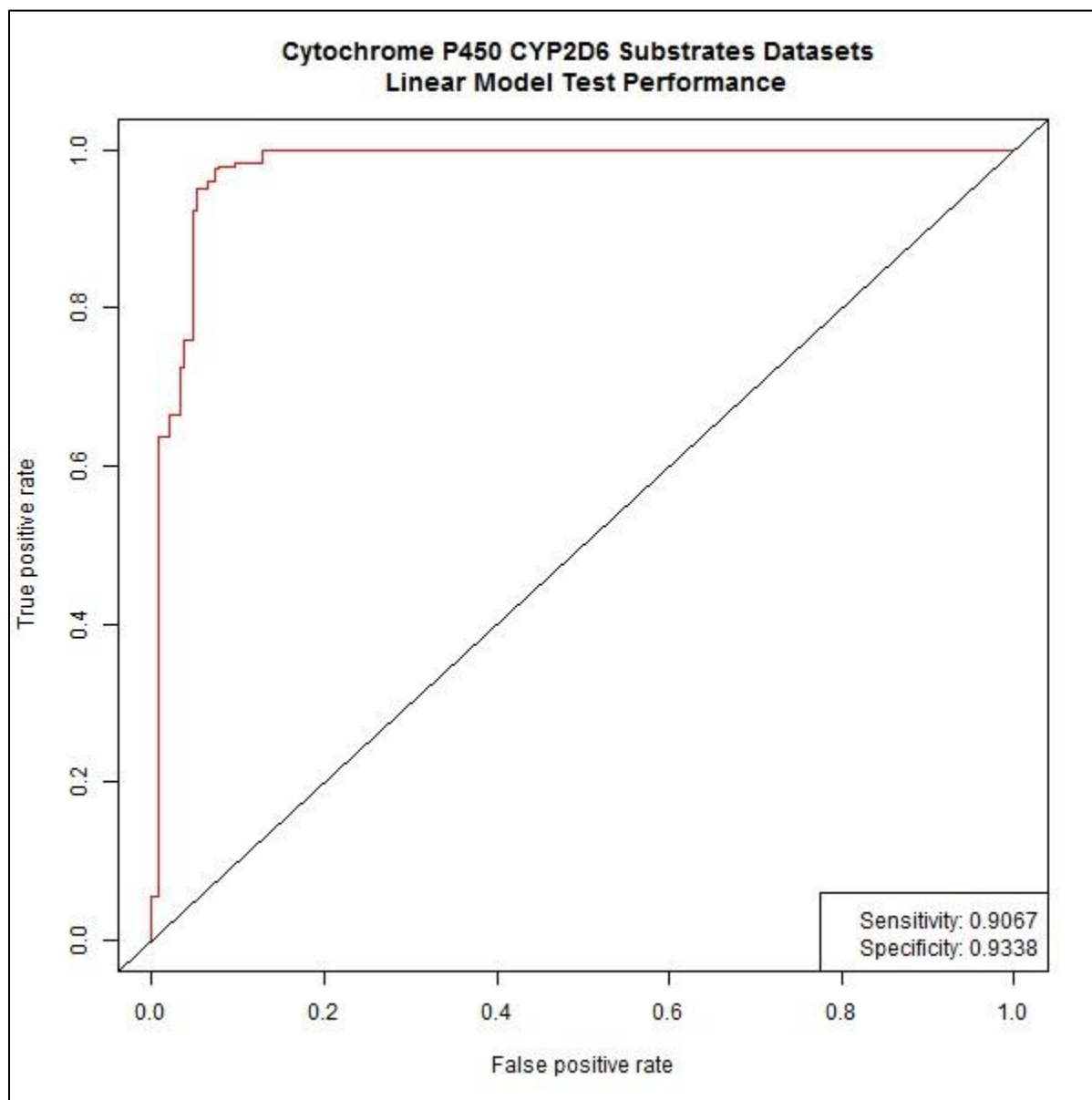
Figure 125: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2E1 Inhibitors Class
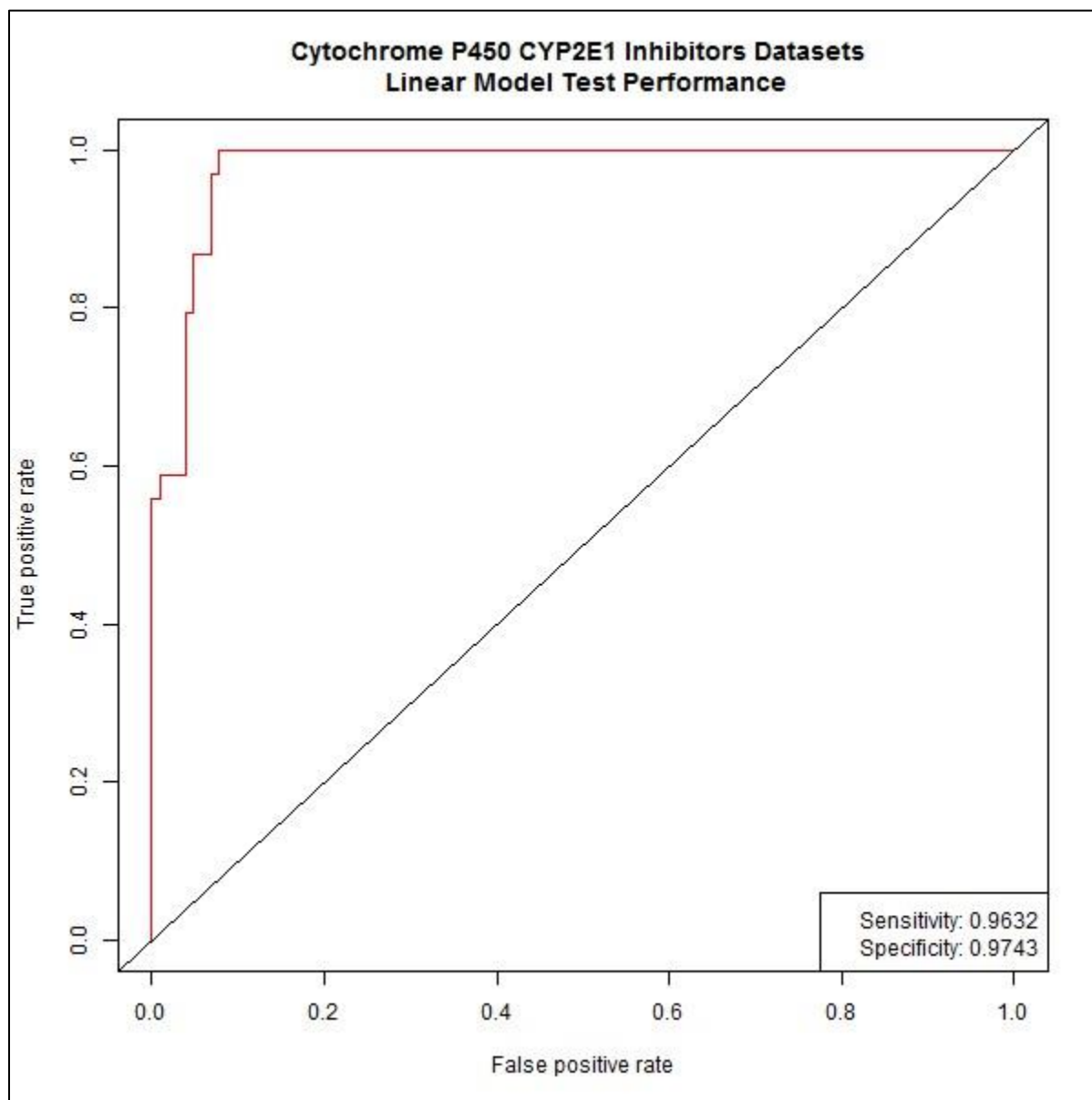
Figure 126: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP2E1 Substrates Class
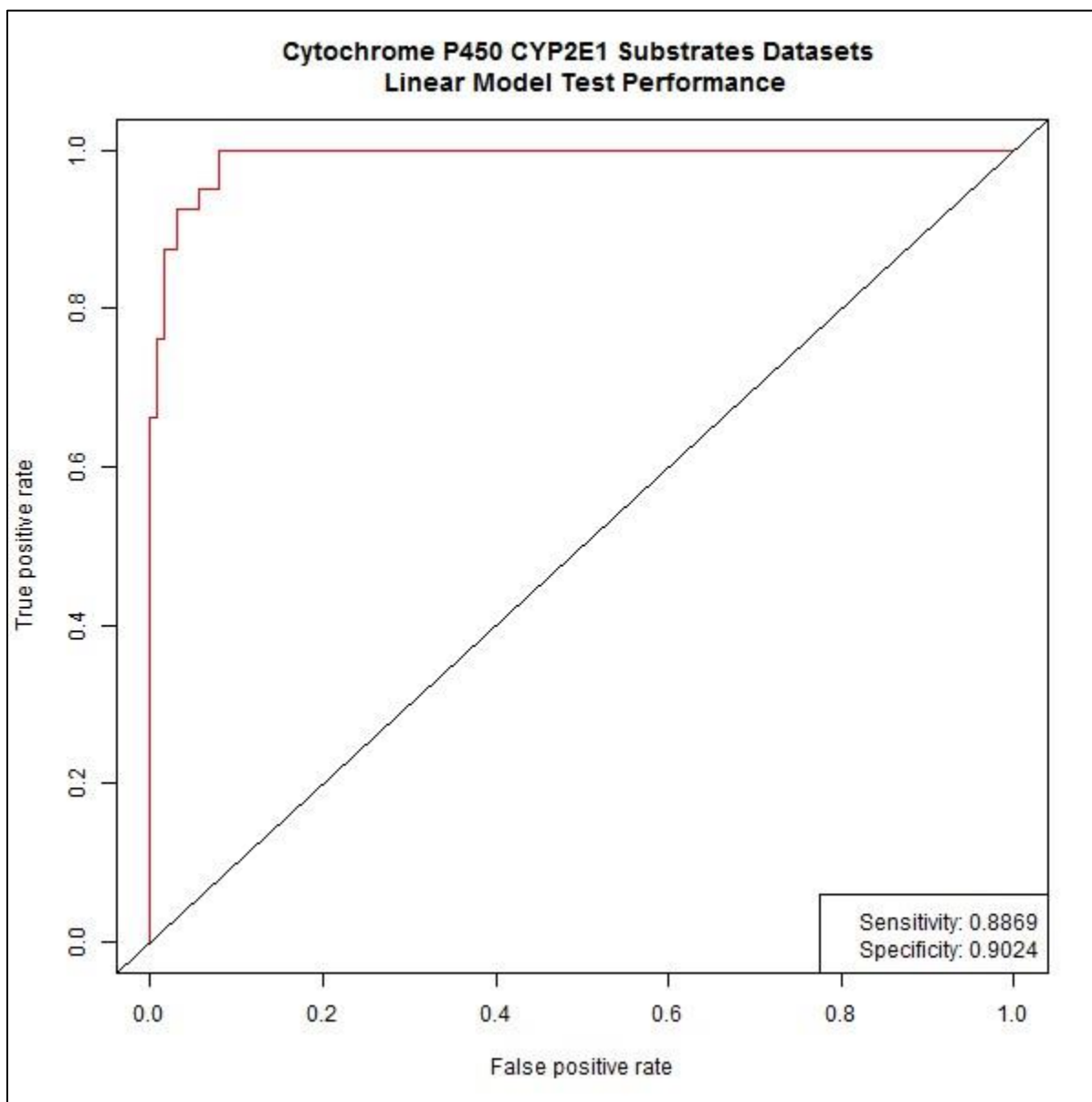
Figure 127: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP3A4 Substrates Class
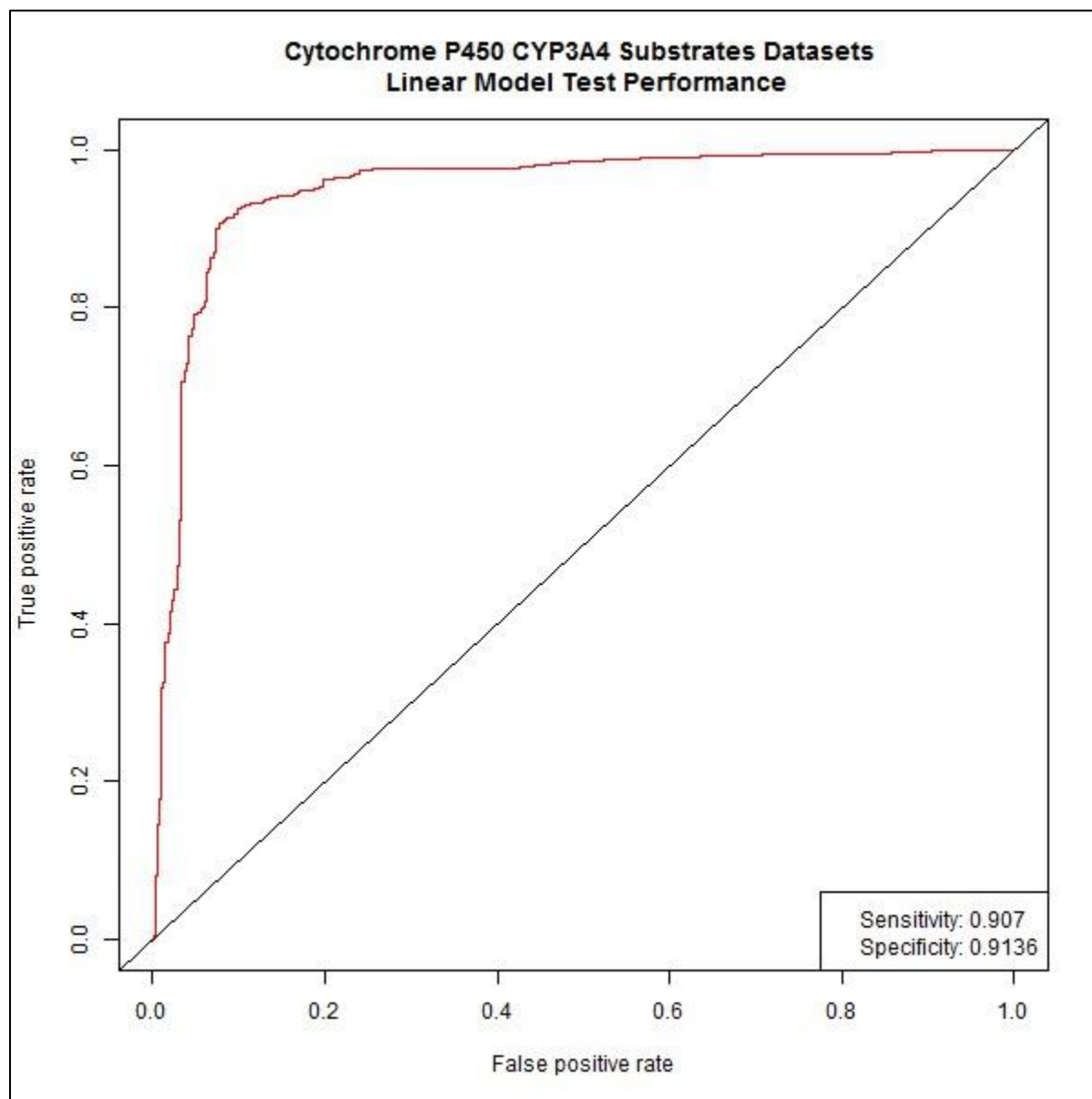
Figure 128: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP3A Inducers Class

Cytochrome P450 CYP3A Inducers Datasets
Linear Model Test Performance

Sensitivity: 0.9863
Specificity: 0.9785
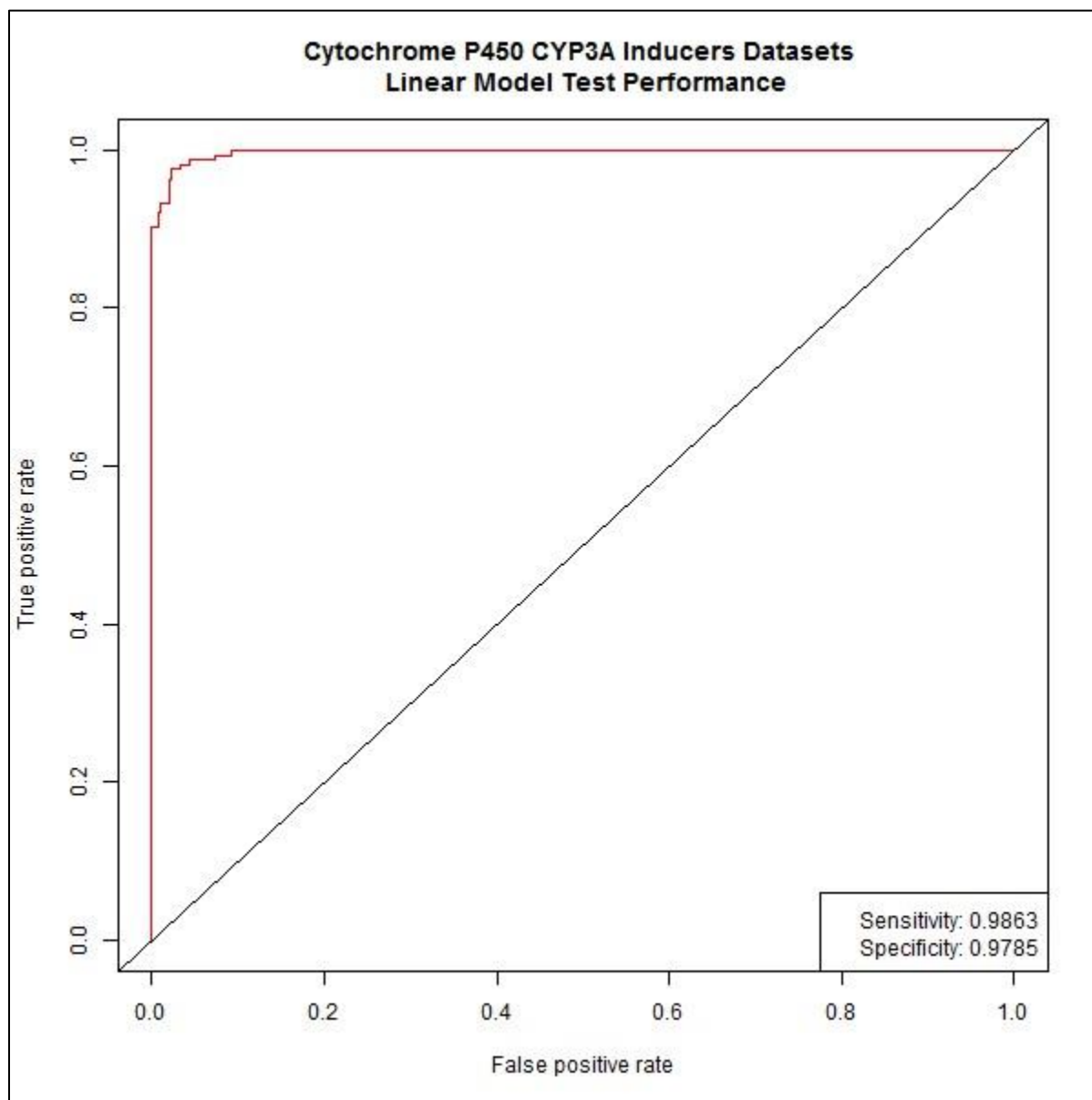
Figure 129: Receiver Operating Characteristic Curve for Cytochrome P-450 CYP3A Inhibitors Class
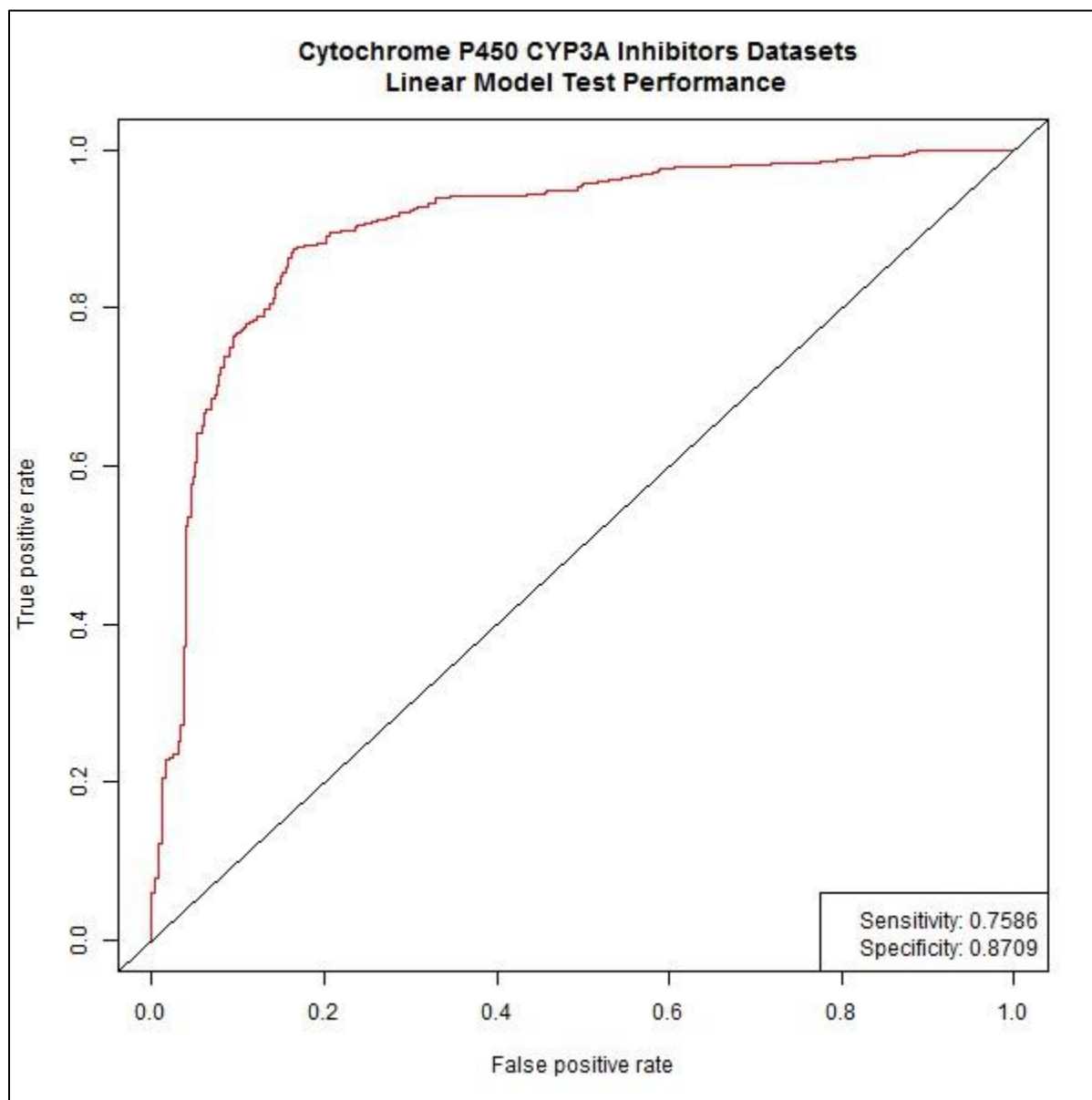
Figure 130: Receiver Operating Characteristic Curve for Cytochrome P-450 Enzyme Inhibitors Class
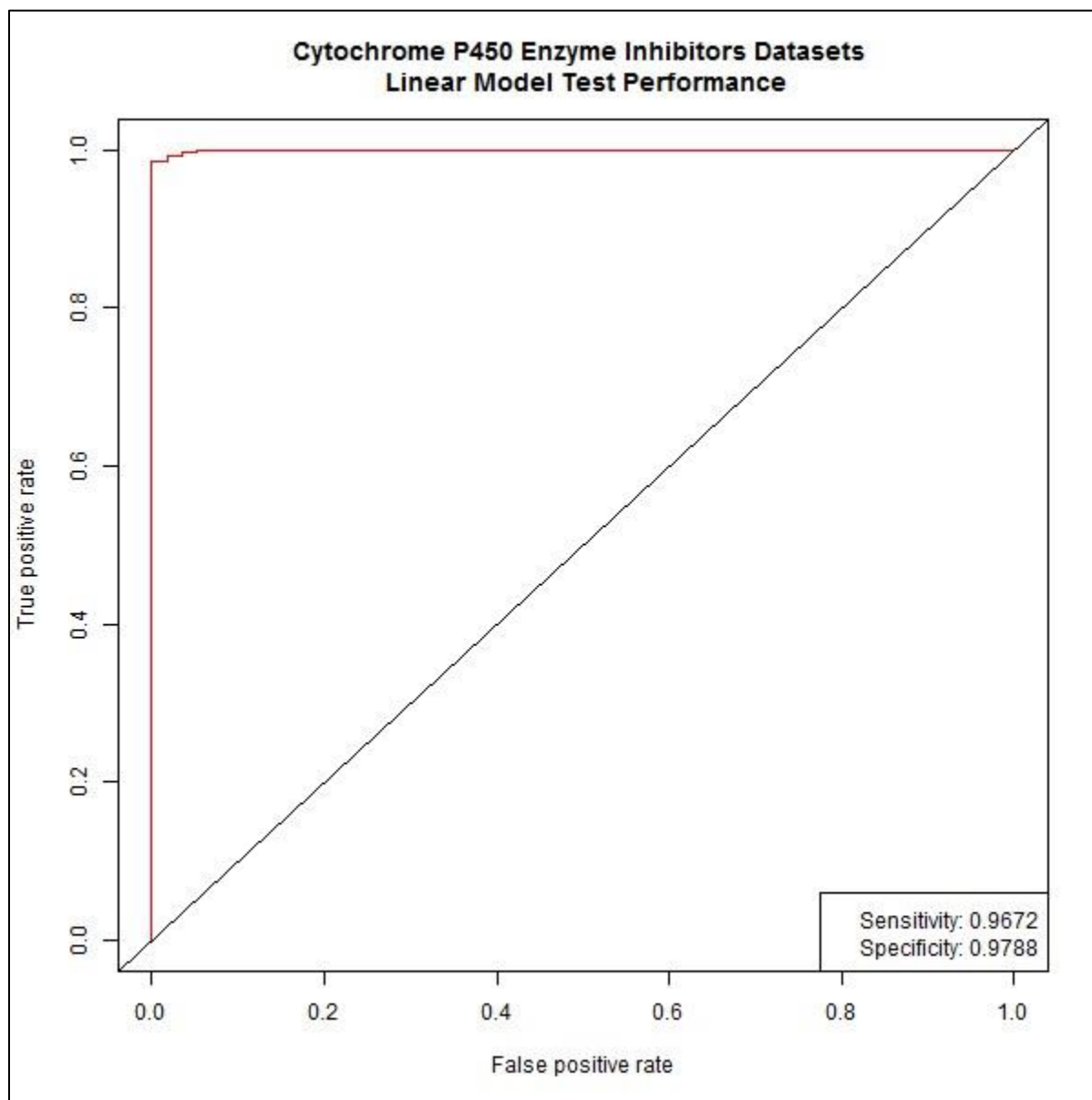
Figure 131: Receiver Operating Characteristic Curve for Dermatologicals Class
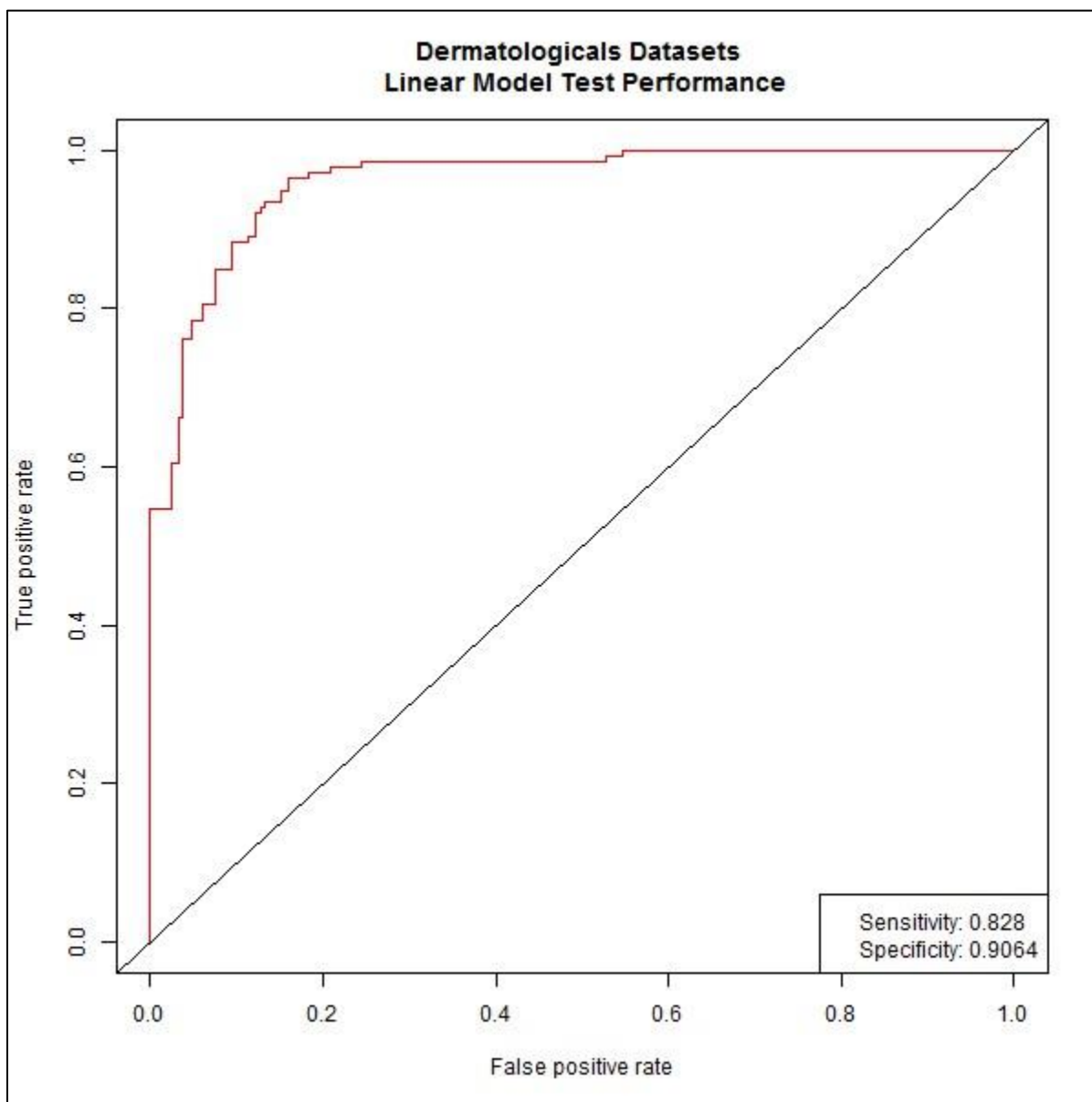
Figure 132: Receiver Operating Characteristic Curve for Drugs for Acid Related Disorders Class
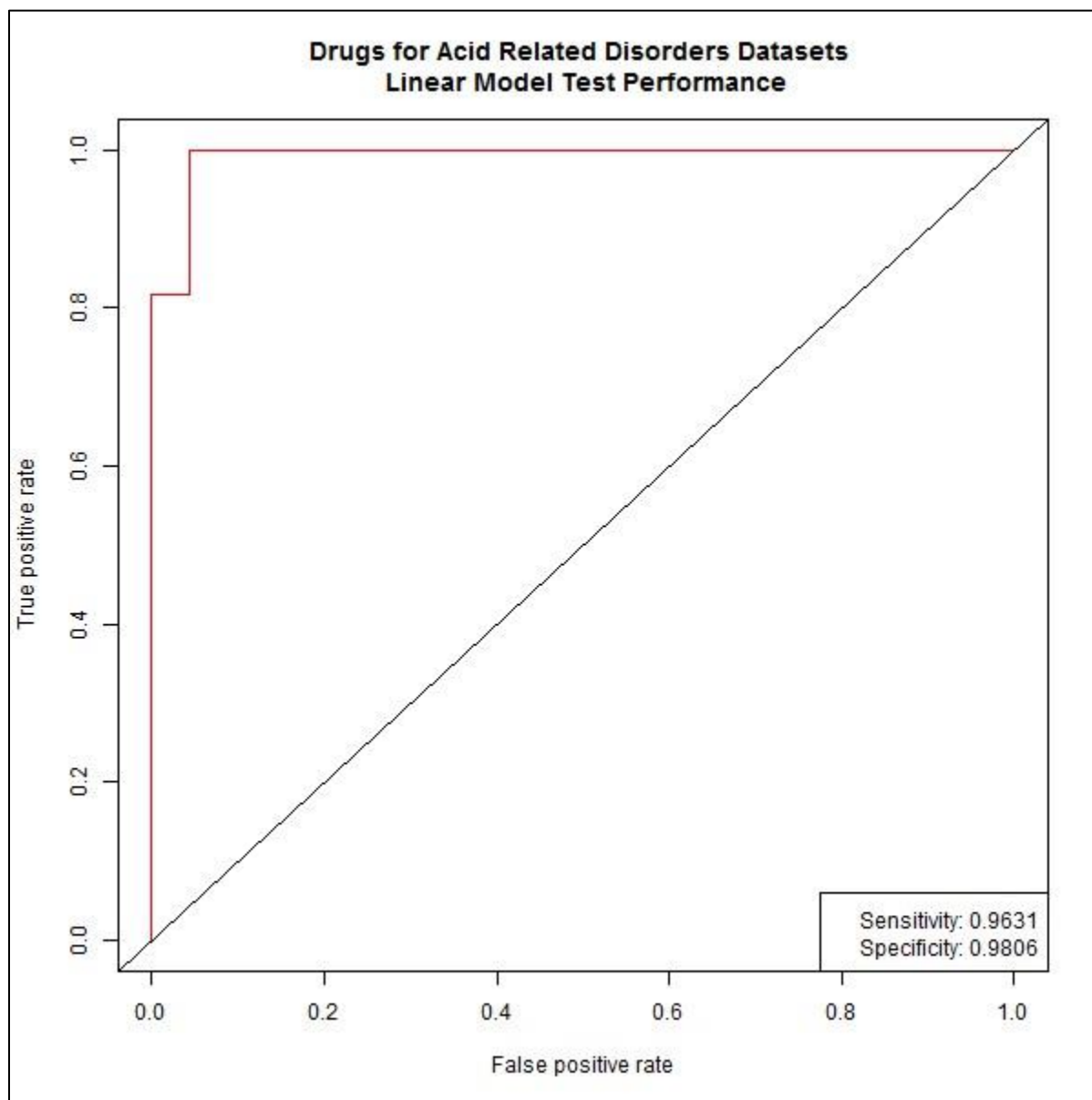
Figure 133: Receiver Operating Characteristic Curve for Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD) Class

Drugs for Peptic Ulcers & GORD Datasets
Linear Model Weighted QT: 0.7 NQT: 0.3
Test Performance

Sensitivity: 0.9425
Specificity: 0.9575
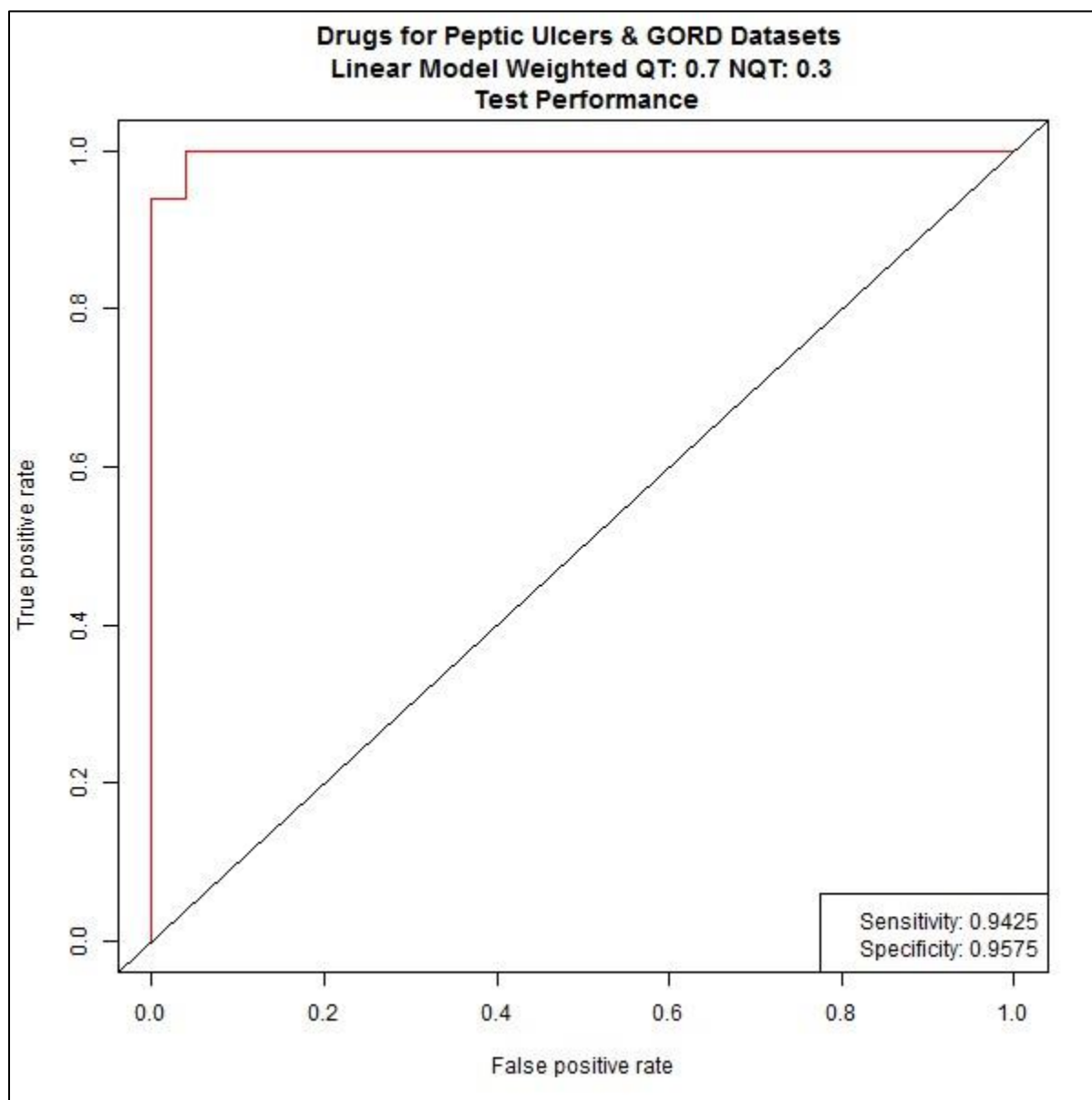
Figure 134: Receiver Operating Characteristic Curve for Enzyme Inhibitors Class
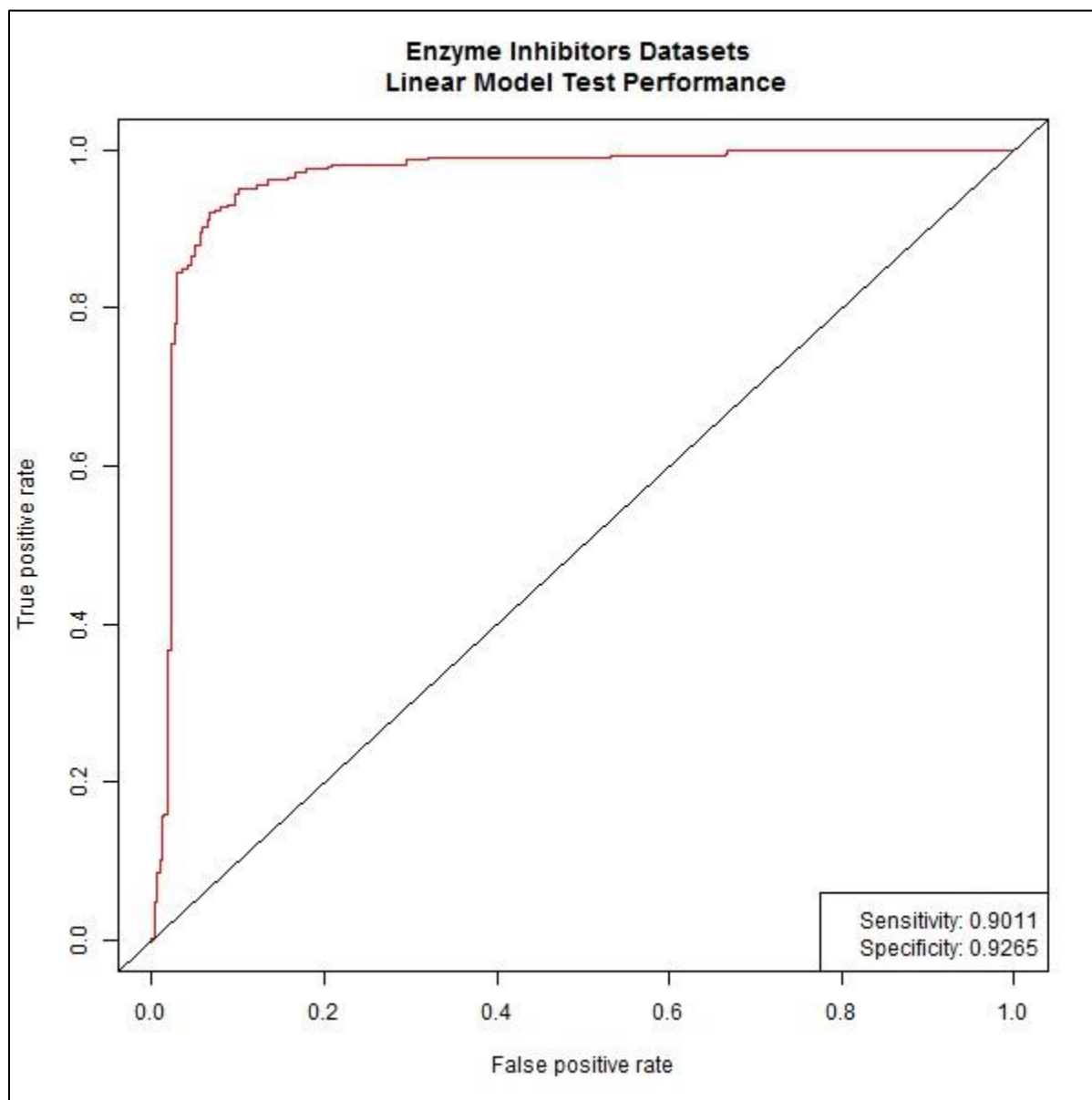
Figure 135: Receiver Operating Characteristic Curve for Estrogen Antagonists Class
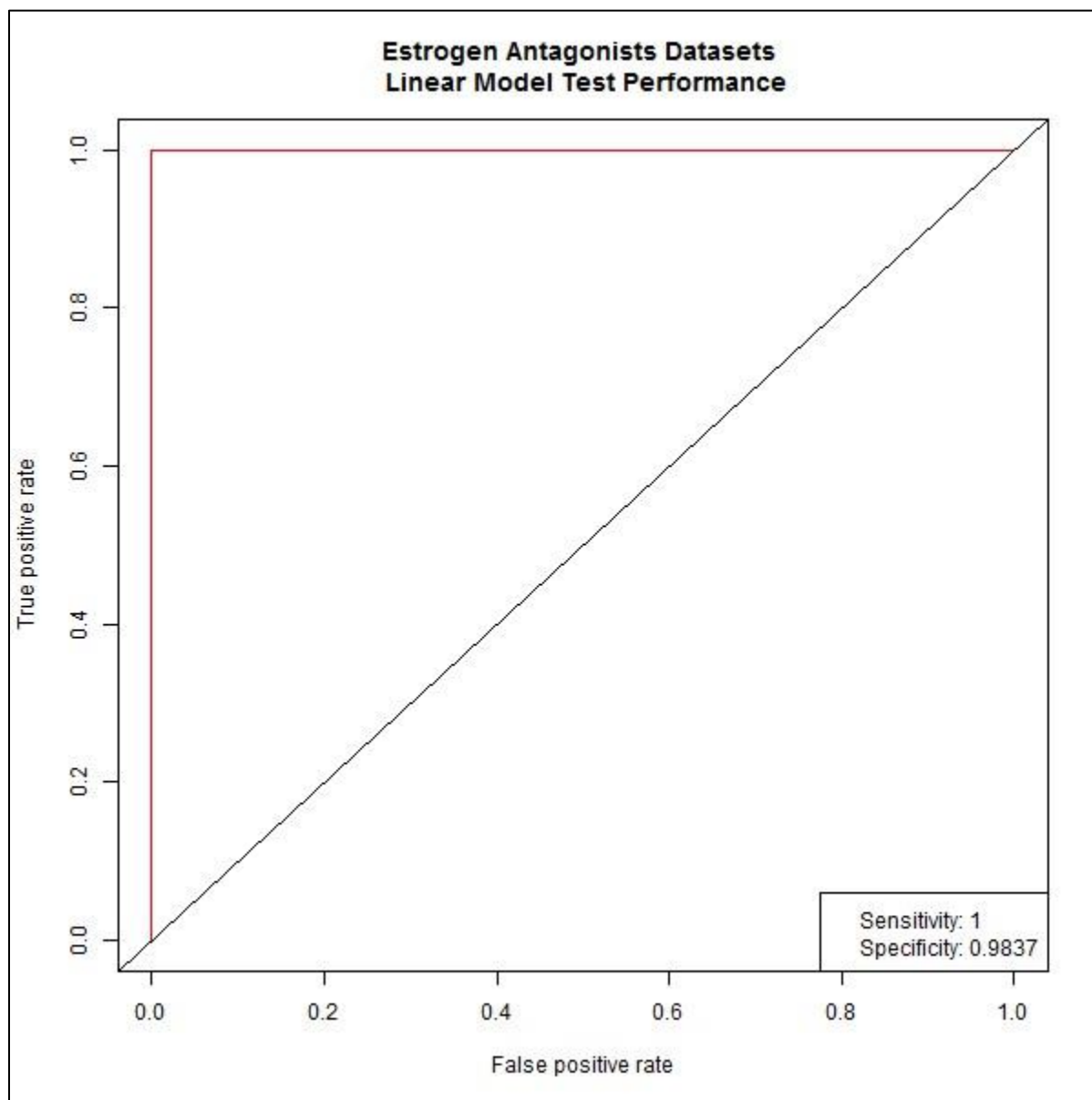
Figure 136: Receiver Operating Characteristic Curve for Fluoroquinolones Class
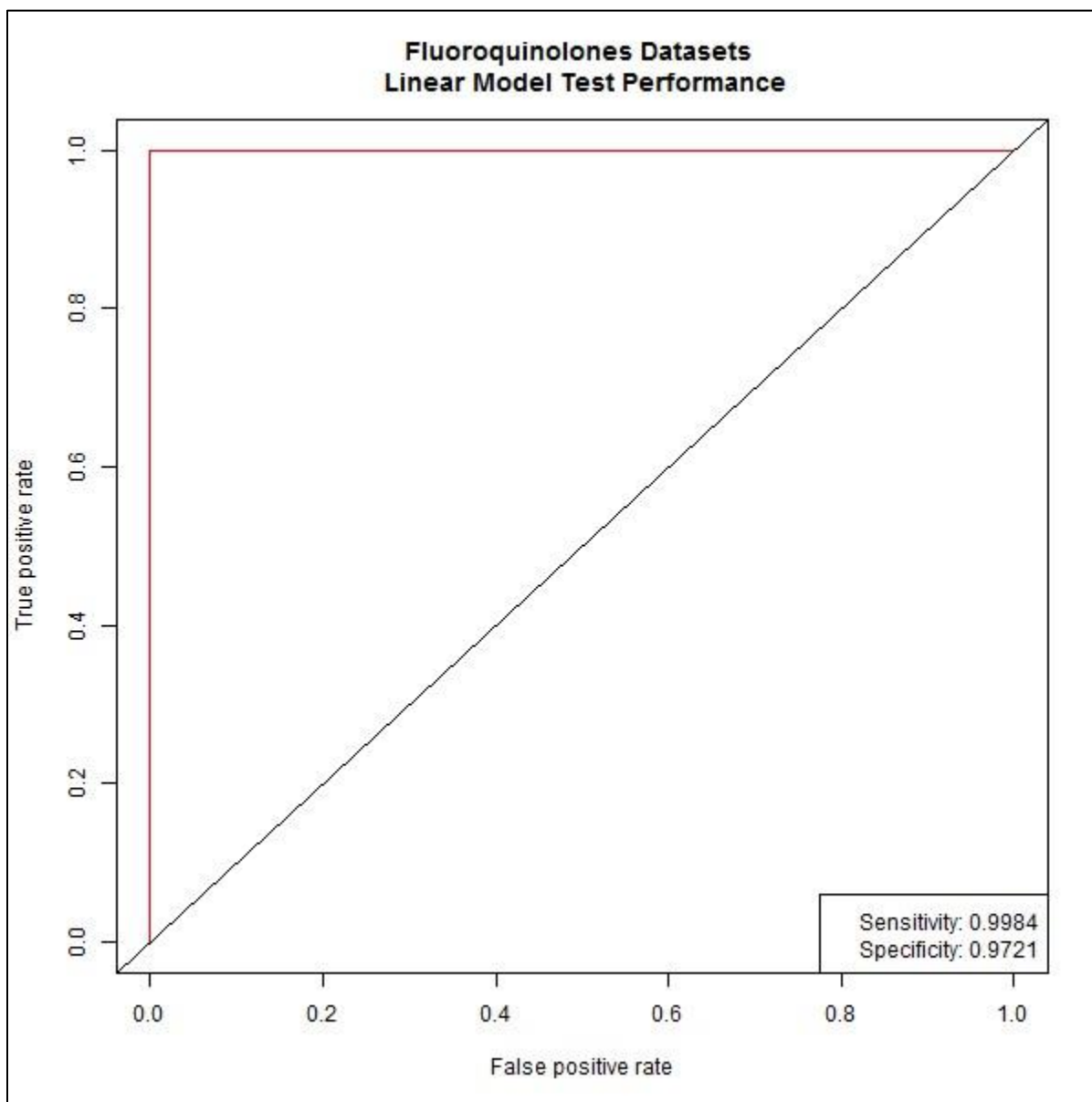
Figure 137: Receiver Operating Characteristic Curve for Gastrointestinal Agents Class
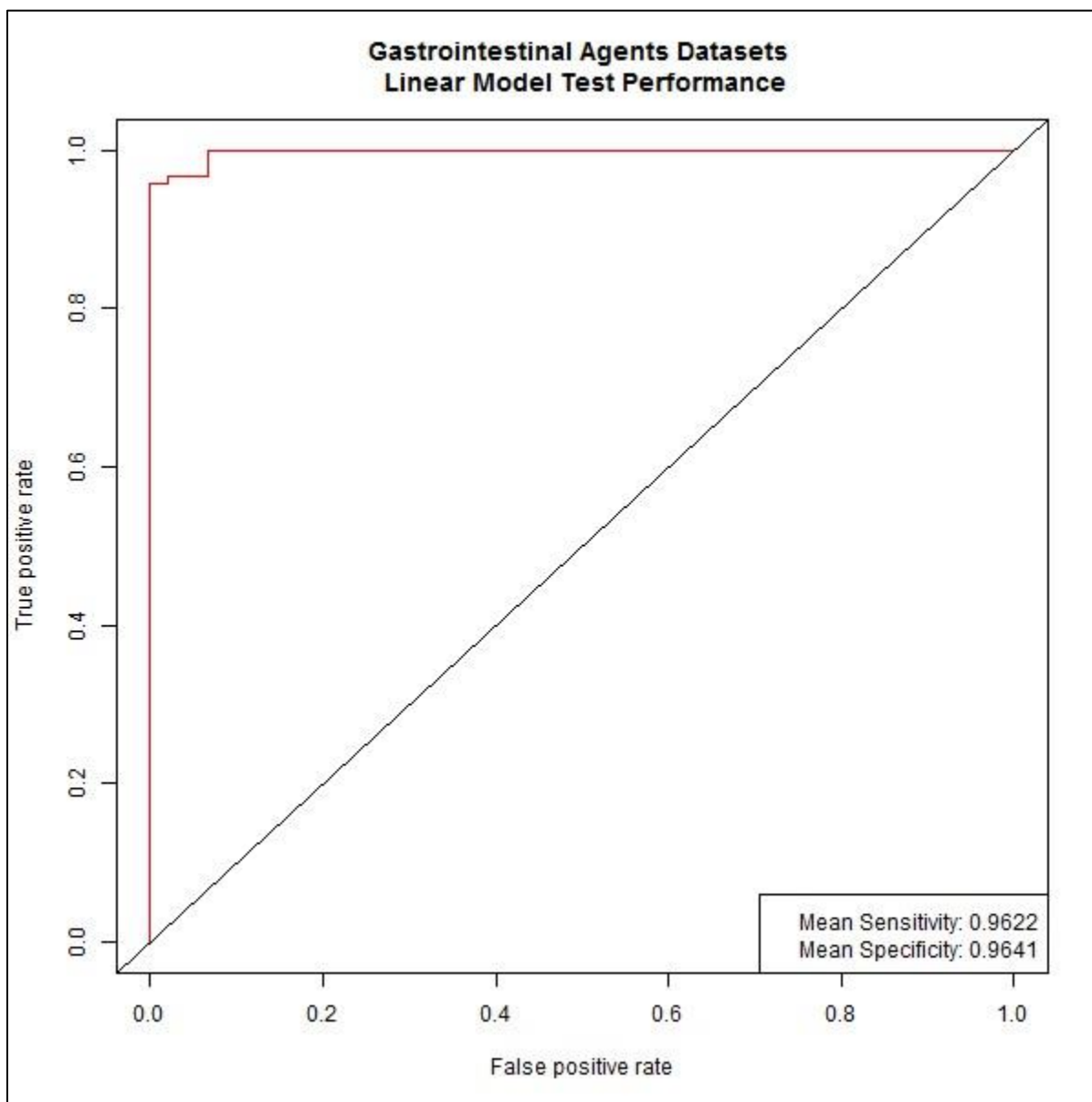
Figure 138: Receiver Operating Characteristic Curve for Heterocyclic Compounds Class
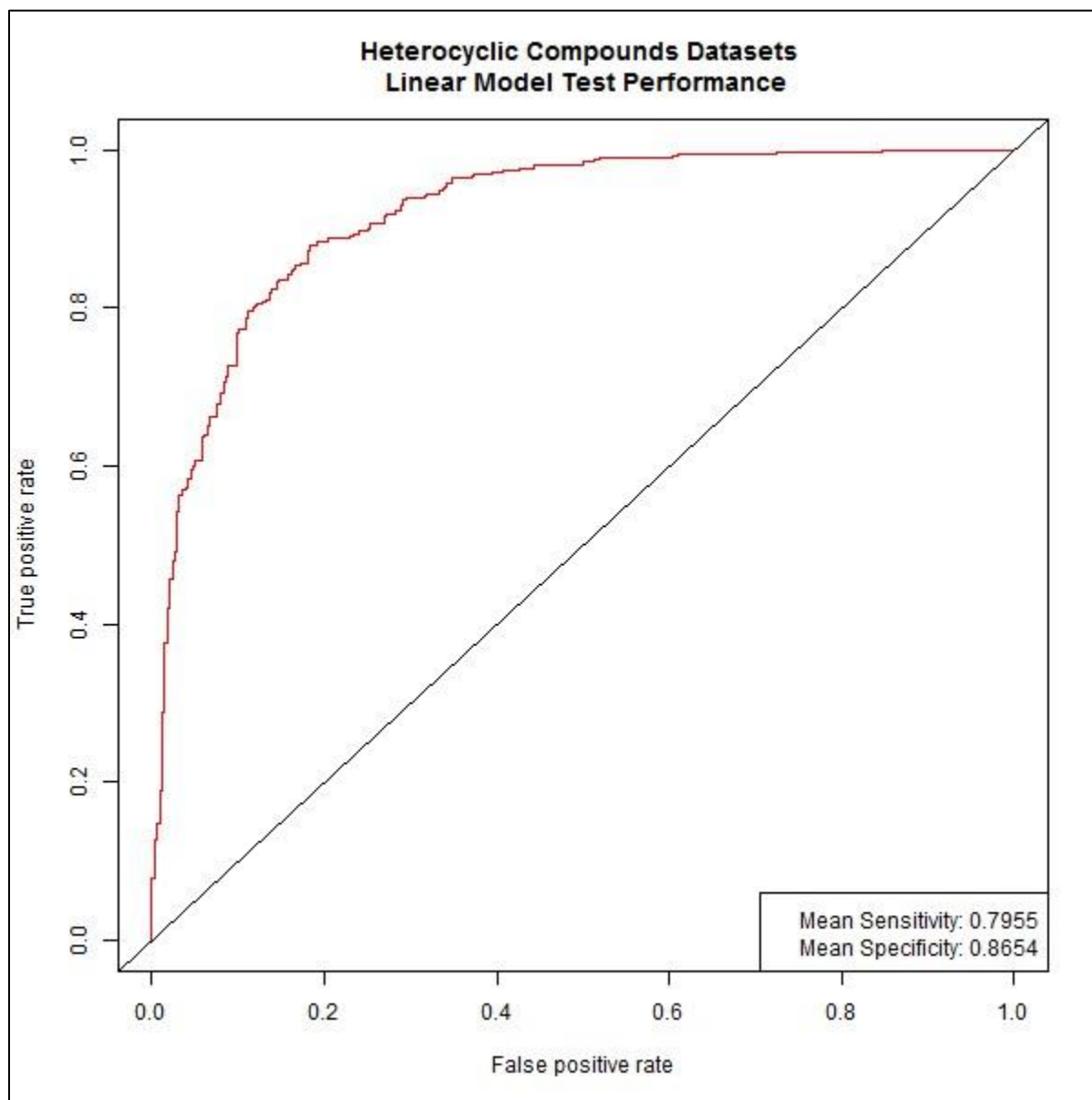
Figure 139: Receiver Operating Characteristic Curve for Heterocyclic Compounds – 1 Ring Class
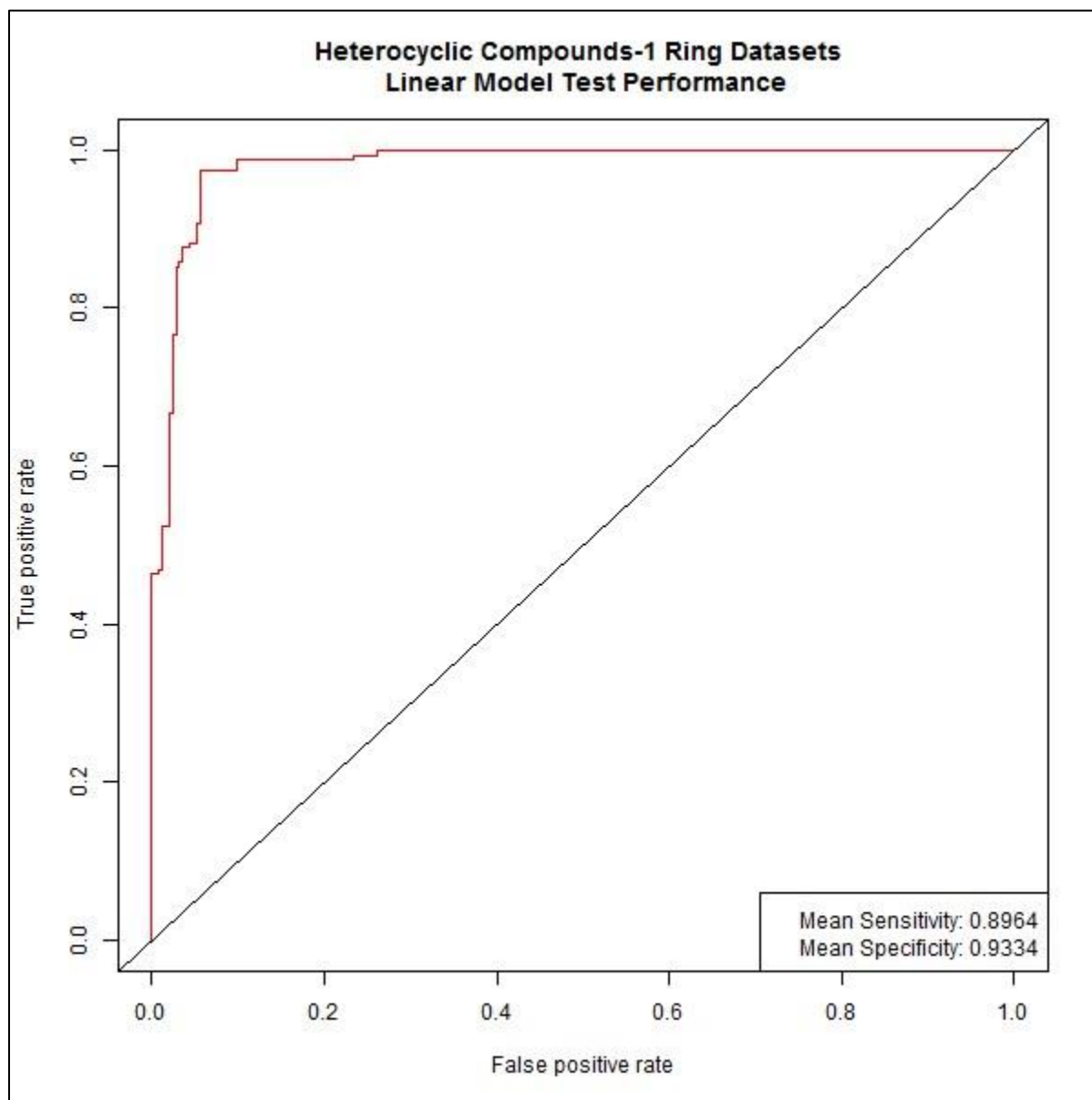
Figure 140: Receiver Operating Characteristic Curve for Heterocyclic Compounds – 2 Ring Class
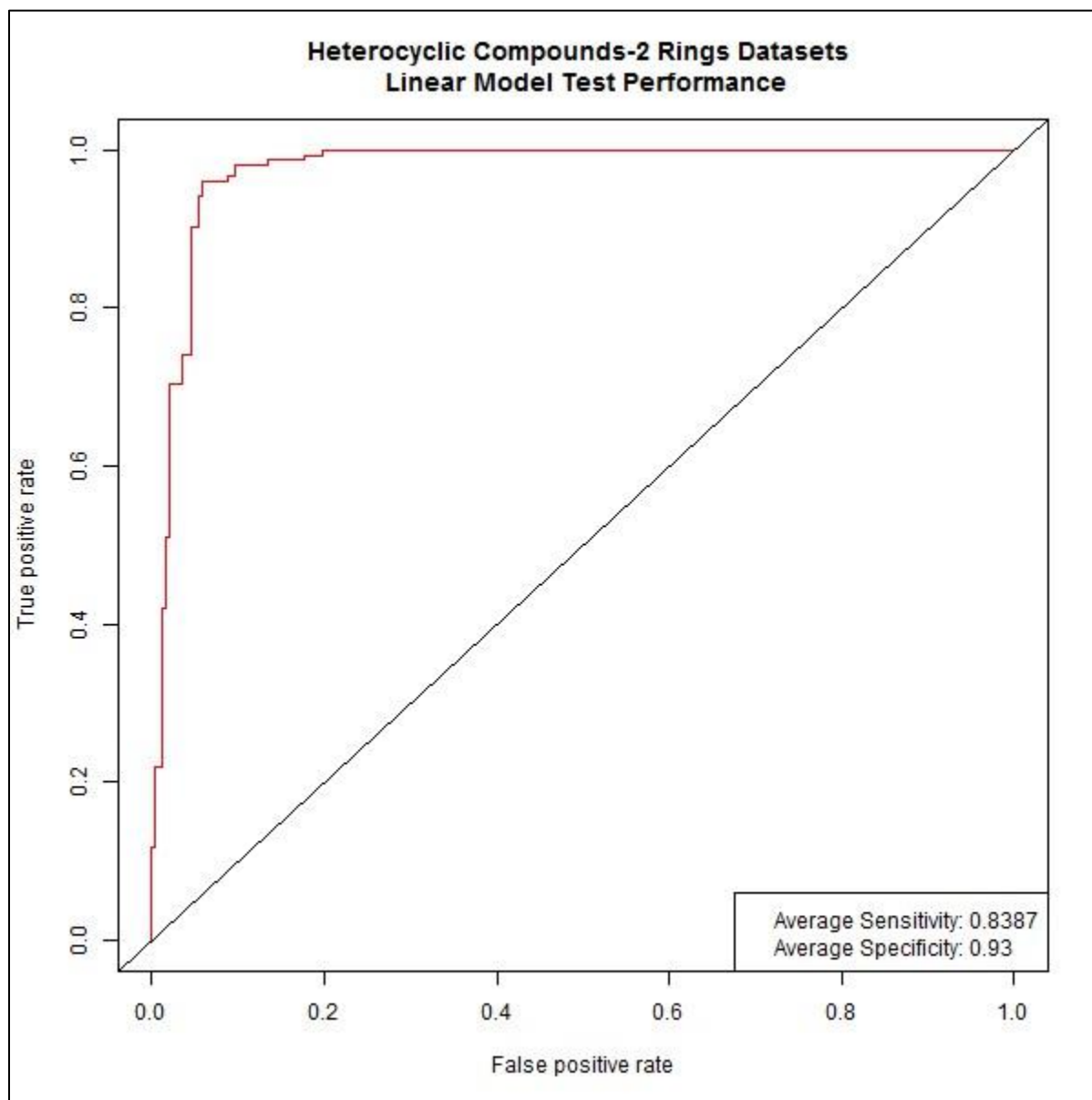
Figure 141: Receiver Operating Characteristic Curve for Hormone Antagonists Class
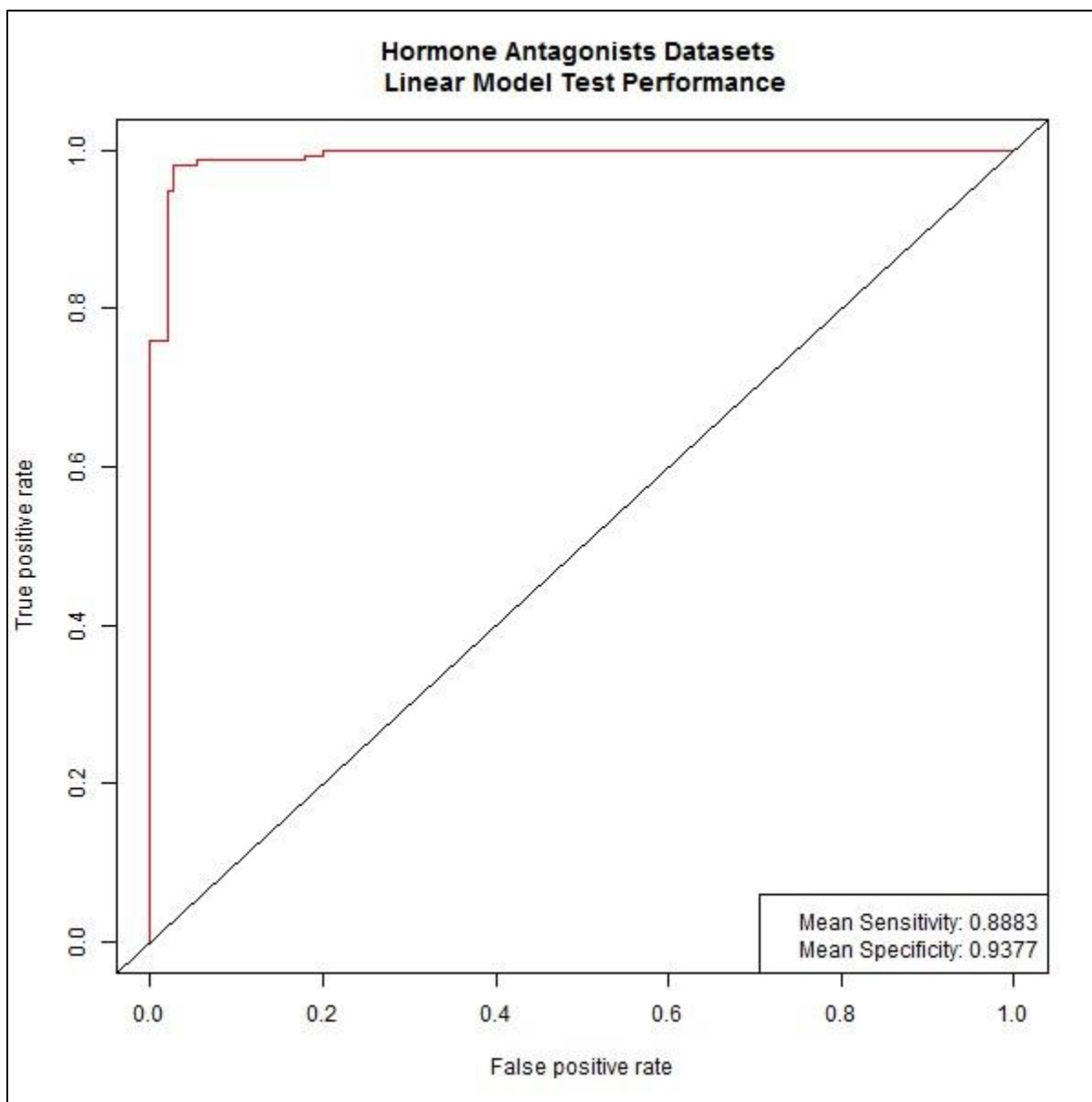
Figure 142: Receiver Operating Characteristic Curve for Hormones, Hormone Substitutes, and Hormone Antagonists Class
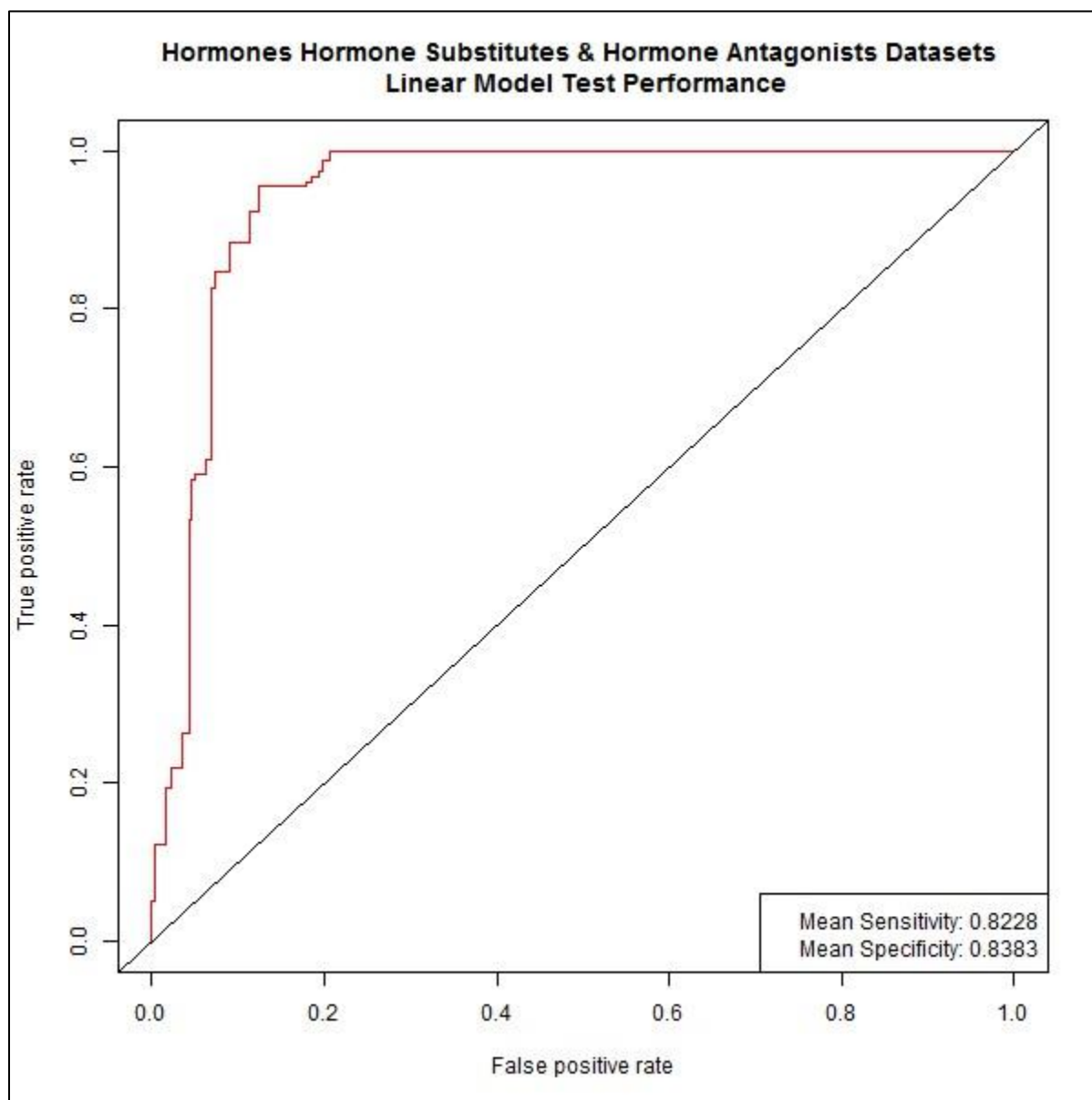
Figure 143: Receiver Operating Characteristic Curve for Hydrocarbons Class
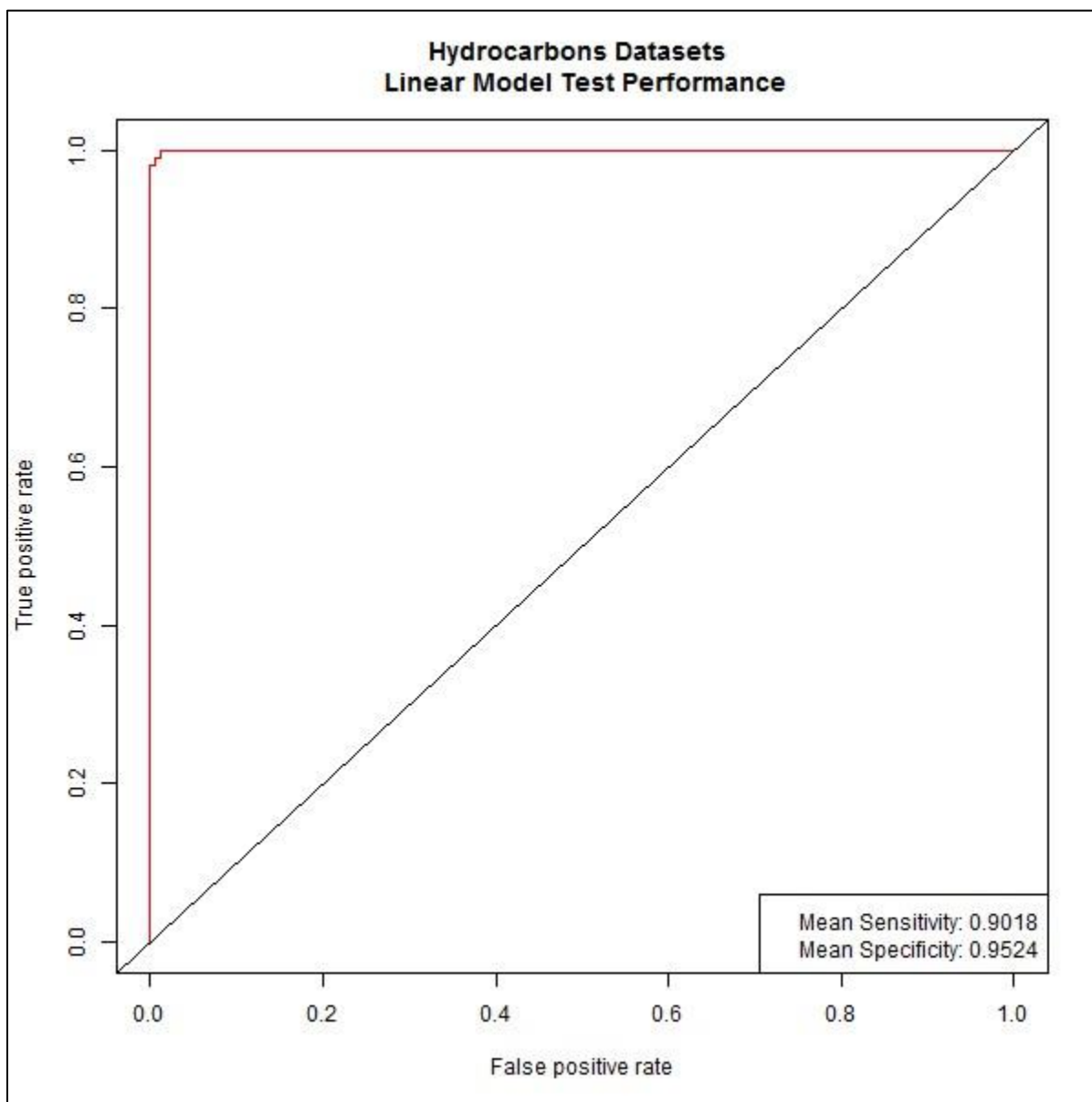
Figure 144: Receiver Operating Characteristic Curve for Hydrocarbons, Aromatic Class
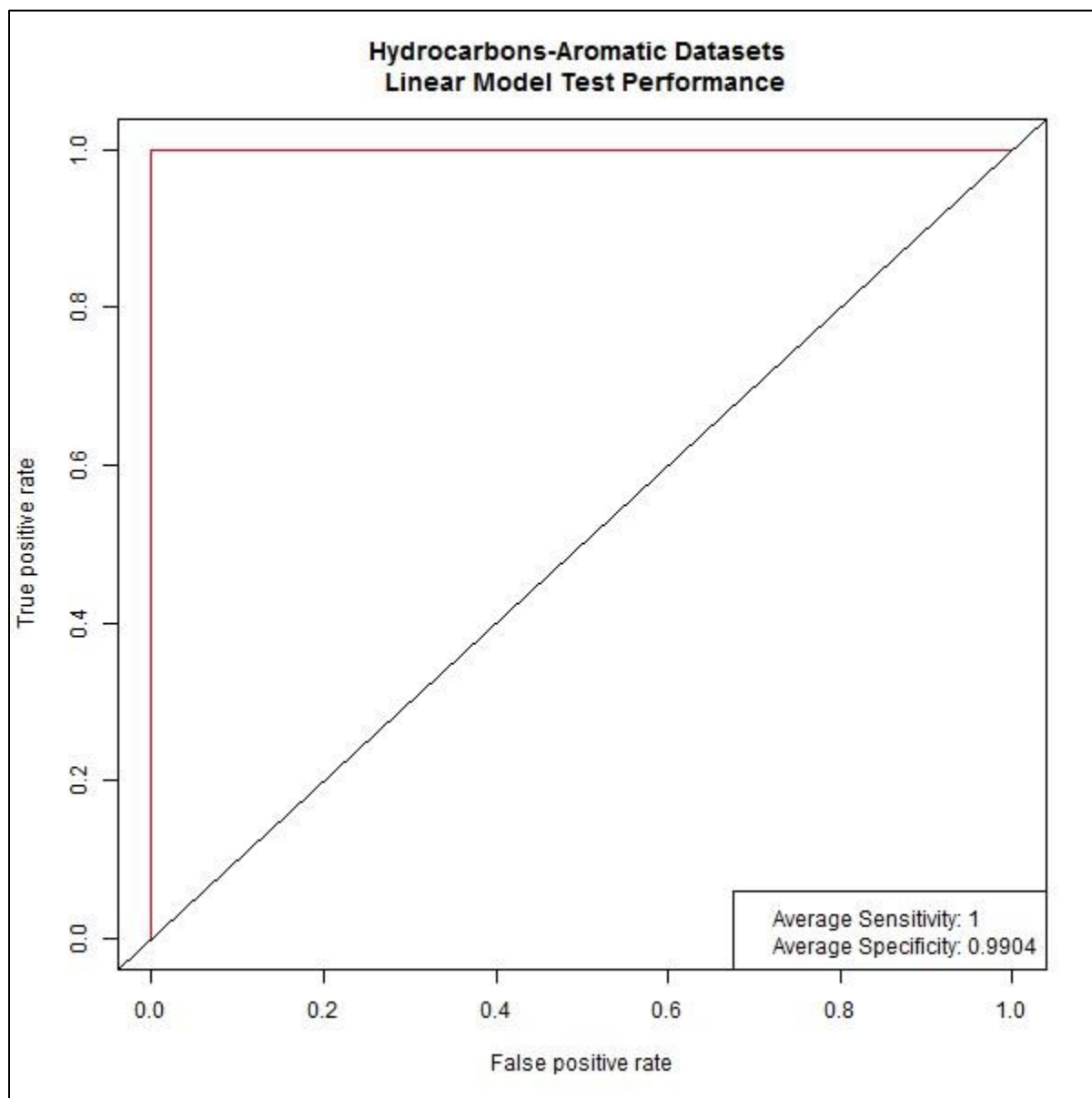
Figure 145: Receiver Operating Characteristic Curve for Hydrocarbons, Cyclic Class
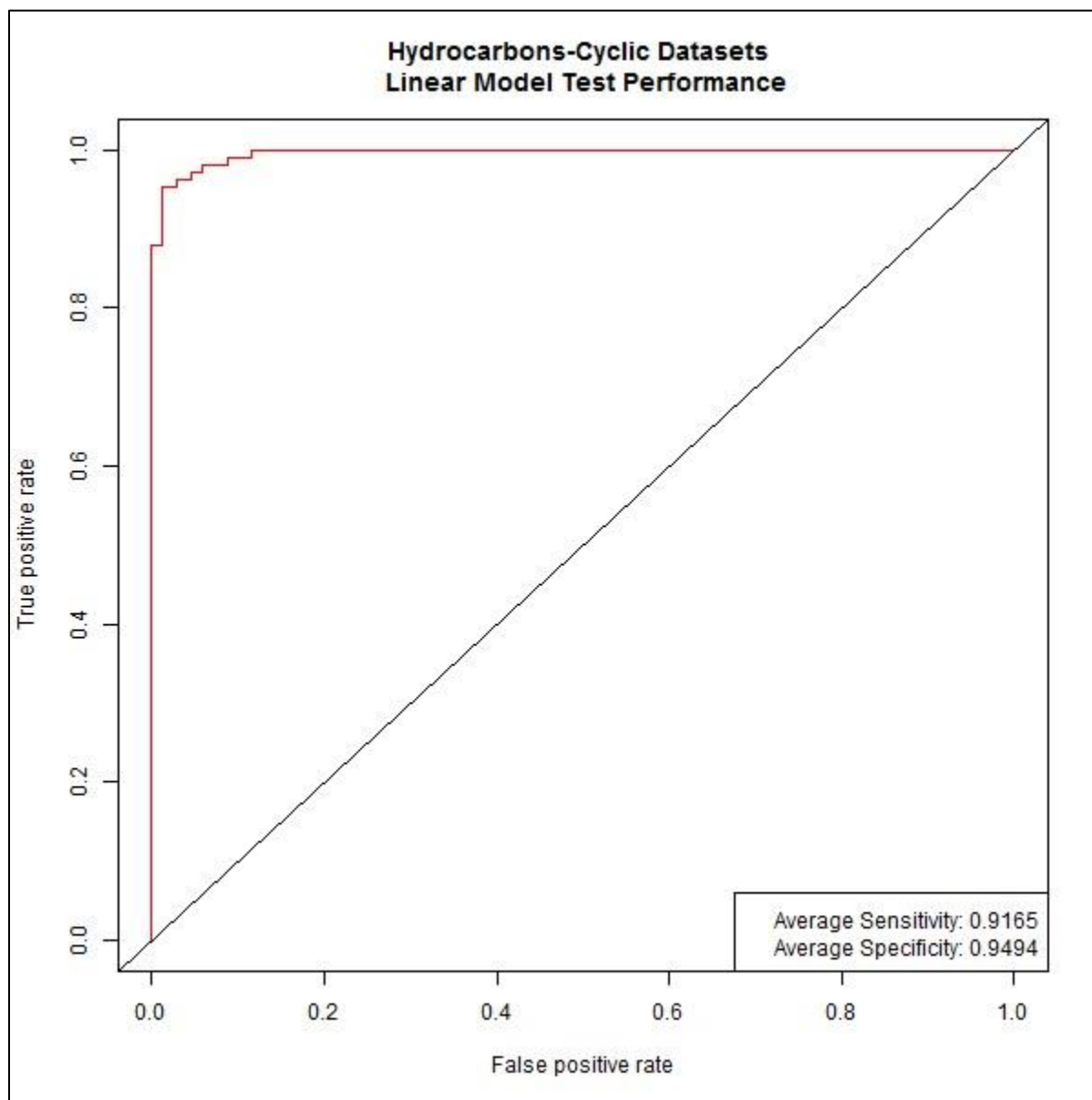
Figure 146: Receiver Operating Characteristic Curve for Hyperglycemia-Associated Agents Class
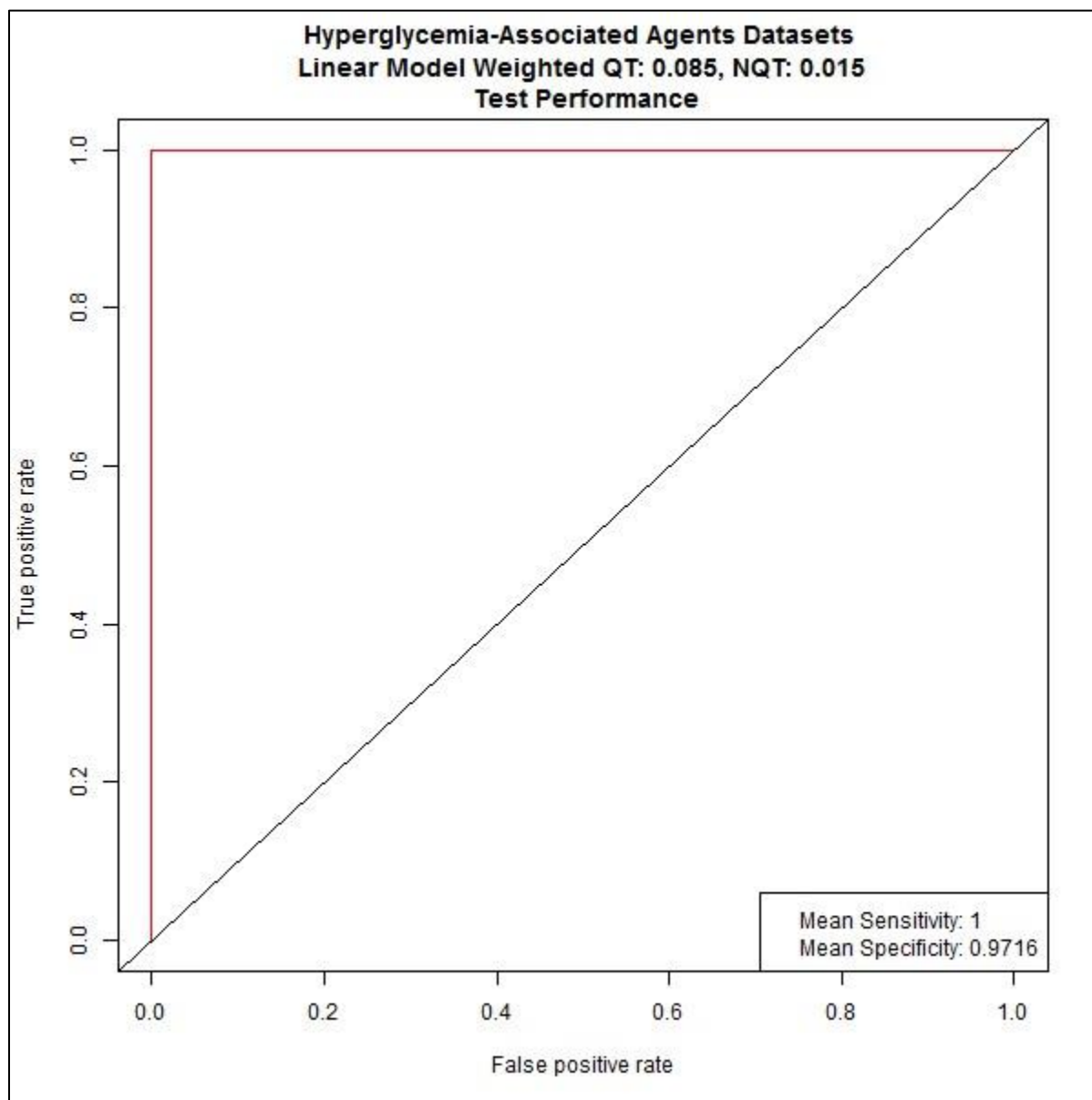
Figure 147: Receiver Operating Characteristic Curve for Hypotensive Agents Class
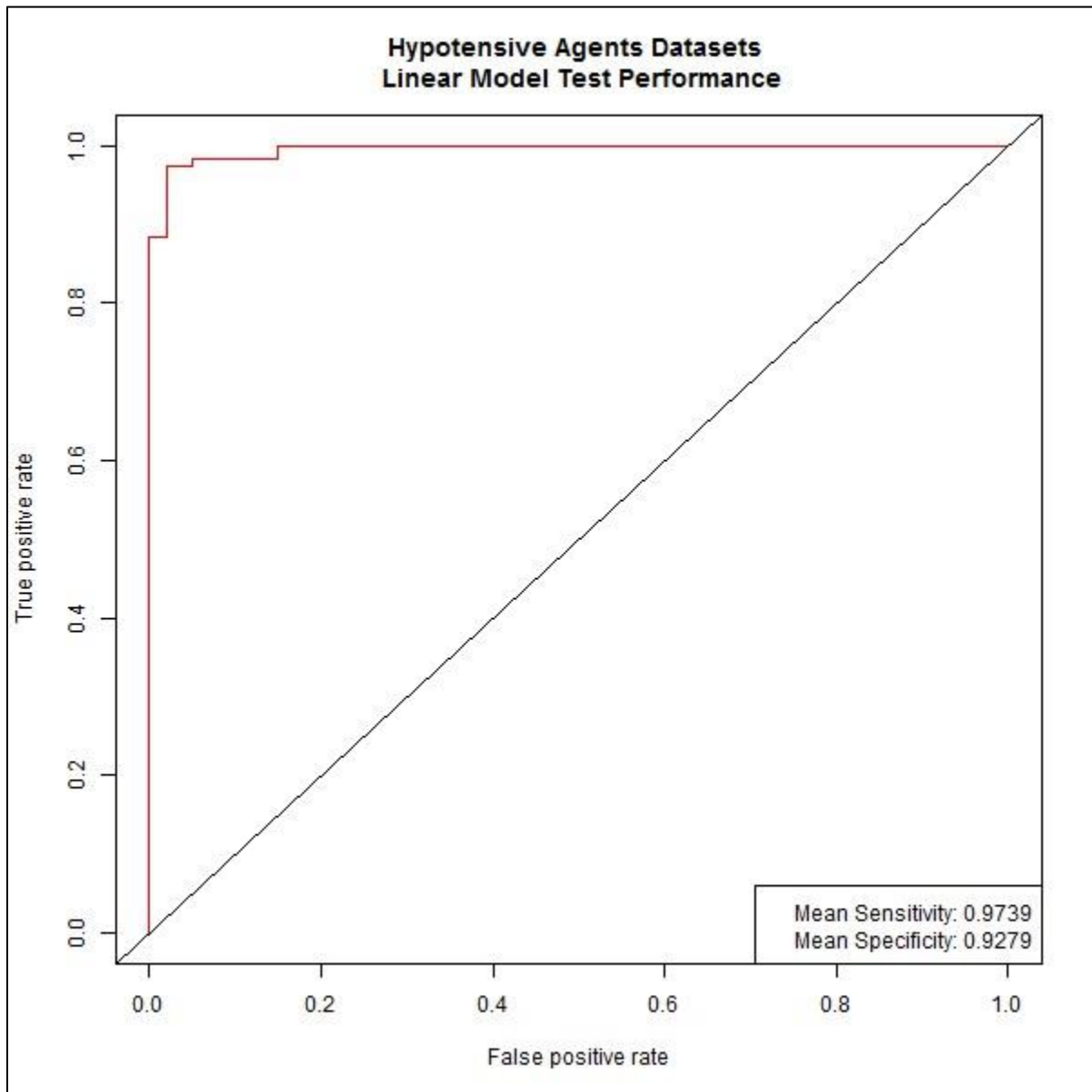
Figure 148: Receiver Operating Characteristic Curve for Imidazole Derivatives Class
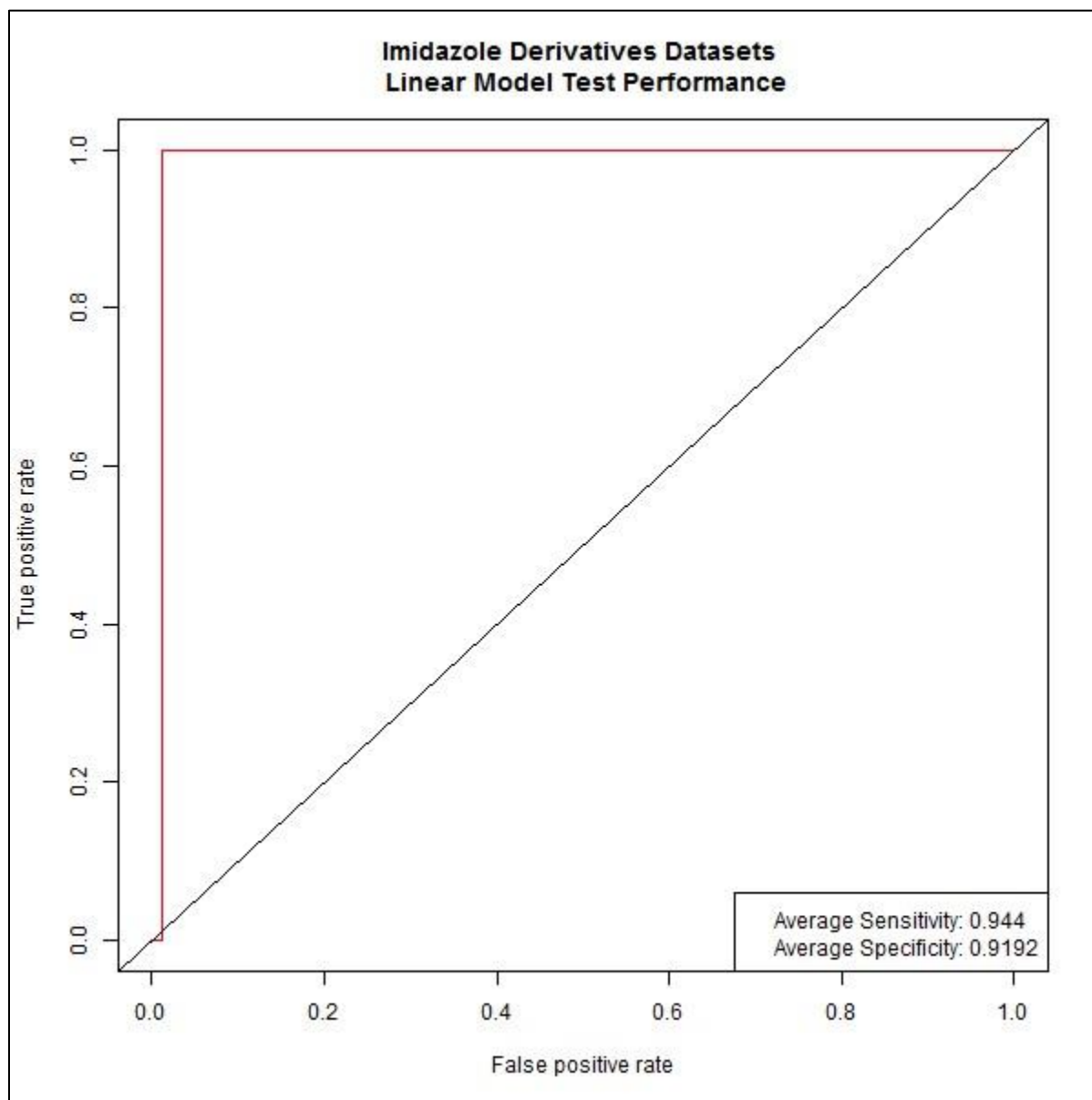
Figure 149: Receiver Operating Characteristic Curve for Inorganic Chemicals Class
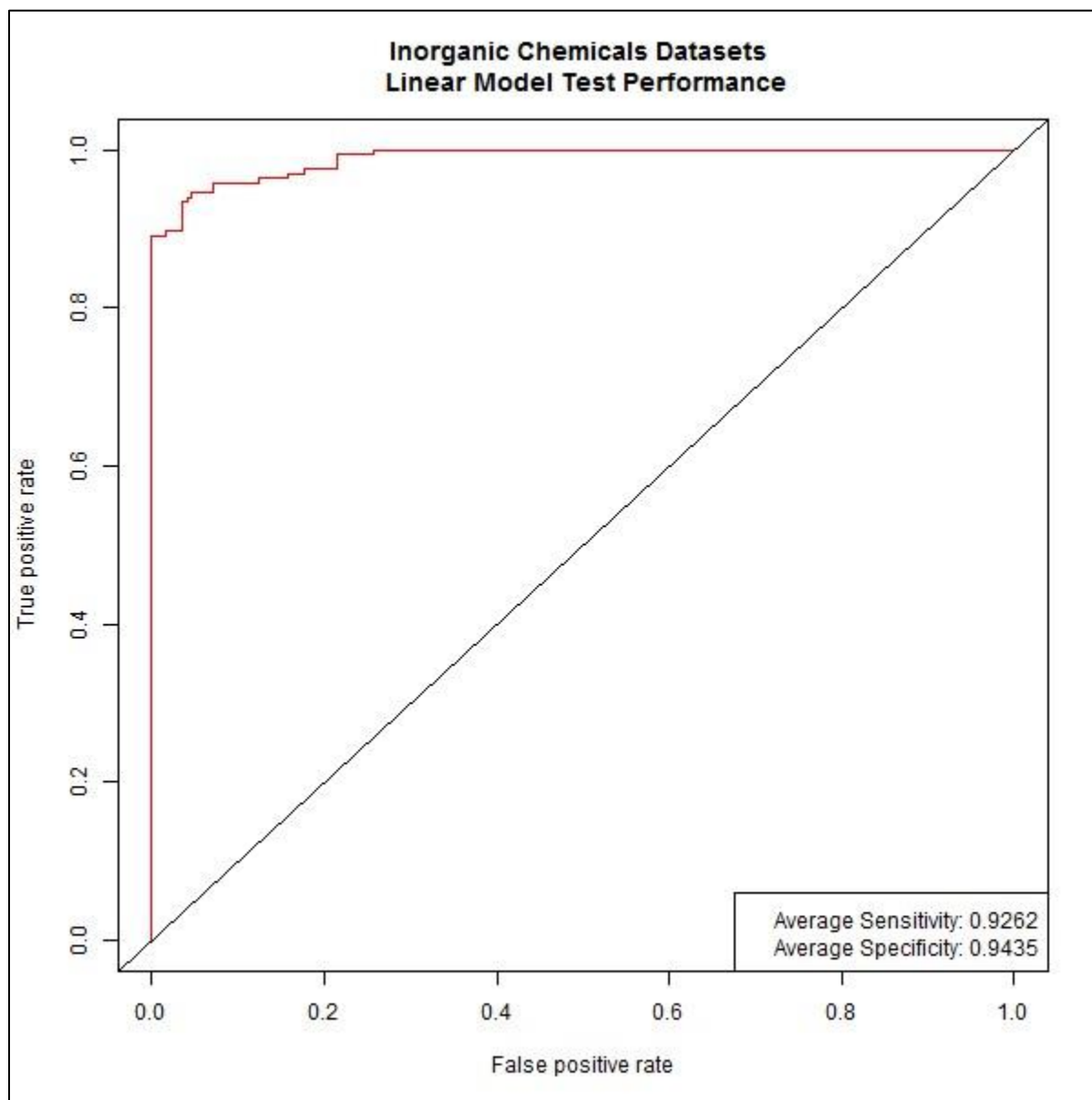
Figure 150: Receiver Operating Characteristic Curve for Nervous System Class
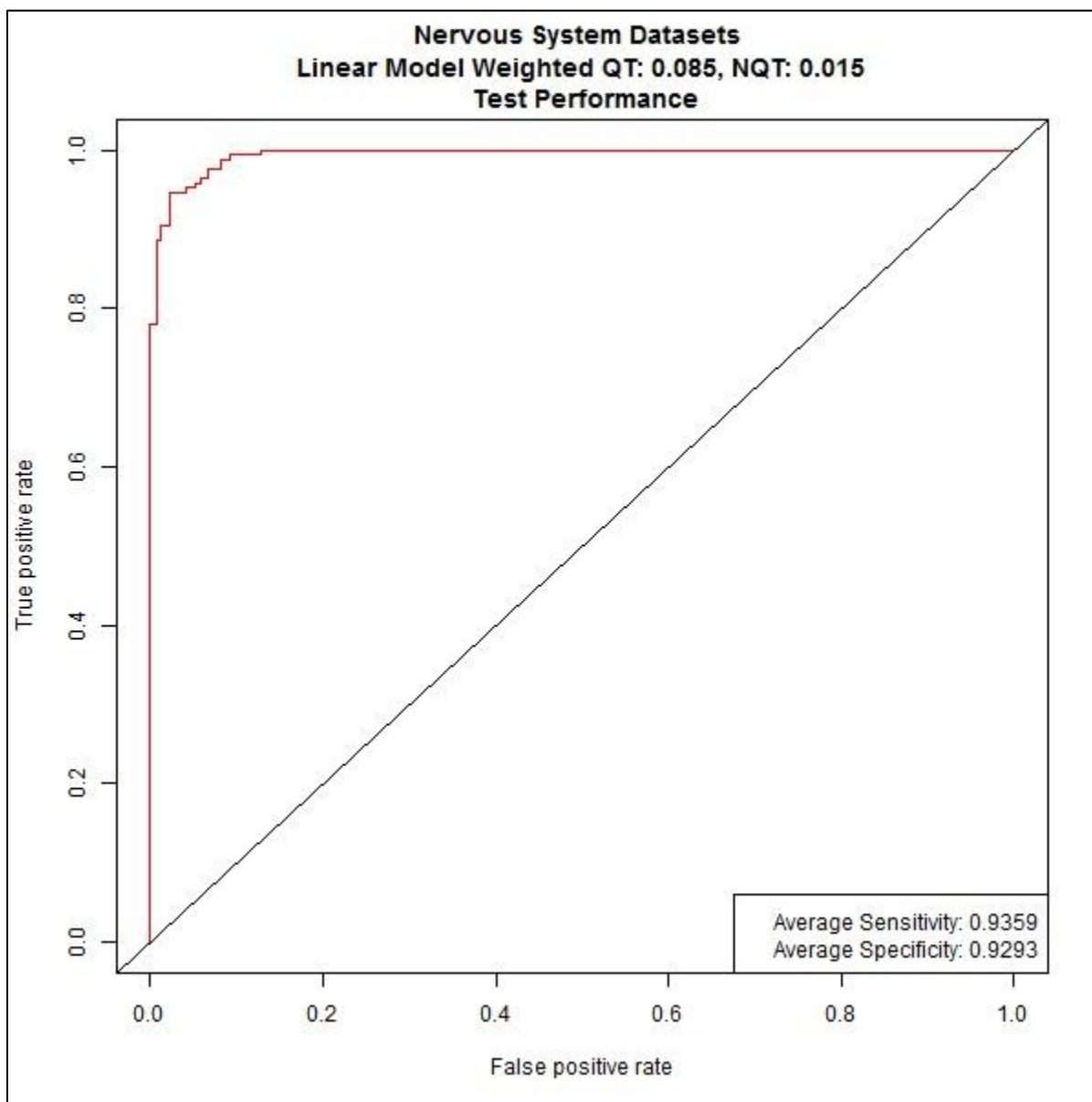
Figure 151: Receiver Operating Characteristic Curve for Neurotransmitter Agents Class
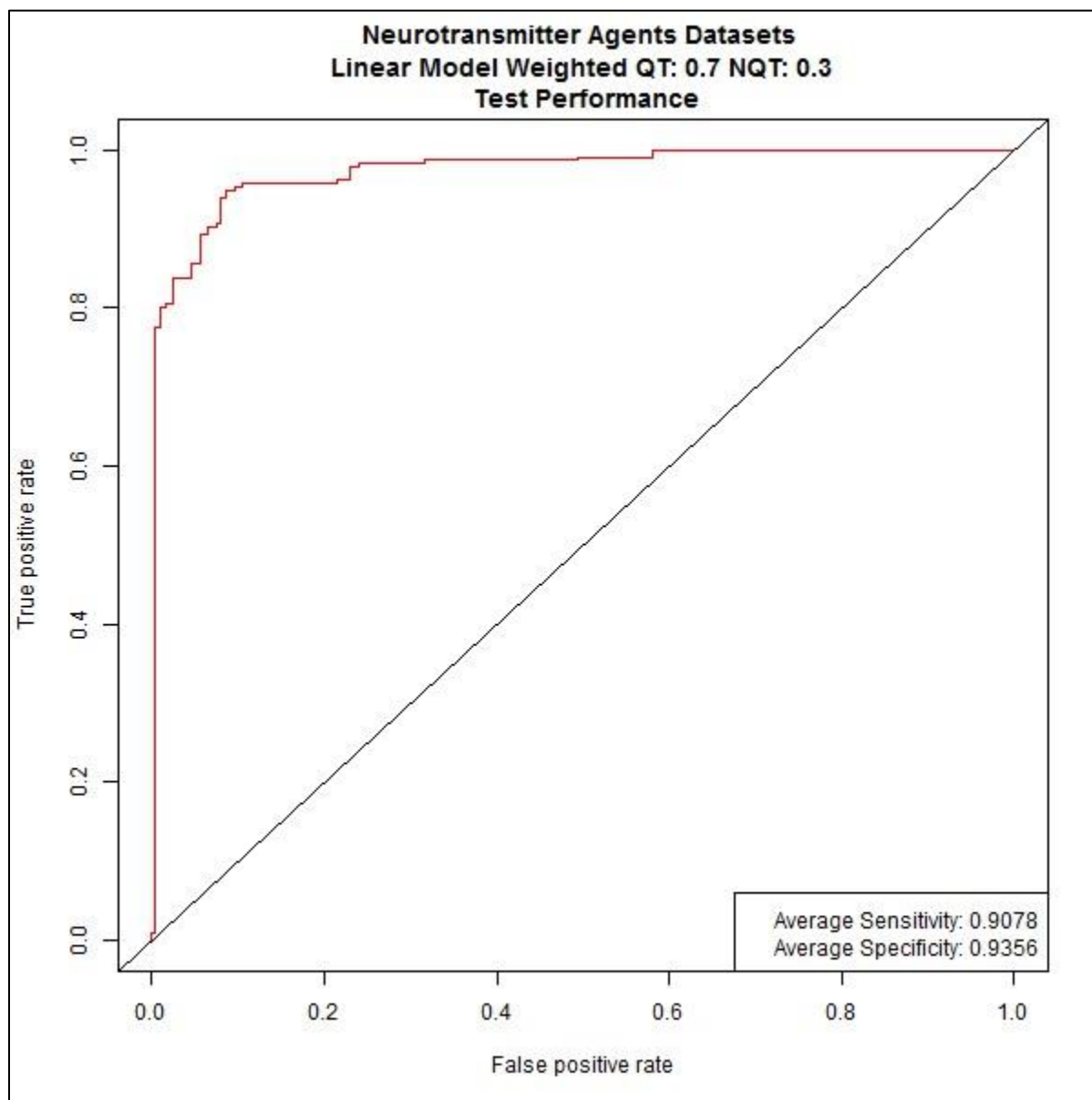
Figure 152: Receiver Operating Characteristic Curve for Ophthalmologicals Class
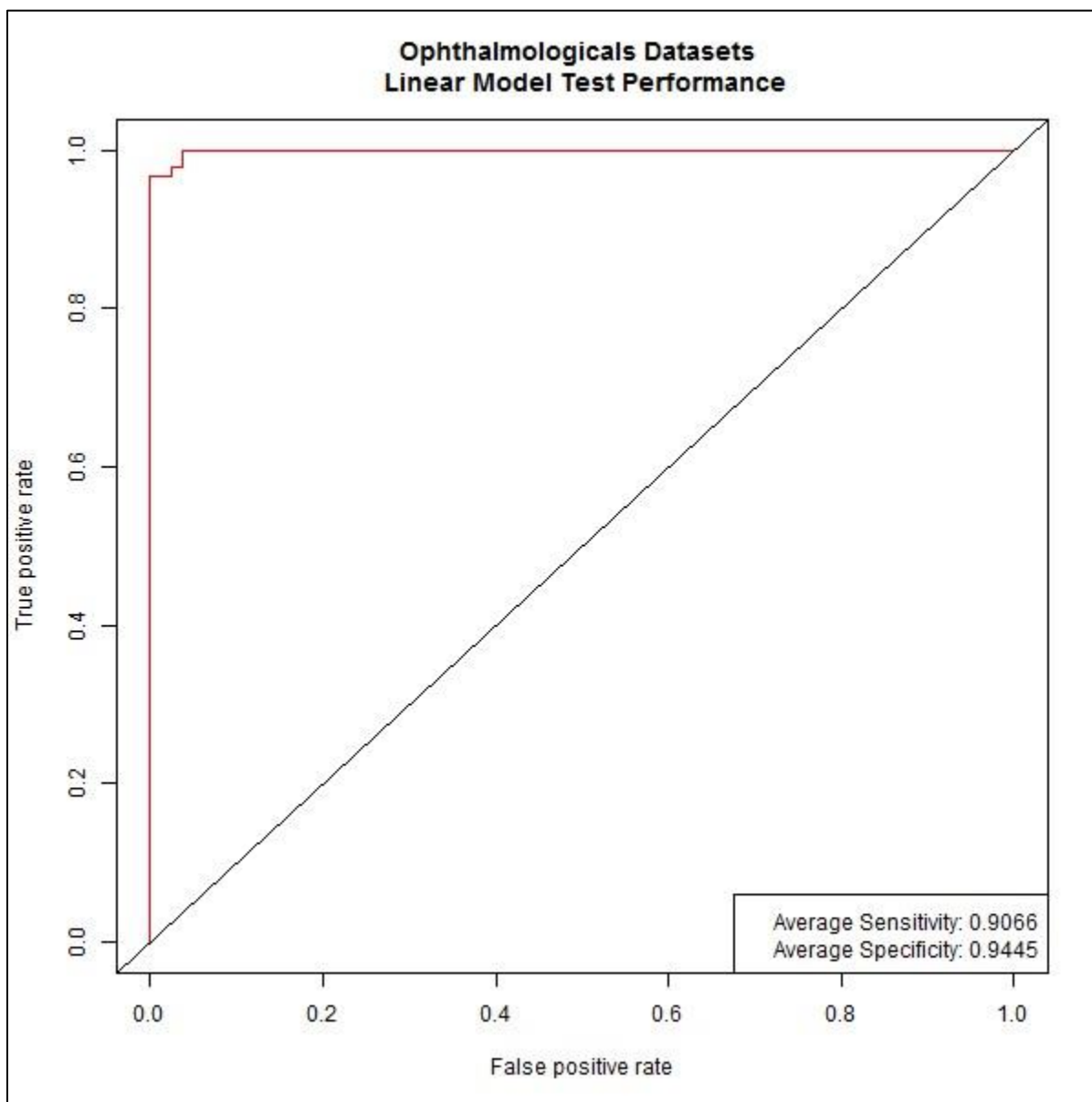
Figure 153: Receiver Operating Characteristic Curve for Peripheral Nervous System Agents Class

Peripheral Nervous System Agents Datasets
Linear Model Weighted QT: 0.7 NQT: 0.3
Test Performance

Average Sensitivity: 0.9319
Average Specificity: 0.9228
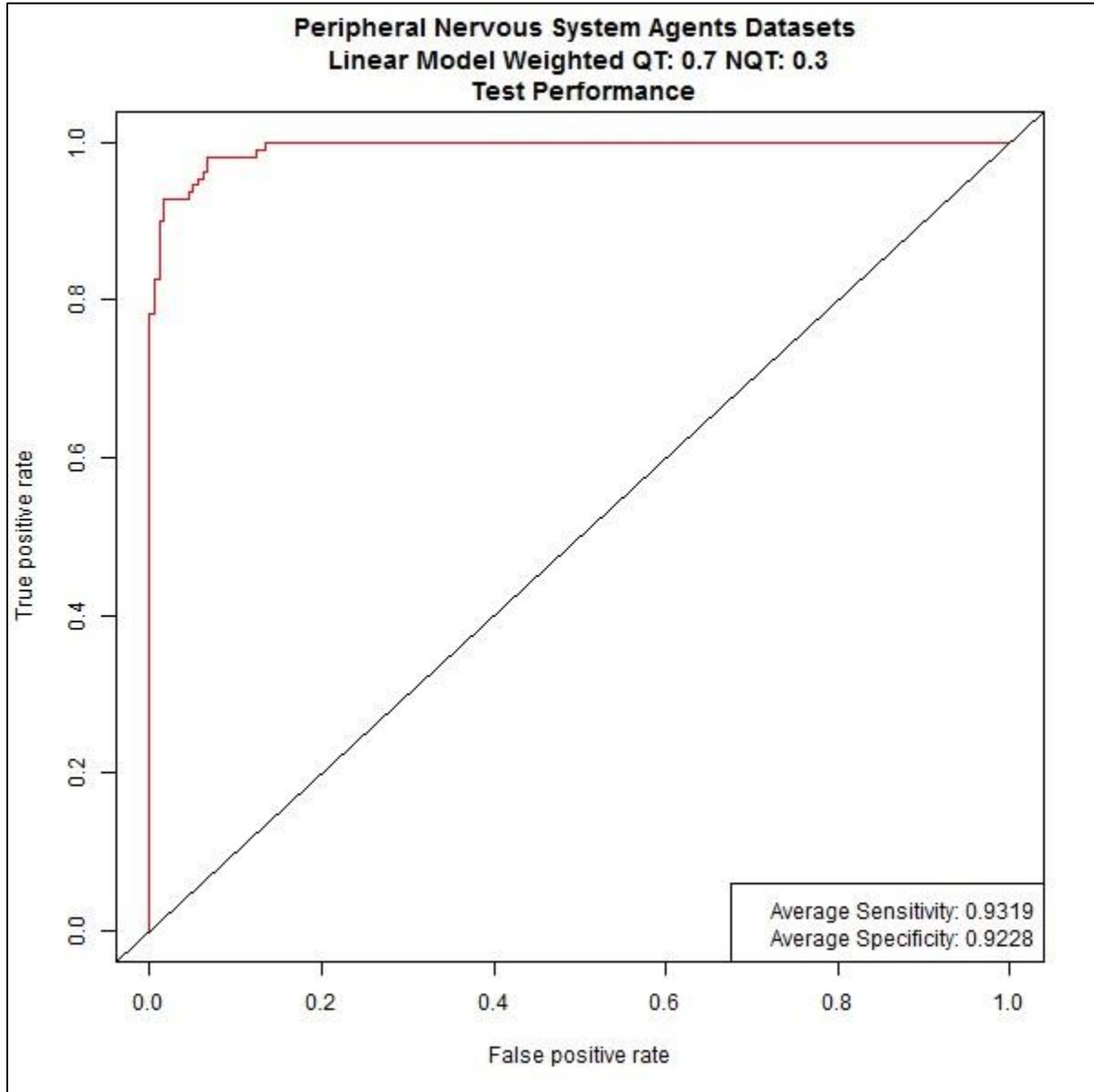
Figure 154: Receiver Operating Characteristic Curve for P-Glycoprotein/ABCB1 Inducers Class
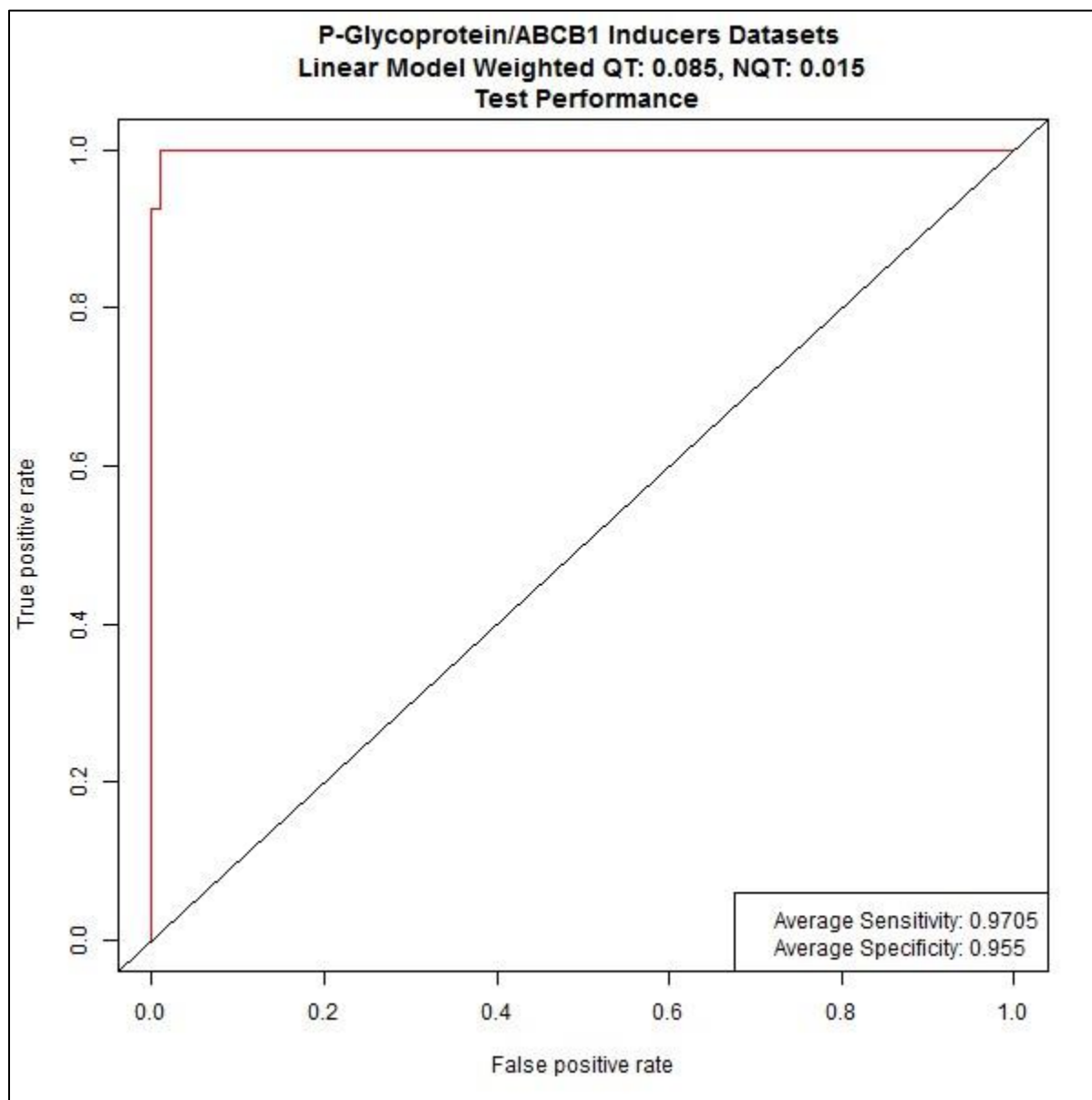
Figure 155: Receiver Operating Characteristic Curve for P-Glycoprotein/ABCB1 Inhibitors Class
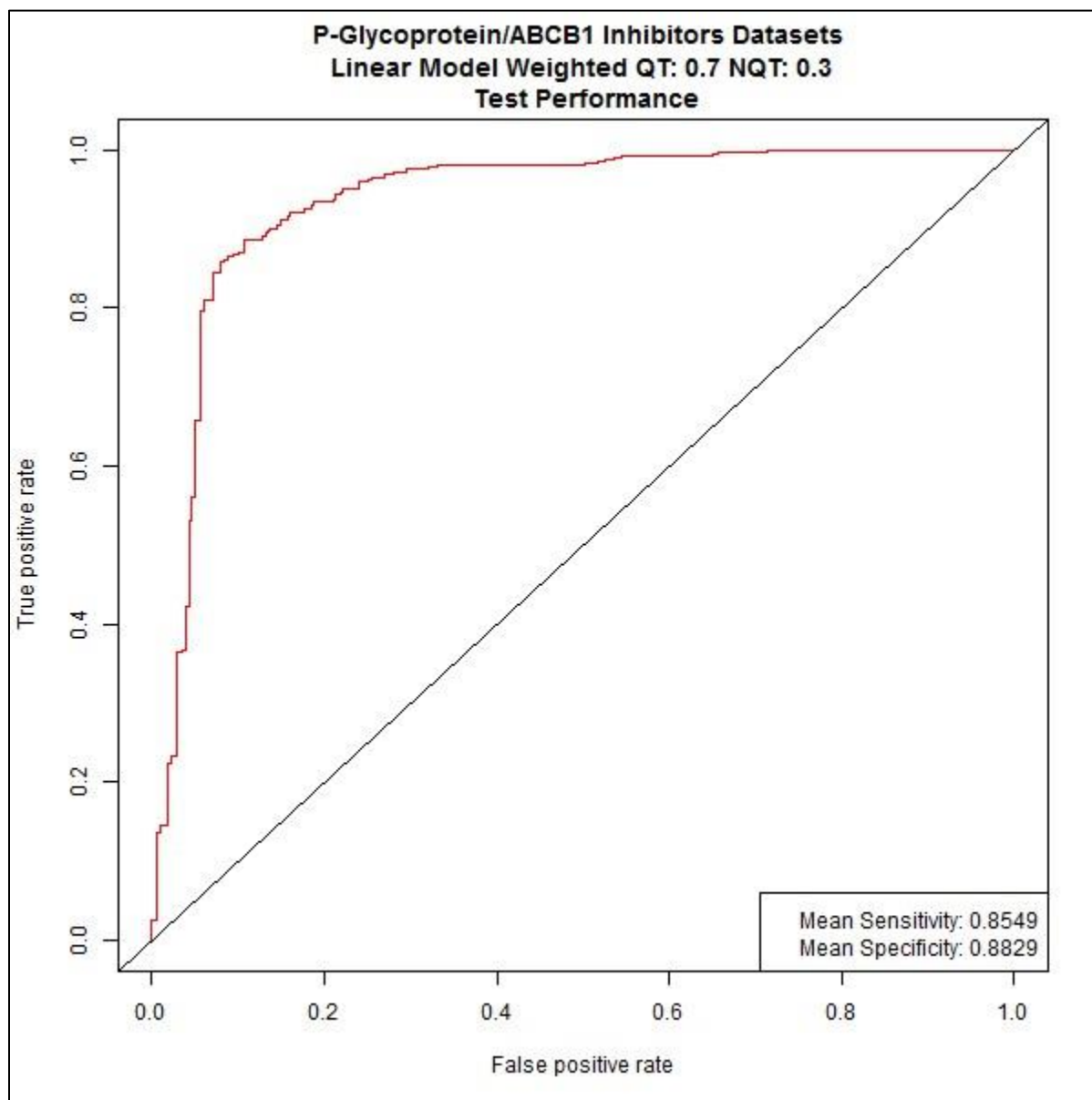
Figure 156: Receiver Operating Characteristic Curve for P-Glycoprotein/ABCB1 Substrates Class
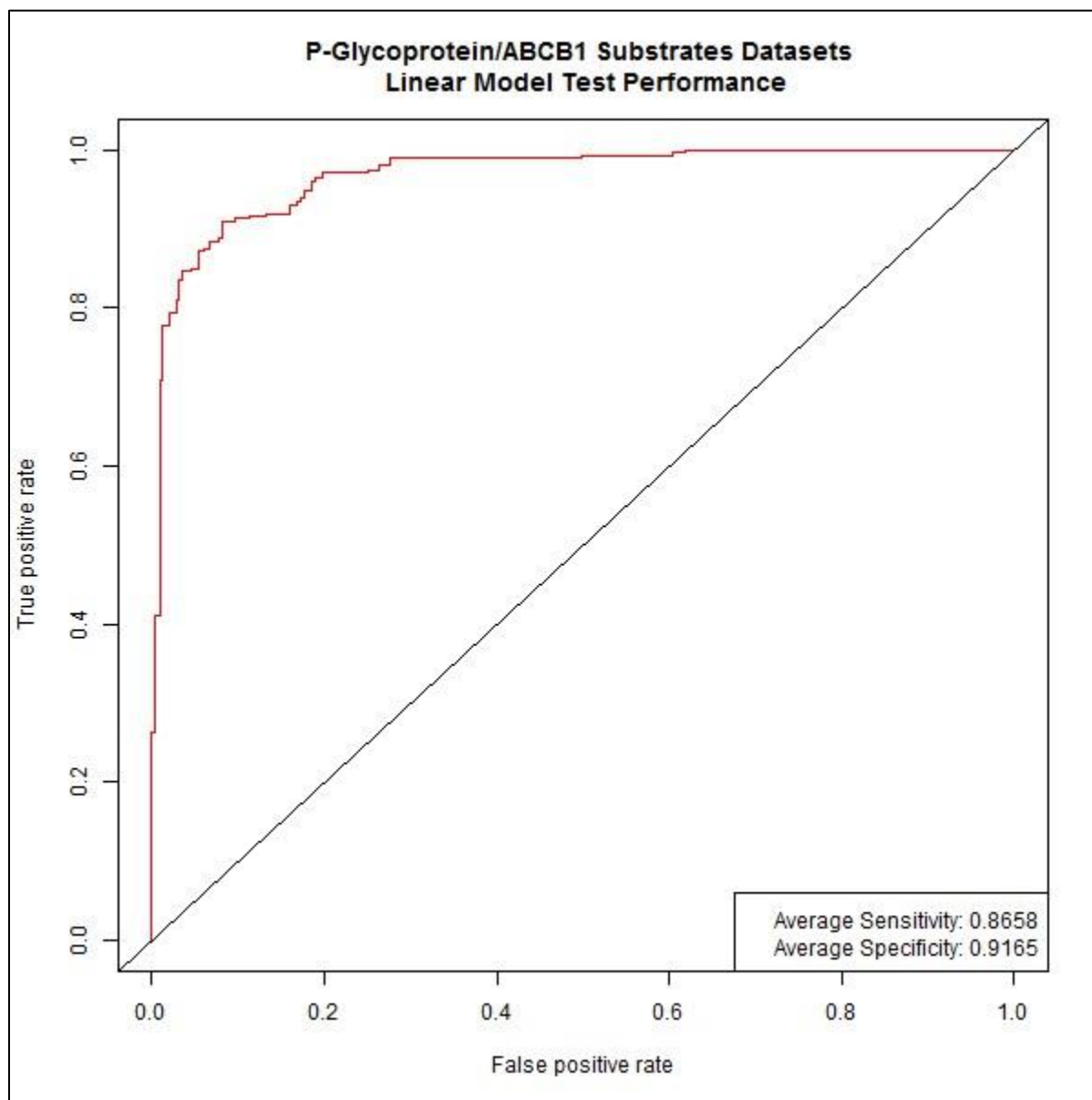
Figure 157: Receiver Operating Characteristic Curve for Piperazines Class
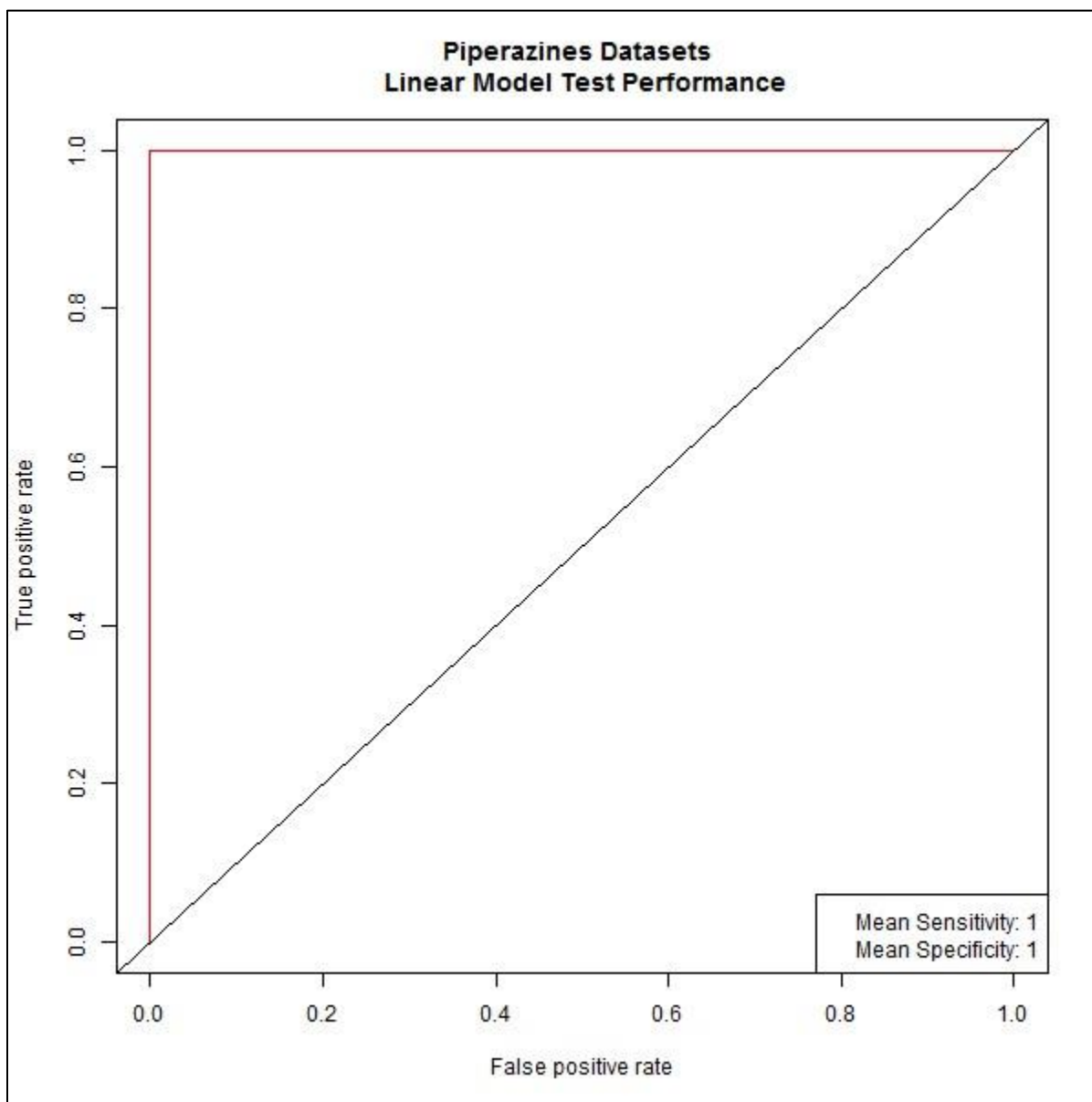
Figure 158: Receiver Operating Characteristic Curve for Polycyclic Compounds Class
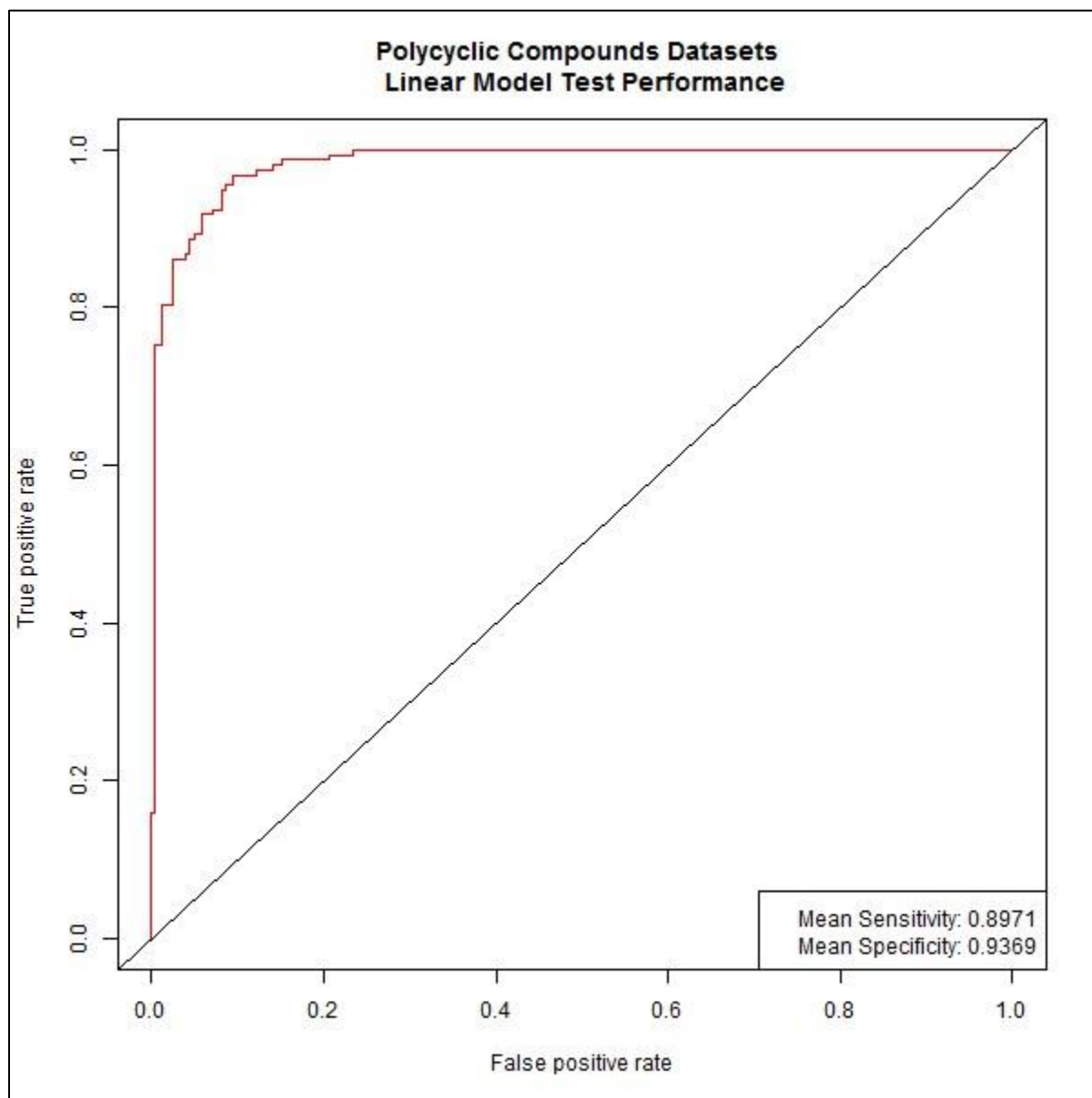
Figure 159: Receiver Operating Characteristic Curve for Psycholeptics Class
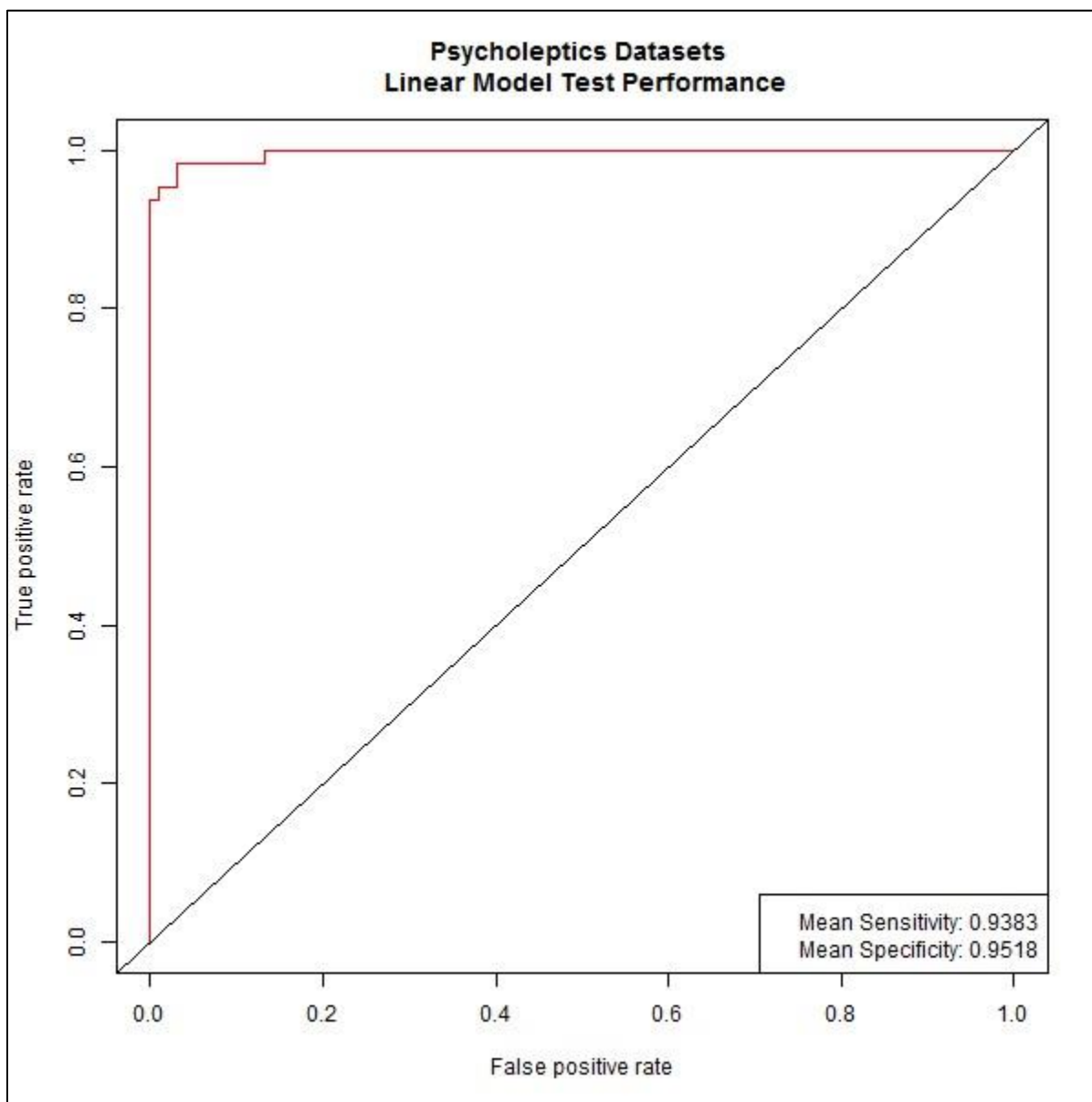
Figure 160: Receiver Operating Characteristic Curve for Respiratory System Class
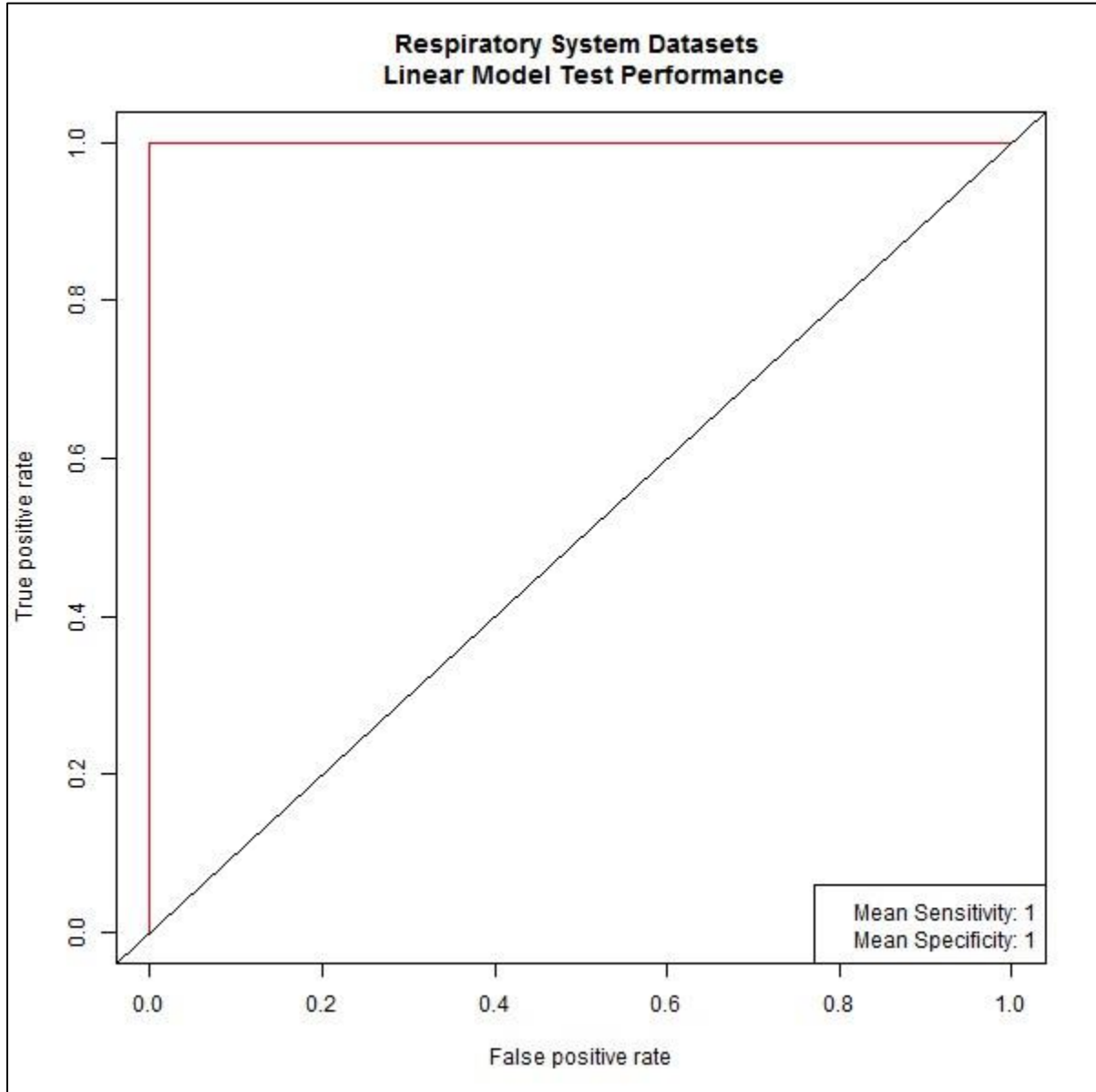
Figure 161: Receiver Operating Characteristic Curve for Sensory Organs Class
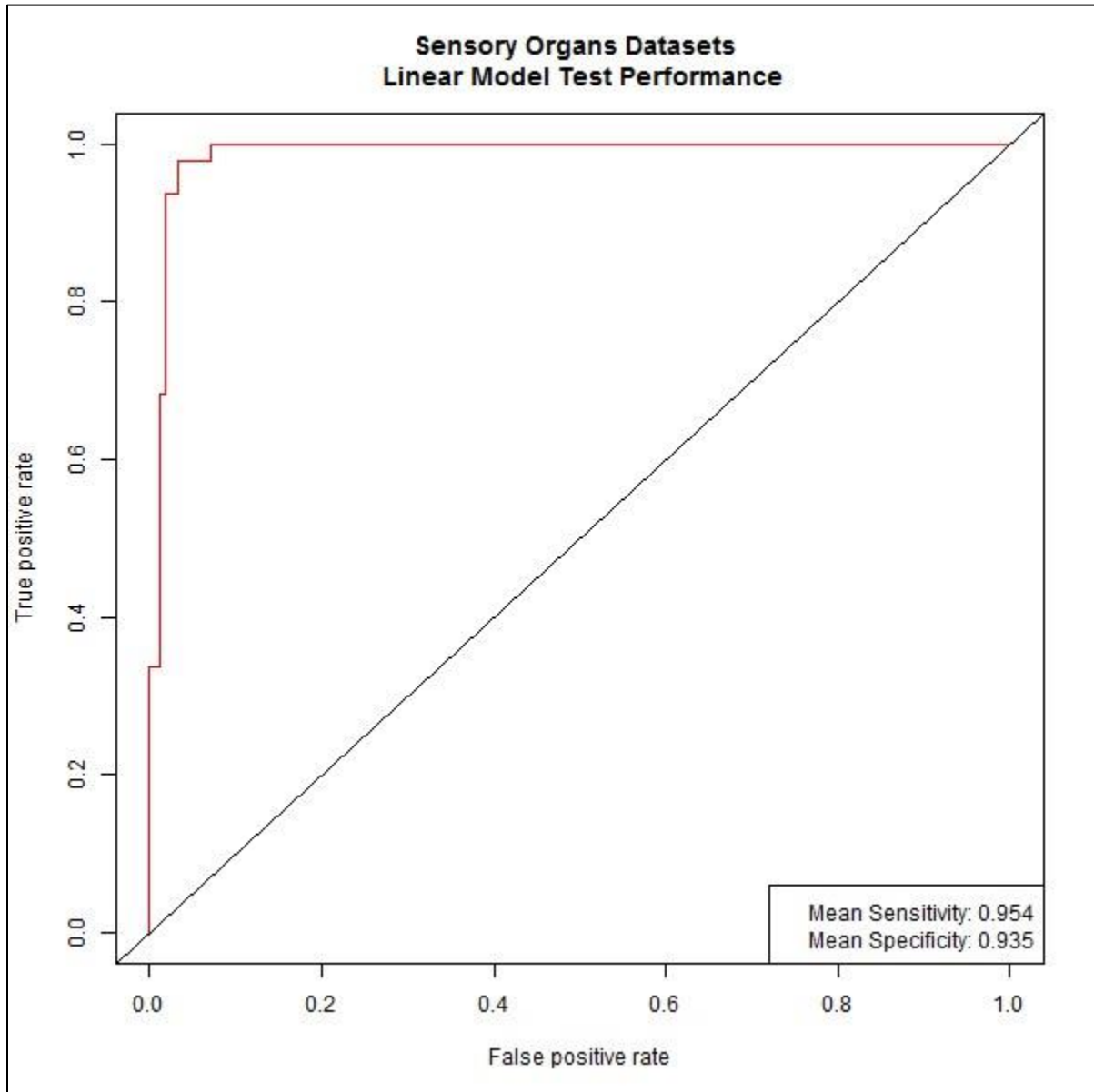
Figure 162: Receiver Operating Characteristic Curve for Steroid Synthesis Inhibitors Class
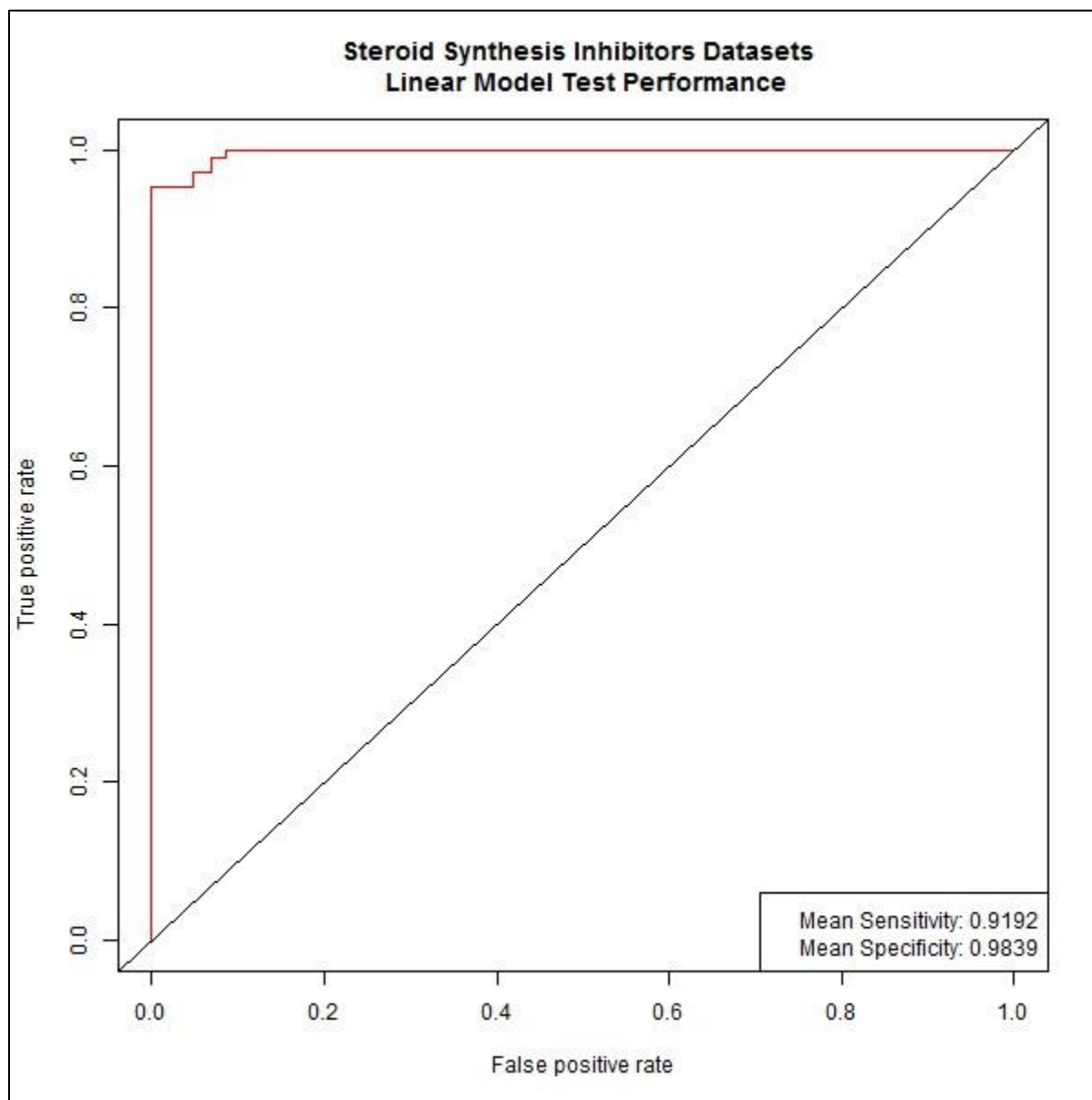
Figure 163: Receiver Operating Characteristic Curve for Sulfonamides Class
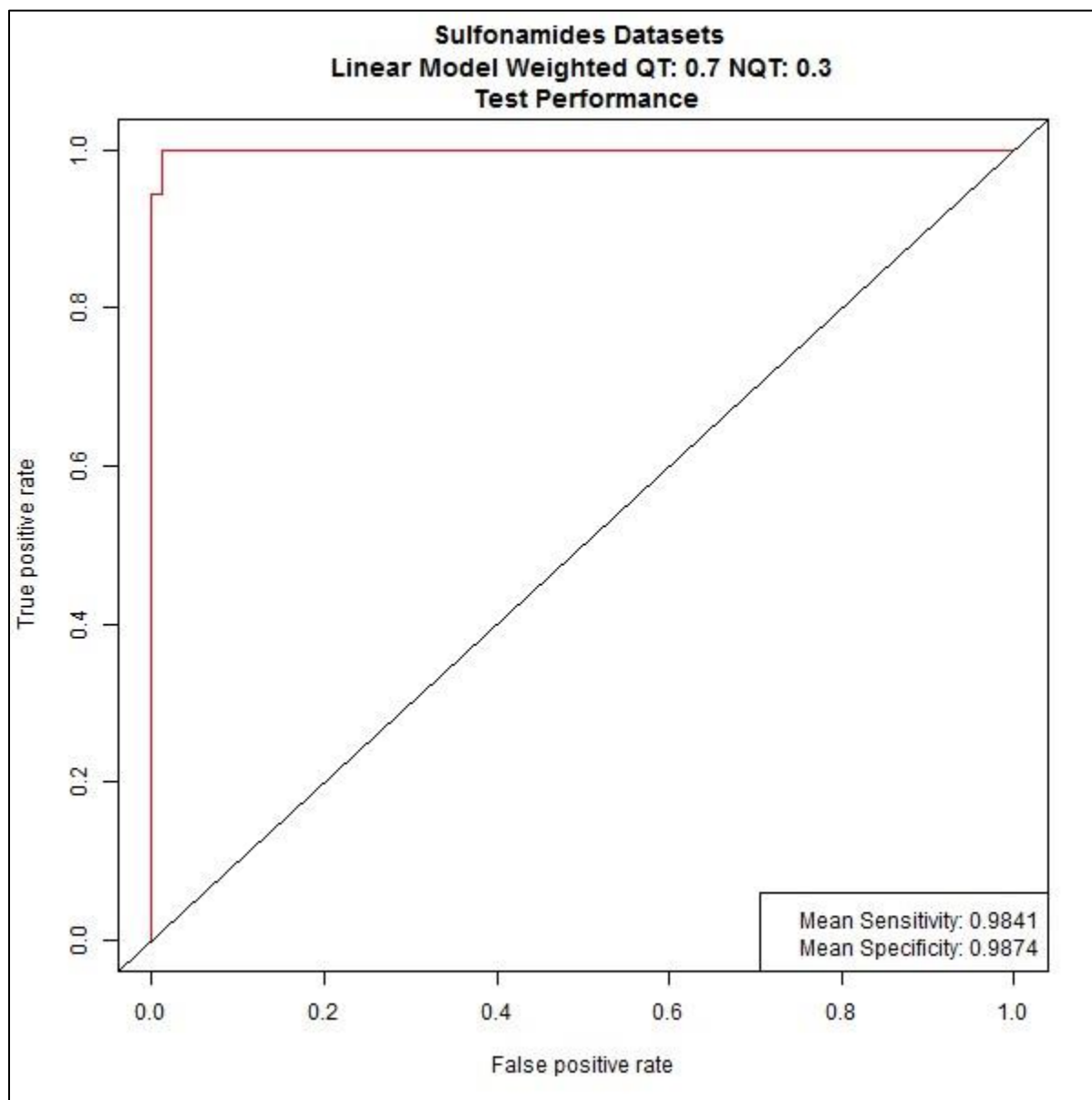
Figure 164: Receiver Operating Characteristic Curve for Sulfones Class
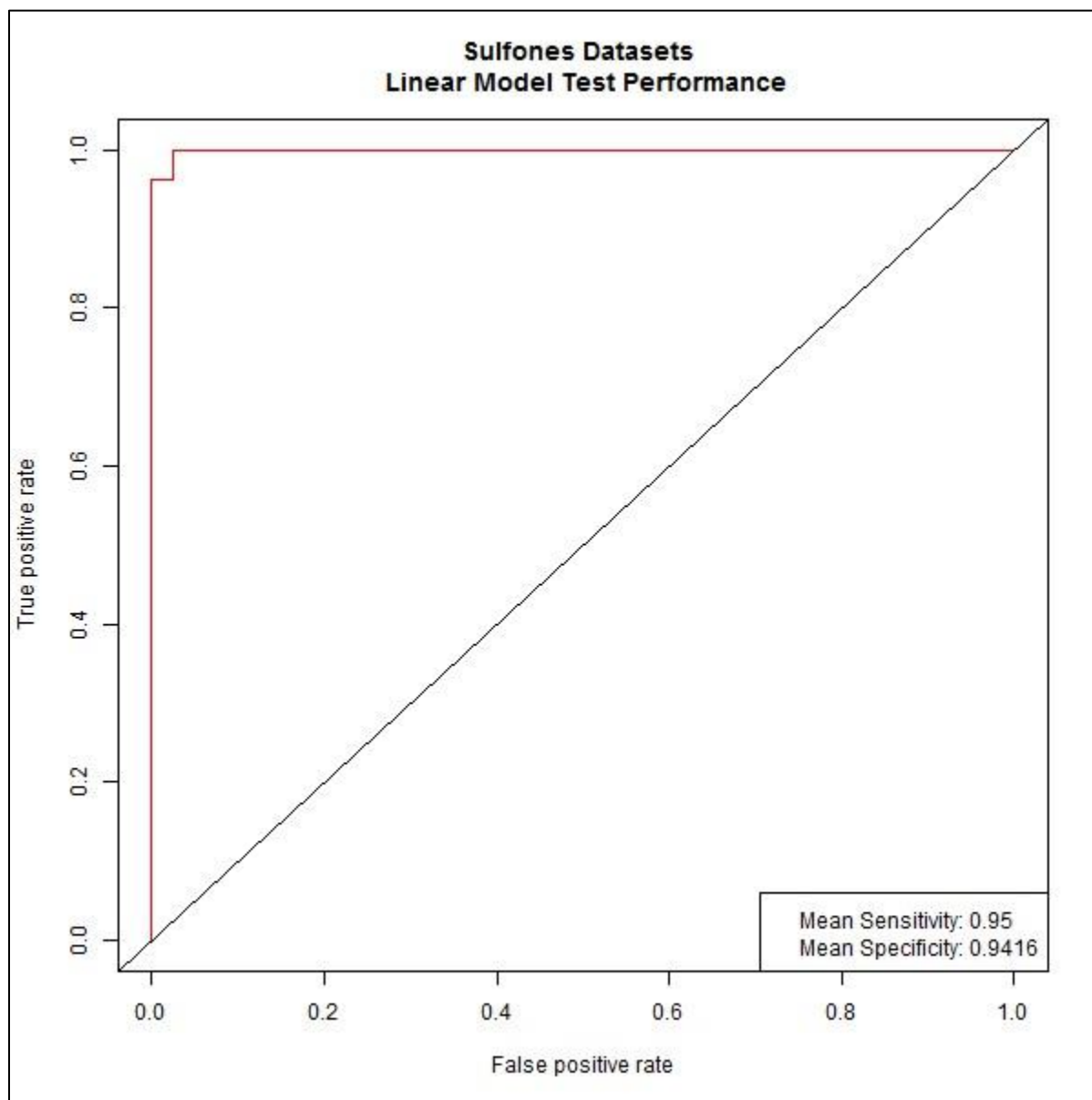
Figure 165: Receiver Operating Characteristic Curve for Sulfur Compounds Class

Sulfur Compounds Datasets
Linear Model Test Performance

Mean Sensitivity: 0.9134
Mean Specificity: 0.9384
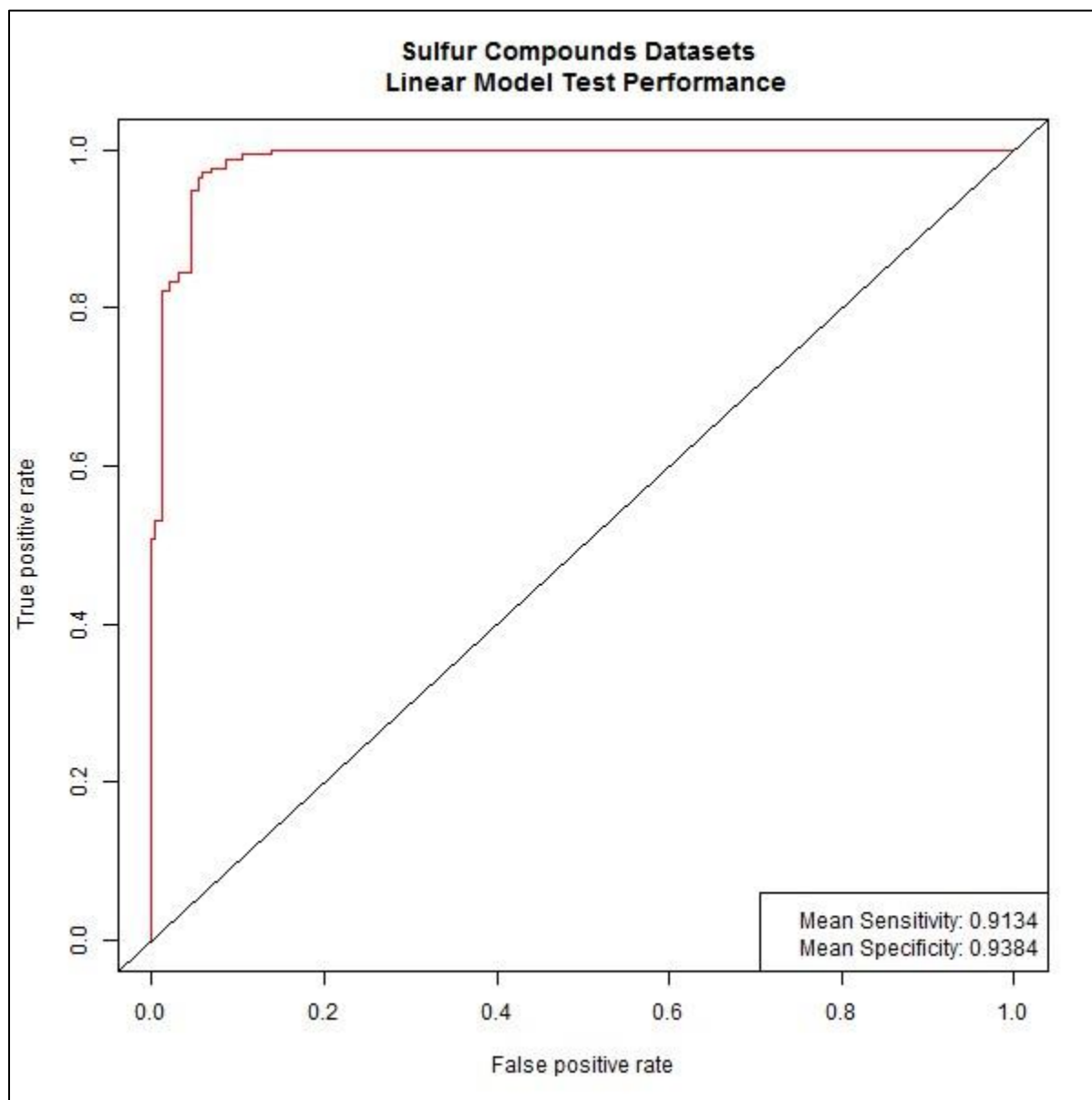
Figure 166: Receiver Operating Characteristic Curve for Topoisomerase II Inhibitors Class
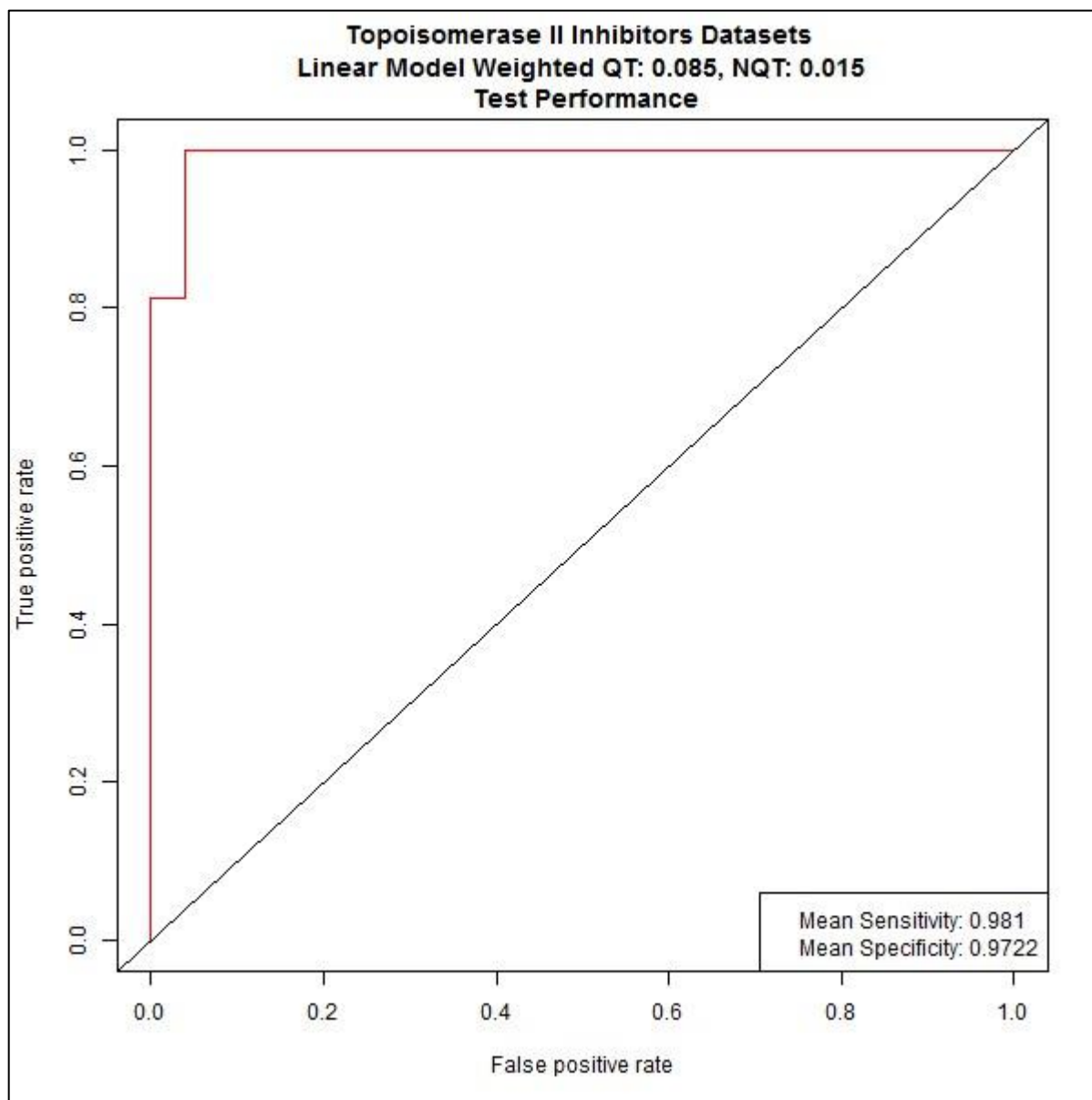
Representative Listing of APCluster Results by Category

Sample data names are in column 1. Column 2 contains the target label, where "0" represents a QT drug and a label of "1" represents an NQT drug.

All Drugs (QT versus Non-QT)

Number of Samples = 1045

Number of Clusters = 214

There were no large "All QT" clusters identified, although cluster 3 shows a "mostly QT" cluster.

Table LXXXVI: Representative Clusters using All Drugs (QT versus Non-QT)

Cluster 3 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
primaquine_45mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
busulfan_9mg3d_fc	1
omeprazole_30mg5d_fc	1
zomepirac_2800ug3d_fc	1

Alimentary Tract and Metabolism

Number of Samples = 150

Number of Clusters = 39

No "All QT" clusters were found. The closest was cluster 1 which contained all of the QT drug samples

and approximately the same number of NQT samples.

Table LXXXVII: Representative Clusters using Drugs Classified in DrugBank as Alimentary Tract and Metabolism

Cluster 1	
Exemplar: granisetron_175mg5d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
aspirin_35mg6h_fc	1
cholecalciferol_8mg1d_fc	1
cholicAcid_1402mg1d_fc	1
doxycycline_1g1d_fc	1
doxycycline_14mg1d_fc	1
glimepiride_2500mg3d_fc	1
glimepiride_2500mg5d_fc	1
glimepiride_2500mg6h_fc	1
glipizide_2500mg1d_fc	1
glipizide_2500mg3d_fc	1
glipizide_2500mg5d_fc	1
glipizide_2500mg6h_fc	1
metronidazole_50mg1d_fc	1
metronidazole_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1

Amides

Number of Samples = 86

Number of Clusters = 16

No "All QT" clusters were found. The closest was cluster 1 which contained all of the QT drug samples

and slightly more than the same number of NQT samples.

Table LXXXVIII: Representative Clusters using Drugs Classified in DrugBank as Amides

Cluster 1	
Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
phenacetin_619mg6h_fc	1
procarbazine_27mg5d_fc	1
procarbazine_54mg5d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_420mg5d_fc	1
sildenafil_14600ug5d_fc	1
sulfaphenazole_1695mg6h_fc	1
sulfathiazole_31mg6h_fc	1
tocainide_67mg1d_fc	1
tocainide_67mg3d_fc	1
tocainide_67mg5d_fc	1
tocainide_67mg6h_fc	1
tocainide_224mg1d_fc	1
tocainide_224mg3d_fc	1
tocainide_224mg5d_fc	1
tocainide_224mg6h_fc	1
zaleplon_100mg1d_fc	1
zaleplon_100mg3d_fc	1
zaleplon_100mg5d_fc	1

Antifungal Agents
Number of Samples = 81

Number of Clusters = 18

Cluster 2 was an "All QT" cluster. Cluster 8 had QT drugs making up slightly less than half of the cluster.

Table LXXIX: Representative Clusters using Drugs Classified in DrugBank as Antifungal Agents

Cluster 2 Exemplar: fluconazole_394mg3d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0
Cluster 8 Exemplar: ketoconazole_25mg3d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
ketoconazole_2274mg6h_fc	0
clotrimazole_52mg1d_fc	1
clotrimazole_52mg3d_fc	1
cyclosporin_70mg6h_fc	1
econazole_43mg1d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg1d_fc	1
mevastatin_1200mg1d_fc	1
mevastatin_1200mg3d_fc	1
miconazole_200mg3d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1

Antifungals for Dermatological Use

Number of Samples = 68

Number of Clusters = 11

There were no "All QT" clusters. Cluster 1 was mostly QT, Cluster 4 was less than half QT, and Cluster 10

was also slightly less than half QT.

Table XC: Representative Clusters using Drugs Classified in DrugBank as Antifungals for Dermatological Use

Cluster 1 Exemplar: fluconazole_10mg1d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg6h_fc	0
salicylicAcid_223mg5d_fc	1
Cluster 4 Exemplar: econazole_334mg1d_fc	
Sample	**Label**
fluconazole_394mg5d_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
clotrimazole_52mg1d_fc	1
clotrimazole_52mg3d_fc	1
clotrimazole_52mg5d_fc	1
clotrimazole_178mg1d_fc	1
econazole_334mg1d_fc	1
econazole_334mg5d_fc	1
miconazole_920mg3d_fc	1
Cluster 10 Exemplar: sulconazole_1200mg3d_fc	
Sample	**Label**
fluconazole_394mg1d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
econazole_43mg5d_fc	1

Table XC: Representative Clusters using Drugs Classified in DrugBank as Antifungals for Dermatological Use (Continued)

Sample	Label
gentianviolet_18mg1d_fc	1
miconazole_200mg1d_fc	1
oxiconazole_1500mg3d_fc	1
oxiconazole_1500mg5d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
sulconazole_1200mg1d_fc	1
sulconazole_1200mg3d_fc	1
sulconazole_1200mg5d_fc	1

Anti-Infective Agents

Number of Samples = 246

Number of Clusters = 44

Clusters 2, 3, 5 and 10 were "All QT" clusters. Cluster 11 was about half QT and half NQT.

Table XCI: Representative Clusters using Drugs Classified in DrugBank as Anti-Infective Agents

Cluster 2	
Exemplar: ciprofloxacin_72mg5d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg6h_fc	0
sparfloxacin_29mg1d_fc	0
Cluster 3	
Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
Cluster 5	
Exemplar: fluconazole_10mg5d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
Cluster 10	
Exemplar: ketoconazole_114mg3d_fc	
Sample	**Label**
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0

Table XCI: Representative Clusters using Drugs Classified in DrugBank as Anti-Infective Agents (Continued)

Cluster 11	
Exemplar: roxithromycin_312mg3d_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
clarithromycin_476mg3d_fc	0
erythromycin_1500mg1d_fc	0
fluconazole_10mg1d_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
primaquine_45mg1d_fc	0
primaquine_45mg3d_fc	0
primaquine_45mg5d_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
roxithromycin_312mg5d_fc	0
sparfloxacin_29mg3d_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
cyclosporin_350mg5d_fc	1
doxycycline_1g3d_fc	1
doxycycline_14mg6h_fc	1
econazole_43mg5d_fc	1
econazole_334mg1d_fc	1
econazole_334mg6h_fc	1
famciclovir_112mg1d_fc	1
lamivudine_1300mg1d_fc	1
miconazole_200mg6h_fc	1
nevirapine_200mg3d_fc	1
oxytetracycline_1500mg1d_fc	1
sulfathiazole_31mg6h_fc	1
thalidomide_113mg1d_fc	1
thalidomide_113mg3d_fc	1
thalidomide_113mg5d_fc	1
trovafloxacin_600mg1d_fc	1
trovafloxacin_600mg5d_fc	1

Antiinfectives for Systemic Use

Number of Samples = 160

Number of Clusters = 26

Clusters 2 and 9 were "All QT". Cluster 1 was mostly QT, Cluster 11 was slightly more than half QT,

Cluster 12 was all QT except for 1 entry, and Cluster 15 was approximately ¼ QT.

Table XCII: Representative Clusters using Drugs Classified in DrugBank as Antiinfectives for Systemic Use

Cluster 1 Exemplar: azithromycin_50mg6h_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg6h_fc	0
fluconazole_10mg6h_fc	0
itraconazole_1093mg5d_fc	0
enoxacin_100mg5d_fc	1
enoxacin_750mg6h_fc	1
trovafloxacin_600mg5d_fc	1
Cluster 2 Exemplar: clarithromycin_476mg1d_fc	
Sample	**Label**
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
Cluster 9 Exemplar: ketoconazole_114mg1d_fc	
Sample	**Label**
itraconazole_1093mg1d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg6h_fc	0

Table XCII: Representative Clusters using Drugs Classified in DrugBank as Antiinfectives for Systemic Use (Continued)

Cluster 11	
Exemplar: roxithromycin_312mg3d_fc	
Sample	**Label**
clarithromycin_56mg5d_fc	0
clarithromycin_476mg3d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_2274mg6h_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
roxithromycin_312mg5d_fc	0
sulfisoxazole_250mg1d_fc	0
doxycycline_1g3d_fc	1
miconazole_200mg3d_fc	1
pyrazinamide_1500mg1d_fc	1
tetracycline_1500mg1d_fc	1
tetracycline_1500mg3d_fc	1
Cluster 12	
Exemplar: sparfloxacin_29mg3d_fc	
Sample	**Label**
azithromycin_50mg5d_fc	0
azithromycin_225mg5d_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
clarithromycin_56mg6h_fc	0
fluconazole_10mg1d_fc	0
ketoconazole_2274mg1d_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
famciclovir_112mg1d_fc	1
Cluster 15	
Exemplar: famciclovir_1200mg6h_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
clarithromycin_476mg5d_fc	0
ketoconazole_25mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
enoxacin_750mg3d_fc	1
famciclovir_112mg3d_fc	1
famciclovir_112mg6h_fc	1
famciclovir_1200mg1d_fc	1
famciclovir_1200mg3d_fc	1
famciclovir_1200mg5d_fc	1
famciclovir_1200mg6h_fc	1
isoniazid_50mg1d_fc	1
lamivudine_35mg1d_fc	1
miconazole_200mg6h_fc	1
nevirapine_29mg1d_fc	1

Table XCII: Representative Clusters using Drugs Classified in DrugBank as Antiinfectives for Systemic Use (Continued)

Sample	Label
nevirapine_29mg3d_fc	1
nevirapine_29mg6h_fc	1
nevirapine_200mg3d_fc	1
nevirapine_200mg6h_fc	1

Antineoplastic Agents

Number of Samples = 248

Number of Clusters = 53

There were no "All QT" clusters. Cluster 1 contained all of the QT samples, which were approximately

1/3 of the samples in the cluster.

Table XCIII: Representative Clusters using Drugs Classified in DrugBank as Antineoplastic Agents

Cluster 1	
Exemplar: tamoxifen_64mg3d_fc	
Sample	Label
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
albendazole_62mg3d_fc	1
busulfan_3mg5d_fc	1
busulfan_9mg1d_fc	1
busulfan_9mg3d_fc	1
busulfan_9mg5d_fc	1
busulfan_9mg6h_fc	1
busulfan_36mg6h_fc	1
carboplatin_6mg6h_fc	1
carboplatin_14mg6h_fc	1
carmustine_4mg3d_fc	1
carmustine_4mg5d_fc	1
cisplatin_2mg3d_fc	1
cisplatin_1170ug3d_fc	1
cytarabine_23mg6h_fc	1

Table XCIII: Representative Clusters using Drugs Classified in DrugBank as Antineoplastic Agents (Continued)

Sample	Label
cytarabine_487mg3d_fc	1
cytarabine_487mg5d_fc	1
dexamethasone_150mg1d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_3mg6h_fc	1
enoxacin_750mg6h_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
genistein_20mg6h_fc	1
genistein_375mg3d_fc	1
ifosfamide_17mg1d_fc	1
ifosfamide_143mg6h_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg3d_fc	1
letrozole_250mg5d_fc	1
lomefloxacin_2g3d_fc	1
lomefloxacin_2g5d_fc	1
lomustine_4200ug1d_fc	1
lomustine_4200ug3d_fc	1
lomustine_4200ug5d_fc	1
lomustine_4200ug6h_fc	1
lomustine_8750ug1d_fc	1
lomustine_8750ug3d_fc	1
lomustine_8750ug5d_fc	1
lomustine_8750ug6h_fc	1
mebendazole_50mg6h_fc	1
mebendazole_714mg3d_fc	1
methotrexate_27mg6h_fc	1
mitomycinC_1700ug3d_fc	1
procarbazine_27mg6h_fc	1
procarbazine_54mg3d_fc	1
thalidomide_113mg5d_fc	1

Azoles

Number of Samples = 170

Number of Clusters = 31

Cluster 1 was "All QT". Clusters 2 and 3 contained a small portion, less than ¼ QT, and Cluster 4 was

"Mostly QT".

Table XCIV: Representative Clusters using Drugs Classified in DrugBank as Azoles

Cluster 1 Exemplar: fluconazole_10mg3d_fc	
Sample	**Label**
fluconazole_10mg3d_fc	0
fluconazole_394mg5d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_1093mg6h_fc	0
Cluster 2 Exemplar: fluconazole_394mg1d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
acetazolamide_250mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
carbimazole_400mg5d_fc	1
clotrimazole_52mg1d_fc	1
clotrimazole_52mg5d_fc	1
econazole_43mg5d_fc	1
econazole_334mg1d_fc	1
econazole_334mg5d_fc	1
econazole_334mg6h_fc	1
leflunomide_30mg1d_fc	1
leflunomide_60mg3d_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug6h_fc	1
methimazole_28mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1
pioglitazone_3mg1d_fc	1
pioglitazone_300mg1d_fc	1
pioglitazone_1500mg5d_fc	1

Table XCIV: Representative Clusters using Drugs Classified in DrugBank as Azoles (Continued)

Sample	Label
rofecoxib_3mg3d_fc	1
rofecoxib_3mg5d_fc	1
rofecoxib_250mg1d_fc	1
rofecoxib_250mg3d_fc	1
rofecoxib_800mg1d_fc	1
rofecoxib_800mg3d_fc	1
sulconazole_1200mg3d_fc	1
sulfathiazole_2629mg1d_fc	1
sulfathiazole_2629mg3d_fc	1
Cluster 3	
Exemplar: granisetron_175mg5d_fc	
Sample	Label
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
acetazolamide_47mg5d_fc	1
atorvastatin_300mg6h_fc	1
carbimazole_400mg3d_fc	1
clotrimazole_52mg6h_fc	1
leflunomide_30mg3d_fc	1
leflunomide_30mg5d_fc	1
leflunomide_60mg6h_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg6h_fc	1
meloxicam_600ug3d_fc	1
methimazole_28mg6h_fc	1
methimazole_100mg1d_fc	1
methimazole_100mg3d_fc	1
metronidazole_50mg1d_fc	1
metronidazole_50mg6h_fc	1
metronidazole_1500mg3d_fc	1
miconazole_200mg1d_fc	1
oxymetazoline_500ug1d_fc	1
oxymetazoline_500ug3d_fc	1
oxymetazoline_500ug6h_fc	1
pioglitazone_3mg6h_fc	1
pioglitazone_300mg3d_fc	1
rofecoxib_3mg6h_fc	1
rofecoxib_775mg6h_fc	1
rosiglitazone_10mg1d_fc	1
rosiglitazone_10mg3d_fc	1
rosiglitazone_10mg5d_fc	1
rosiglitazone_10mg6h_fc	1
rosiglitazone_1800mg6h_fc	1
sulfathiazole_31mg6h_fc	1
thiabendazole_10mg1d_fc	1
thiabendazole_10mg6h_fc	1
thiabendazole_92mg3d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_100mg5d_fc	1
zomepirac_2800ug6h_fc	1

Table XCIV: Representative Clusters using Drugs Classified in DrugBank as Azoles (Continued)

Cluster 4	
Exemplar: itraconazole_30mg3d_fc	
Sample	Label
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_30mg3d_fc	0
itraconazole_30mg6h_fc	0
itraconazole_1093mg1d_fc	0
acetazolamide_47mg6h_fc	1
atorvastatin_2500ug3d_fc	1
troglitazone_100mg1d_fc	1

BCRP/ABCG2 Substrates

Number of Samples = 85

Number of Clusters = 13

There were no "All QT" clusters. Cluster 1 contained all of the QT samples, which comprised slightly less

than half of the samples in the cluster.

Table XCV: Representative Clusters using Drugs Classified in DrugBank as BCRP/ABCG2 Substrates

Cluster 1 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
carboplatin_6mg1d_fc	1
carboplatin_14mg1d_fc	1
carboplatin_14mg3d_fc	1
cisplatin_2mg1d_fc	1
cisplatin_1170ug1d_fc	1
cisplatin_1170ug3d_fc	1
etoposide_100mg1d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg5d_fc	1
zidovudine_1540mg6h_fc	1

Benzamidazoles

Number of Samples = 29

Number of Clusters = 5

Cluster 1 was "All QT" and it contained all of the possible QT samples in this sub-class.

Table XCVI: Representative Clusters using Drugs Classified in DrugBank as Benzamidazoles

Cluster 1 Exemplar: lansoprazole_600mg5d_fc	
Sample	**Label**
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
albendazole_62mg1d_fc	0
albendazole_62mg3d_fc	0
albendazole_62mg5d_fc	0
albendazole_62mg6h_fc	0
lansoprazole_600mg1d_fc	0
lansoprazole_600mg3d_fc	0
lansoprazole_600mg5d_fc	0

Cardiovascular Agents

Number of Samples = 143

Number of Clusters = 30

There were no "All QT" clusters. Custer 1 contained approximately half QT and half NQT. Cluster 2 was

approximately 1/8 QT samples and the remainder were NQT.

Table XCVII: Representative Clusters using Drugs Classified in DrugBank as Cardiovascular Agents

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
isoproterenol_15mg1d_fc	0
isoproterenol_15mg3d_fc	0
isoproterenol_15mg5d_fc	0
sotalol_2g1d_fc	0
sotalol_2g3d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
acetazolamide_250mg5d_fc	1
amlodipine_19mg5d_fc	1
amlodipine_19mg6h_fc	1
aspirin_375mg5d_fc	1
carvedilol_2g1d_fc	1
digoxin_11mg3d_fc	1
digoxin_11mg5d_fc	1
niacin_2625mg1d_fc	1
niacin_2625mg5d_fc	1
oxymetazoline_500ug1d_fc	1
perhexiline_325mg1d_fc	1
perhexiline_325mg3d_fc	1
ticrynafen_570mg5d_fc	1
tocainide_224mg6h_fc	1
Cluster 2 Exemplar: torsemide_3mg3d_fc	
Sample	**Label**
sotalol_2g5d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0

Table XCVII: Representative Clusters using Drugs Classified in DrugBank as Cardiovascular Agents (Continued)

Sample	Label
acetazolamide_250mg1d_fc	1
acetazolamide_250mg6h_fc	1
amlodipine_19mg1d_fc	1
amlodipine_19mg3d_fc	1
amlodipine_200ug1d_fc	1
amlodipine_200ug3d_fc	1
amlodipine_200ug5d_fc	1
amlodipine_200ug6h_fc	1
aspirin_167mg1d_fc	1
aspirin_375mg6h_fc	1
aspirin_500mg1d_fc	1
atropine_2300ug1d_fc	1
atropine_2300ug6h_fc	1
digoxin_11mg1d_fc	1
digoxin_11mg6h_fc	1
digoxin_260ug6h_fc	1
glimepiride_2500mg3d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_12mg6h_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug5d_fc	1
indomethacin_4500ug6h_fc	1
indomethacin_9600ug1d_fc	1
indomethacin_9600ug3d_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug6h_fc	1
tocainide_67mg5d_fc	1
tocainide_67mg6h_fc	1
Cluster 2	
Exemplar: torsemide_3mg3d_fc	
Sample	**Label**
tocainide_224mg1d_fc	1
tocainide_224mg3d_fc	1

Cardiovascular System

Number of Samples = 187

Number of Clusters = 34

No "All QT" clusters were found. Cluster 3 contained all of the QT samples, which comprised

approximately ¼ of the samples in the cluster.

Table XCVIII: Representative Clusters using Drugs Classified in DrugBank as Cardiovascular System

Cluster 3 Exemplar: aspirin_500mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
isoproterenol_15mg1d_fc	0
isoproterenol_15mg3d_fc	0
isoproterenol_15mg5d_fc	0
sotalol_2g1d_fc	0
sotalol_2g3d_fc	0
sotalol_2g5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
amlodipine_19mg1d_fc	1
amlodipine_19mg3d_fc	1
amlodipine_19mg5d_fc	1
amlodipine_19mg6h_fc	1
amlodipine_200ug1d_fc	1
amlodipine_200ug3d_fc	1
amlodipine_200ug5d_fc	1
amlodipine_200ug6h_fc	1
aspirin_35mg1d_fc	1
aspirin_35mg3d_fc	1
aspirin_35mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg3d_fc	1
aspirin_500mg1d_fc	1

Table XCVIII: Representative Clusters using Drugs Classified in DrugBank as Cardiovascular System (Continued)

Sample	Label
aspirin_500mg3d_fc	1
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
benzocaine_1100mg1d_fc	1
benzocaine_1100mg3d_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
carvedilol_2g1d_fc	1
carvedilol_2g3d_fc	1
carvedilol_2g5d_fc	1
cerivastatin_50ug1d_fc	1
cerivastatin_50ug6h_fc	1
clofibrate_130mg1d_fc	1
cyclandelate_1500mg1d_fc	1
dexamethasone_1mg1d_fc	1
dexamethasone_1mg6h_fc	1
dexamethasone_150mg1d_fc	1
dexamethasone_150mg6h_fc	1
digoxin_11mg1d_fc	1
digoxin_11mg3d_fc	1
digoxin_11mg5d_fc	1
digoxin_11mg6h_fc	1
digoxin_260ug1d_fc	1
digoxin_260ug3d_fc	1
digoxin_260ug6h_fc	1
fluvastatin_5mg1d_fc	1
fluvastatin_5mg3d_fc	1
fluvastatin_5mg6h_fc	1
fluvastatin_94mg6h_fc	1
gemfibrozil_100mg1d_fc	1
gemfibrozil_100mg3d_fc	1
gemfibrozil_100mg6h_fc	1
gemfibrozil_700mg6h_fc	1
hydralazine_280mg1d_fc	1
hydralazine_280mg3d_fc	1
hydralazine_280mg5d_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg3d_fc	1
hydrocortisone_56mg5d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug5d_fc	1
indomethacin_4500ug6h_fc	1
indomethacin_9600ug1d_fc	1
indomethacin_9600ug6h_fc	1
niacin_2625mg1d_fc	1
niacin_2625mg3d_fc	1
niacin_2625mg5d_fc	1

Table XCVIII: Representative Clusters using Drugs Classified in DrugBank as Cardiovascular System (Continued)

Sample	Label
niacin_2625mg6h_fc	1
nisoldipine_15mg1d_fc	1
nisoldipine_15mg3d_fc	1
nisoldipine_15mg5d_fc	1
nisoldipine_15mg6h_fc	1
nisoldipine_1125mg1d_fc	1
nisoldipine_1125mg3d_fc	1
nisoldipine_1125mg5d_fc	1
nisoldipine_1125mg6h_fc	1
perhexiline_325mg1d_fc	1
perhexiline_325mg3d_fc	1
perhexiline_325mg5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
prednisolone_184mg5d_fc	1
simvastatin_15mg1d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1
ticrynafen_570mg1d_fc	1
ticrynafen_570mg3d_fc	1
ticrynafen_570mg5d_fc	1
tocainide_67mg3d_fc	1
tocainide_67mg5d_fc	1
tocainide_224mg1d_fc	1
tocainide_224mg3d_fc	1
tocainide_224mg5d_fc	1
tocainide_224mg6h_fc	1

Central Nervous System Agents

Number of Samples = 283

Number of Clusters = 72

No "All QT" clusters were found. Cluster 1 was comprised of approximately 1/3 QT samples. Cluster 2

was also comprised of approximately 1/3 QT samples.

Table XCIX: Representative Clusters using Drugs Classified in DrugBank as Central Nervous System Agents

Cluster 1 Exemplar: amantadine_58mg6h_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg5d_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg5d_fc	0
alprazolam_115mg1d_fc	1
alprazolam_115mg3d_fc	1
atropine_2300ug1d_fc	1
atropine_2300ug6h_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
clonazepam_2500mg1d_fc	1
clonazepam_2500mg6h_fc	1
diclofenac_10mg1d_fc	1
disulfiram_100mg6h_fc	1
indomethacin_4500ug6h_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1

Table XCIX: Representative Clusters using Drugs Classified in DrugBank as Central Nervous System Agents (Continued)

Sample	Label
mefenamicAcid_93mg6h_fc	1
melatonin_2g6h_fc	1
meloxicam_600ug3d_fc	1
modafinil_17500ug1d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg3d_fc	1
nitrazepam_310mg5d_fc	1
olanzapine_23mg5d_fc	1
pentobarbital_20mg6h_fc	1
pentobarbital_70mg3d_fc	1
phenacetin_619mg6h_fc	1
phenobarbital_25mg1d_fc	1
phenobarbital_25mg6h_fc	1
phenobarbital_54mg1d_fc	1
phenobarbital_54mg3d_fc	1
rofecoxib_3mg3d_fc	1
salicylicAcid_223mg1d_fc	1
secobarbital_20mg6h_fc	1
secobarbital_70mg3d_fc	1
zaleplon_100mg1d_fc	1
zaleplon_100mg3d_fc	1
zaleplon_100mg5d_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg6h_fc	1
Cluster 2 **Exemplar: chlorpromazine_18mg6h_fc**	
Sample	Label
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
clomipramine_115mg5d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
promazine_100mg5d_fc	0
bupropion_895mg5d_fc	1
diclofenac_3_5mg5d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg6h_fc	1
dimenhydrinate_165mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1

Table XCIX: Representative Clusters using Drugs Classified in DrugBank as Central Nervous System Agents (Continued)

Sample	Label
etodolac_24mg1d_fc	1
indomethacin_4500ug3d_fc	1
megestrolAcetate_132mg1d_fc	1
megestrolAcetate_132mg3d_fc	1
megestrolAcetate_132mg5d_fc	1
meloxicam_33mg5d_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug5d_fc	1
meloxicam_600ug6h_fc	1
modafinil_17500ug6h_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
pentobarbital_70mg5d_fc	1
phenobarbital_54mg5d_fc	1
rofecoxib_3mg6h_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
secobarbital_70mg1d_fc	1
secobarbital_70mg5d_fc	1
sulindac_23mg1d_fc	1
sulindac_23mg5d_fc	1
sulindac_23mg6h_fc	1
valproicAcid_235mg1d_fc	1
valproicAcid_235mg3d_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_850mg3d_fc	1
valproicAcid_850mg5d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg3d_fc	1
valproicAcid_1340mg5d_fc	1
valproicAcid_1340mg6h_fc	1
zomepirac_11mg3d_fc	1
zomepirac_2800ug1d_fc	1

Central Nervous System Depressants

Number of Samples = 112

Number of Clusters = 29

No "All QT" clusters were found. Both Clusters 1 and 2 were comprised of slightly more than half QT

samples.

Table C: Representative Clusters using Drugs Classified in DrugBank as Central Nervous System Depressants

Cluster 1 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
clomipramine_115mg5d_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
dimenhydrinate_165mg1d_fc	1
fluphenazine_22mg5d_fc	1
nitrazepam_310mg3d_fc	1
pentobarbital_70mg5d_fc	1
secobarbital_70mg5d_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg3d_fc	1
valproicAcid_1340mg5d_fc	1
valproicAcid_1340mg6h_fc	1
Cluster 2 Exemplar: clomipramine_115mg1d_fc	
Sample	**Label**
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0

Table C: Representative Clusters using Drugs Classified in DrugBank as Central Nervous System Depressants (Continued)

Sample	Label
promethazine_113mg6h_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
alprazolam_115mg3d_fc	1
chlorzoxazone_763mg3d_fc	1
fluphenazine_22mg3d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg5d_fc	1
thalidomide_113mg3d_fc	1
thalidomide_113mg5d_fc	1
zaleplon_100mg5d_fc	1
zopiclone_414mg1d_fc	1

Chemically-Induced Disorders

Number of Samples = 127

Number of Clusters = 18

Cluster 5 was "All QT" and Cluster 6 was all but one QT. Cluster 1 was comprised of approximately 2/3

QT samples. Cluster 8 was comprised of approximately 1/3 QT samples.

Table CI: Representative Clusters using Drugs Classified in DrugBank as Chemically-Induced Disorders

Cluster 1 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg6h_fc	0
fluoxetine_52mg1d_fc	0
bupropion_895mg1d_fc	1
clotrimazole_89mg6h_fc	1
enoxacin_750mg1d_fc	1
enoxacin_750mg6h_fc	1
gemfibrozil_100mg6h_fc	1
gemfibrozil_700mg6h_fc	1
modafinil_17500ug6h_fc	1
nevirapine_29mg6h_fc	1
troglitazone_1200mg5d_fc	1
Cluster 5 Exemplar: itraconazole_30mg3d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg3d_fc	0

Table CI: Representative Clusters using Drugs Classified in DrugBank as Chemically-Induced Disorders (Continued)

Sample	Label
itraconazole_1093mg1d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
Cluster 6	
Exemplar: itraconazole_1093mg5d_fc	
Sample	Label
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
enoxacin_100mg3d_fc	1
Cluster 8	
Exemplar: ketoconazole_25mg3d_fc	
Sample	Label
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
fluconazole_394mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
bupropion_895mg5d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_178mg6h_fc	1
econazole_43mg3d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg1d_fc	1
econazole_334mg6h_fc	1
enoxacin_100mg1d_fc	1
enoxacin_100mg5d_fc	1
enoxacin_100mg6h_fc	1
enoxacin_750mg3d_fc	1
enoxacin_750mg5d_fc	1
gemfibrozil_100mg1d_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1
modafinil_17500ug1d_fc	1
nevirapine_29mg1d_fc	1
nevirapine_200mg3d_fc	1
nevirapine_200mg6h_fc	1
pentobarbital_20mg1d_fc	1
pentobarbital_20mg6h_fc	1
pentobarbital_70mg1d_fc	1

Table CI: Representative Clusters using Drugs Classified in DrugBank as Chemically-Induced Disorders (Continued)

Sample	Label
pentobarbital_70mg3d_fc	1
pentobarbital_70mg5d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_100mg5d_fc	1
troglitazone_1200mg1d_fc	1
troglitazone_1200mg3d_fc	1

Combined Inducers of CYP3A4 and P-Glycoprotein

Number of Samples = 55

Number of Clusters = 11

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¾ QT samples.

Table CII: Representative Clusters using Drugs Classified in DrugBank as Combined Inducers of CYP3A4 and P-Glycoprotein

Cluster 1 Exemplar: tamoxifen_32mg5d_fc	
Sample	**Label**
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
mifepristone_3mg6h_fc	1
progesterone_164mg3d_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug5d_fc	1
progesterone_11300ug6h_fc	1

Combined Inhibitors of CYP3A4 and P-Glycoprotein

Number of Samples = 211

Number of Clusters = 36

Clusters 2 and 3 were "All QT". Clusters 1 and 33 were comprised of mostly QT samples. Cluster 10 was comprised of approximately 2/3 QT samples. Clusters 4, 9, 10 and 16 were comprised of approximately half QT samples.

Table CIII: Representative Clusters using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
erythromycin_1500mg5d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg5d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
itraconazole_1093mg6h_fc	0
tamoxifen_32mg5d_fc	0
dexamethasone_150mg1d_fc	1
omeprazole_30mg6h_fc	1
Cluster 2 Exemplar: azithromycin_50mg5d_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_225mg6h_fc	0
Sample	**Label**
tamoxifen_64mg6h_fc	0
Cluster 3 Exemplar: azithromycin_225mg3d_fc	
Sample	**Label**
azithromycin_50mg6h_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
itraconazole_1093mg1d_fc	0

Table CIII: Representative Clusters using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein (Continued)

Cluster 4 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
erythromycin_1500mg1d_fc	0
fluconazole_394mg1d_fc	0
itraconazole_30mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug6h_fc	1
dexamethasone_1mg1d_fc	1
hydrocortisone_56mg1d_fc	1
lansoprazole_600mg3d_fc	1
progesterone_11300ug6h_fc	1
vinorelbine_1500ug1d_fc	1
Cluster 9 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
azithromycin_225mg1d_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluoxetine_52mg3d_fc	0
ketoconazole_114mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
amlodipine_200ug6h_fc	1
atorvastatin_2500ug5d_fc	1
clotrimazole_52mg6h_fc	1
cyclosporin_350mg3d_fc	1
etoposide_100mg3d_fc	1
miconazole_200mg3d_fc	1
mifepristone_300mg6h_fc	1
nisoldipine_1125mg3d_fc	1
simvastatin_15mg1d_fc	1
Cluster 10 Exemplar: venlafaxine_320mg5d_fc	
Sample	**Label**
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg6h_fc	0
itraconazole_30mg6h_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg6h_fc	0

Table CIII: Representative Clusters using Drugs Classified in DrugBank as Combined Inhibitors of CYP3A4 and P-Glycoprotein (Continued)

Sample	Label
tamoxifen_32mg1d_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
amlodipine_19mg6h_fc	1
atorvastatin_300mg6h_fc	1
lansoprazole_600mg5d_fc	1
progesterone_164mg6h_fc	1
Cluster 16	
Exemplar: clotrimazole_89mg5d_fc	
Sample	Label
erythromycin_1500mg3d_fc	0
ketoconazole_114mg5d_fc	0
sertraline_210mg1d_fc	0
tamoxifen_2_5mg1d_fc	0
clotrimazole_89mg3d_fc	1
clotrimazole_89mg5d_fc	1
clotrimazole_89mg6h_fc	1
dexamethasone_150mg6h_fc	1
progesterone_164mg5d_fc	1
Cluster 33	
Exemplar: omeprazole_415mg1d_fc	
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
amlodipine_19mg5d_fc	1
omeprazole_30mg1d_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1

CYP2D6 Inhibitors (Weak)

Number of Samples = 123

Number of Clusters = 25

No "All QT" clusters were found. Cluster 1 was comprised of slightly more than half QT samples.

Table CIV: Representative Clusters using Drugs Classified in DrugBank as CYP2D6 Inhibitors (Weak)

Cluster 1 Exemplar: promethazine_2300ug1d_fc	
Sample	**Label**
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
methimazole_28mg6h_fc	1

CYP3A4 Inhibitors (Weak)

Number of Samples = 59

Number of Clusters = 12

No "All QT" clusters were found. Cluster 1 was comprised of approximately 1/3 QT samples.

Table CV: Representative Clusters using Drugs Classified in DrugBank as CYP3A4 Inhibitors (Weak)

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
amlodipine_19mg5d_fc	1
amlodipine_200ug3d_fc	1
amlodipine_200ug5d_fc	1
atorvastatin_300mg1d_fc	1
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_89mg6h_fc	1
cyclosporin_70mg3d_fc	1
cyclosporin_70mg5d_fc	1
cyclosporin_70mg6h_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg3d_fc	1
isoniazid_79mg5d_fc	1

Cytochrome P-450 CYP1A2 Inhibitors
Number of Samples = 274

Number of Clusters = 64

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¼ QT samples. Cluster 2

was comprised of approximately 2/3 QT samples. Clusters 56 and 57 were comprised of approximately

1/3 and ¼ QT samples, respectively.

Table CVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors

Cluster 1 Exemplar: citalopram_90mg1d_fc	
Sample	**Label**
ciprofloxacin_450mg1d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
ketoconazole_114mg5d_fc	0
albendazole_62mg6h_fc	1
amlodipine_19mg1d_fc	1
amlodipine_200ug3d_fc	1
atropine_2300ug1d_fc	1
enoxacin_100mg6h_fc	1
enoxacin_750mg1d_fc	1
fluphenazine_22mg6h_fc	1
fluphenazine_2500ug6h_fc	1
isoniazid_79mg1d_fc	1
lomefloxacin_2g1d_fc	1
lomefloxacin_2g5d_fc	1
nevirapine_200mg5d_fc	1
sulconazole_1200mg3d_fc	1
tocainide_67mg1d_fc	1
tocainide_67mg3d_fc	1
tocainide_67mg6h_fc	1
valproicAcid_1340mg1d_fc	1
Cluster 2 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
azithromycin_225mg6h_fc	0
ciprofloxacin_72mg1d_fc	0

Table CVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Continued)

Sample	Label
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
fluoxetine_52mg1d_fc	0
ketoconazole_114mg3d_fc	0
primaquine_45mg1d_fc	0
amlodipine_200ug1d_fc	1
isoniazid_50mg1d_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg5d_fc	1
nisoldipine_15mg5d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_30mg6h_fc	1
valproicAcid_850mg3d_fc	1
Cluster 3 **Exemplar: roxithromycin_312mg3d_fc**	
Sample	Label
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
erythromycin_1500mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
primaquine_45mg3d_fc	0
primaquine_45mg5d_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
roxithromycin_312mg5d_fc	0
amlodipine_19mg6h_fc	1
clomiphene_250mg5d_fc	1
isoniazid_79mg3d_fc	1
oxymetholone_1170mg1d_fc	1
oxymetholone_1170mg3d_fc	1
oxymetholone_1170mg5d_fc	1
Cluster 56 **Exemplar: tocainide_224mg3d_fc**	
Sample	Label
citalopram_40mg5d_fc	0
citalopram_90mg3d_fc	0
clarithromycin_476mg3d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0

Table CVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Continued)

Sample	Label
amlodipine_19mg3d_fc	1
amlodipine_200ug5d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg6h_fc	1
enoxacin_750mg5d_fc	1
fluphenazine_22mg5d_fc	1
fluvastatin_5mg1d_fc	1
fluvastatin_5mg3d_fc	1
fluvastatin_5mg5d_fc	1
miconazole_920mg6h_fc	1
modafinil_325mg5d_fc	1
modafinil_17500ug5d_fc	1
nevirapine_29mg5d_fc	1
nisoldipine_1125mg5d_fc	1
sulindac_23mg5d_fc	1
tocainide_67mg5d_fc	1
tocainide_224mg1d_fc	1
tocainide_224mg3d_fc	1
tocainide_224mg5d_fc	1
valproicAcid_850mg5d_fc	1
Cluster 57 **Exemplar: tocainide_224mg6h_fc**	
Sample	**Label**
azithromycin_50mg6h_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
clarithromycin_56mg6h_fc	0
ketoconazole_25mg6h_fc	0
amlodipine_200ug6h_fc	1
atropine_2300ug6h_fc	1
clomiphene_250mg1d_fc	1
clomiphene_250mg3d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg6h_fc	1
enoxacin_750mg6h_fc	1
fluvastatin_5mg6h_fc	1
fluvastatin_94mg6h_fc	1
gemfibrozil_100mg6h_fc	1
modafinil_17500ug6h_fc	1
rofecoxib_775mg6h_fc	1
rosiglitazone_10mg6h_fc	1
sulindac_64mg1d_fc	1
sulindac_64mg6h_fc	1
sulindac_132mg6h_fc	1
thiabendazole_10mg6h_fc	1
tocainide_224mg6h_fc	1
valproicAcid_1340mg6h_fc	1

Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

Number of Samples = 39

Number of Clusters = 6

No "All QT" clusters were found. Cluster 1 was comprised of approximately 2/3 QT samples.

Table CVII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Moderate)

Cluster 1 Exemplar: azithromycin_225mg1d_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
azithromycin_225mg6h_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg5d_fc	0
citalopram_40mg6h_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
nevirapine_29mg1d_fc	1
nevirapine_29mg5d_fc	1
nevirapine_29mg6h_fc	1

Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Number of Samples = 164

Number of Clusters = 26

Cluster 1 was "All QT". Cluster 2 was comprised of approximately ½ QT samples. Cluster 3 contained

approximately 3/4 QT samples. Clusters 9 and 22 were comprised of approximately ½ QT samples.

Table CVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak)

Cluster 1 Exemplar: azithromycin_50mg6h_fc	
Sample	**Label**
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg6h_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg6h_fc	0
fluoxetine_52mg1d_fc	0
Cluster 2 Exemplar: citalopram_40mg6h_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_225mg5d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
citalopram_90mg3d_fc	0
clarithromycin_476mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
clotrimazole_178mg6h_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg5d_fc	1
disulfiram_100mg6h_fc	1
fluvastatin_94mg6h_fc	1
mifepristone_3mg6h_fc	1
mifepristone_300mg6h_fc	1
nevirapine_200mg3d_fc	1
nisoldipine_1125mg3d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg6h_fc	1

Table CVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak) (Continued)

Cluster 3 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
azithromycin_50mg5d_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_394mg1d_fc	0
fluconazole_394mg3d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
fluphenazine_22mg1d_fc	1
isoniazid_50mg5d_fc	1
nevirapine_29mg6h_fc	1
nevirapine_200mg6h_fc	1
omeprazole_30mg5d_fc	1
Cluster 9 Exemplar: clotrimazole_89mg6h_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
citalopram_40mg5d_fc	0
citalopram_90mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0
sertraline_210mg1d_fc	0
amlodipine_19mg1d_fc	1
amlodipine_19mg6h_fc	1
clotrimazole_89mg6h_fc	1
diclofenac_10mg6h_fc	1
fluvastatin_5mg6h_fc	1
isoniazid_79mg3d_fc	1
sulconazole_1200mg1d_fc	1
Cluster 22 Exemplar: nevirapine_29mg5d_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg5d_fc	0
clarithromycin_476mg3d_fc	0
isoniazid_50mg1d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg5d_fc	1
nevirapine_29mg1d_fc	1

Table CVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Inhibitors (Weak) (Continued)

Sample	Label
nevirapine_29mg5d_fc	1
nevirapine_200mg5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
sulconazole_1200mg5d_fc	1

Cytochrome P-450 CYP1A2 Substrates

Number of Samples = 193

Number of Clusters = 37

No "All QT" clusters were found. Cluster 1 contained approximately ¾ QT samples. Cluster 2 contained

approximately ½ QT samples. Cluster 4 contained approximately 1/3 QT samples.

Table CIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Substrates

Cluster 1 Exemplar: amiodarone_147mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg5d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg5d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg3d_fc	0
bupropion_895mg5d_fc	1
chlorzoxazone_763mg3d_fc	1
pyrazinamide_1500mg1d_fc	1
pyrazinamide_1500mg5d_fc	1
thalidomide_113mg1d_fc	1
thalidomide_113mg3d_fc	1
Cluster 2 Exemplar: primaquine_45mg5d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg6h_fc	0
primaquine_45mg1d_fc	0

Table CIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP1A2 Substrates (Continued)

Sample	Label
primaquine_45mg3d_fc	0
primaquine_45mg5d_fc	0
promazine_100mg1d_fc	0
daunorubicin_3_25mg5d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
lomefloxacin_2g1d_fc	1
lomefloxacin_2g3d_fc	1
lomefloxacin_2g5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
olanzapine_23mg5d_fc	1
terbinafine_2g1d_fc	1
thalidomide_113mg5d_fc	1
Cluster 4 **Exemplar: bupropion_895mg3d_fc**	
Sample	Label
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_64mg1d_fc	0
bupropion_895mg3d_fc	1
carvedilol_2g3d_fc	1
chlorzoxazone_763mg1d_fc	1
cinnarizine_750mg1d_fc	1
cinnarizine_750mg5d_fc	1
etoposide_100mg1d_fc	1
progesterone_11300ug3d_fc	1
rofecoxib_1550mg1d_fc	1
rofecoxib_1550mg3d_fc	1
rofecoxib_1550mg5d_fc	1
zileuton_450mg5d_fc	1

Cytochrome P-450 CYP2A6 Inhibitors

Number of Samples = 106

Number of Clusters = 23

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples. Cluster 2

contained all but 2 QT samples.

Table CX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Inhibitors

Cluster 1 Exemplar: amiodarone_147mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg6h_fc	0
clofibrate_130mg1d_fc	1
clomiphene_250mg1d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_178mg6h_fc	1
isoniazid_50mg1d_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg5d_fc	1
methimazole_28mg1d_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
phenobarbital_54mg5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
rosiglitazone_10mg6h_fc	1
Cluster 2 Exemplar: azithromycin_50mg6h_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0

Table CX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Inhibitors (Continued)

Sample	Label
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
azithromycin_225mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
amlodipine_200ug6h_fc	1
clotrimazole_89mg1d_fc	1

Cytochrome P-450 CYP2A6 Substrates

Number of Samples = 77

Number of Clusters = 19

No "All QT" clusters were found. Cluster 1 contained approximately ¾ QT samples.

Table CXI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2A6 Substrates

Cluster 1 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
nevirapine_29mg6h_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug6h_fc	1

Cytochrome P-450 CYP2B6 Substrates

Number of Samples = 91

Number of Clusters = 16

Clusters 2 and 4 were "All QT" clusters. Clusters 1 and 3 contained all but 1 QT sample. Cluster 5

contained all but 2 QT samples.

Table CXII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2B6 Substrates

Cluster 1 Exemplar: fluconazole_10mg5d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
valproicAcid_235mg6h_fc	1
Cluster 2 Exemplar: promethazine_2300ug6h_fc	
Sample	**Label**
promethazine_113mg1d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
Cluster 3 Exemplar: sertraline_210mg3d_fc	
Sample	**Label**
erythromycin_1500mg3d_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
diazepam_710mg3d_fc	1
Cluster 4 Exemplar: tamoxifen_2_5mg6h_fc	
Sample	**Label**
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
Cluster 5 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
erythromycin_1500mg5d_fc	0

Table CXII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2B6 Substrates (Continued)

fluconazole_394mg1d_fc	0
fluconazole_394mg5d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
ifosfamide_17mg1d_fc	1
nevirapine_200mg1d_fc	1

Cytochrome P-450 CYP2C8 Inhibitors

Number of Samples = 221

Number of Clusters = 51

No "All QT" clusters were found. Cluster 21 was comprised of approximately 1/3 QT samples.

Table CXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors

Cluster 21 Exemplar: etoposide_100mg3d_fc	
Sample	**Label**
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
amlodipine_19mg6h_fc	1
amlodipine_200ug1d_fc	1
amlodipine_200ug3d_fc	1
amlodipine_200ug5d_fc	1
amlodipine_200ug6h_fc	1
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
cerivastatin_50ug6h_fc	1
cholecalciferol_8mg1d_fc	1
cholecalciferol_8mg3d_fc	1
cholecalciferol_8mg5d_fc	1
clotrimazole_52mg3d_fc	1
clotrimazole_52mg5d_fc	1
clotrimazole_52mg6h_fc	1

Table CXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors (Continued)

Sample	Label
clotrimazole_89mg1d_fc	1
clotrimazole_89mg3d_fc	1
clotrimazole_89mg5d_fc	1
clotrimazole_89mg6h_fc	1
clotrimazole_178mg6h_fc	1
cyclosporin_70mg6h_fc	1
cyclosporin_350mg3d_fc	1
diethylstilbestrol_2800ug6h_fc	1
etoposide_100mg3d_fc	1
etoposide_100mg6h_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
fluvastatin_94mg6h_fc	1
isoniazid_50mg1d_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg3d_fc	1
isoniazid_79mg5d_fc	1
lansoprazole_600mg1d_fc	1
lansoprazole_600mg3d_fc	1
lovastatin_450mg6h_fc	1
lovastatin_1500mg6h_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
mefenamicAcid_93mg6h_fc	1
meloxicam_33mg1d_fc	1
meloxicam_33mg3d_fc	1
meloxicam_33mg5d_fc	1
meloxicam_33mg6h_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug3d_fc	1
meloxicam_600ug5d_fc	1
meloxicam_600ug6h_fc	1
metronidazole_50mg1d_fc	1
metronidazole_50mg6h_fc	1
metronidazole_1500mg1d_fc	1
metronidazole_1500mg3d_fc	1
pioglitazone_3mg1d_fc	1
pioglitazone_3mg6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_650mg6h_fc	1
raloxifene_6500ug1d_fc	1
raloxifene_6500ug3d_fc	1
raloxifene_6500ug5d_fc	1
rosiglitazone_10mg1d_fc	1
rosiglitazone_10mg3d_fc	1

Table CXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Inhibitors (Continued)

Sample	Label
rosiglitazone_10mg5d_fc	1
rosiglitazone_10mg6h_fc	1
simvastatin_15mg1d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1
sulfaphenazole_1695mg1d_fc	1
sulfaphenazole_1695mg6h_fc	1
ticlopidine_223mg1d_fc	1
ticlopidine_223mg3d_fc	1
ticlopidine_223mg5d_fc	1
troglitazone_100mg5d_fc	1
valproicAcid_235mg1d_fc	1
valproicAcid_235mg3d_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_850mg1d_fc	1
valproicAcid_850mg3d_fc	1
valproicAcid_850mg5d_fc	1
valproicAcid_850mg6h_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg3d_fc	1
valproicAcid_1340mg6h_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug3d_fc	1
warfarin_250ug5d_fc	1

Cytochrome P-450 CYP2C8 Substrates

Number of Samples = 178

Number of Clusters = 37

No "All QT" clusters were found. Cluster 1 contained approximately ¼ QT samples.

Table CXIV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Substrates

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
aspirin_35mg5d_fc	1
aspirin_35mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_375mg5d_fc	1
aspirin_375mg6h_fc	1
aspirin_500mg1d_fc	1
atorvastatin_2500ug6h_fc	1
bupropion_895mg5d_fc	1
cerivastatin_50ug6h_fc	1
diclofenac_10mg6h_fc	1
fluvastatin_5mg1d_fc	1
fluvastatin_5mg6h_fc	1
ifosfamide_17mg1d_fc	1
ifosfamide_17mg6h_fc	1
ifosfamide_143mg3d_fc	1
lansoprazole_600mg1d_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg6h_fc	1
meloxicam_33mg5d_fc	1
meloxicam_600ug5d_fc	1
naproxen_134mg6h_fc	1
omeprazole_30mg5d_fc	1
omeprazole_30mg6h_fc	1
pioglitazone_3mg6h_fc	1

Table CXIV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C8 Substrates (Continued)

Sample	Label
pioglitazone_300mg3d_fc	1
pioglitazone_1500mg5d_fc	1
progesterone_164mg5d_fc	1
progesterone_11300ug6h_fc	1
rofecoxib_3mg5d_fc	1
rosiglitazone_10mg5d_fc	1
rosiglitazone_10mg6h_fc	1
rosiglitazone_1800mg6h_fc	1
terbinafine_2g1d_fc	1
tretinoin_7mg3d_fc	1
warfarin_250ug1d_fc	1
zidovudine_1540mg5d_fc	1
zidovudine_1540mg6h_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg6h_fc	1

Cytochrome P-450 CYP2C9 Inhibitors

Number of Samples = 329

Number of Clusters = 71

No "All QT" clusters were found. Cluster 1 contains approximately ½ QT samples. Cluster 3 contains all

but 1 QT sample. Cluster 6 contains approximately 1/3 QT samples. Cluster 66 contains approximately ¼

QT samples.

Table CXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors

Cluster 1 Exemplar: amiodarone_147mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
fluconazole_10mg6h_fc	0
fluoxetine_52mg1d_fc	0
sertraline_210mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
cisplatin_1170ug5d_fc	1
isoniazid_79mg3d_fc	1
leflunomide_30mg6h_fc	1
omeprazole_415mg5d_fc	1
troglitazone_100mg3d_fc	1
Cluster 3 **Exemplar: ketoconazole_114mg3d_fc**	
Sample	**Label**
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
anastrozole_400mg5d_fc	1
Cluster 6 **Exemplar: tamoxifen_64mg3d_fc**	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
pantoprazole_1100mg1d_fc	0

Table CXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors (Continued)

Sample	Label
pantoprazole_1100mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
sulfisoxazole_250mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
atorvastatin_2500ug6h_fc	1
cholecalciferol_8mg3d_fc	1
cholecalciferol_8mg5d_fc	1
cisplatin_2mg3d_fc	1
cisplatin_2mg5d_fc	1
cisplatin_1170ug3d_fc	1
cisplatin_1170ug6h_fc	1
clotrimazole_89mg5d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg1d_fc	1
diclofenac_10mg3d_fc	1
diclofenac_10mg6h_fc	1
diethylstilbestrol_2800ug6h_fc	1
disulfiram_100mg1d_fc	1
disulfiram_100mg6h_fc	1
disulfiram_500mg1d_fc	1
gemfibrozil_100mg6h_fc	1
imatinib_150mg3d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg5d_fc	1
leflunomide_60mg6h_fc	1
mefenamicAcid_93mg6h_fc	1
meloxicam_33mg6h_fc	1
meloxicam_600ug3d_fc	1
meloxicam_600ug6h_fc	1
methimazole_28mg6h_fc	1
methimazole_100mg3d_fc	1
metronidazole_50mg6h_fc	1
metronidazole_1500mg3d_fc	1
modafinil_17500ug1d_fc	1
nevirapine_29mg1d_fc	1
nevirapine_200mg1d_fc	1
omeprazole_30mg3d_fc	1
progesterone_164mg3d_fc	1
progesterone_164mg5d_fc	1

Table CXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors (Continued)

Sample	Label
progesterone_164mg6h_fc	1
progesterone_11300ug5d_fc	1
progesterone_11300ug6h_fc	1
rosiglitazone_10mg3d_fc	1
rosiglitazone_10mg5d_fc	1
sildenafil_300mg1d_fc	1
sildenafil_420mg1d_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sulfadiazine_1170mg1d_fc	1
sulfadiazine_1170mg3d_fc	1
sulfadiazine_1170mg5d_fc	1
sulfaphenazole_1695mg6h_fc	1
troglitazone_100mg5d_fc	1
valproicAcid_235mg6h_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg6h_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug5d_fc	1
Cluster 66 **Exemplar: sulconazole_1200mg3d_fc**	
Sample	Label
ketoconazole_25mg1d_fc	0
ketoconazole_2274mg6h_fc	0
promethazine_2300ug6h_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_2500mg1d_fc	0
tamoxifen_32mg1d_fc	0
amlodipine_200ug1d_fc	1
atorvastatin_300mg6h_fc	1
cerivastatin_50ug6h_fc	1
clotrimazole_52mg1d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_178mg3d_fc	1
cyclosporin_70mg6h_fc	1
cyclosporin_350mg3d_fc	1
diclofenac_10mg5d_fc	1
leflunomide_30mg3d_fc	1
leflunomide_60mg3d_fc	1
lovastatin_450mg6h_fc	1
lovastatin_1500mg6h_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
meloxicam_33mg3d_fc	1
metronidazole_50mg1d_fc	1
metronidazole_1500mg1d_fc	1
rosiglitazone_10mg6h_fc	1

Table CXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Inhibitors (Continued)

Sample	Label
sulconazole_1200mg1d_fc	1
sulconazole_1200mg3d_fc	1
sulconazole_1200mg5d_fc	1
warfarin_250ug3d_fc	1

Cytochrome P-450 CYP2C9 Substrates

Number of Samples = 304

Number of Clusters = 68

No "All QT" clusters were found. Cluster 1 contained approximately ½ QT samples, and Clusters 19 and

47 contained all but one of the remaining QT Samples.

Table CXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates

Cluster 1 Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
sertraline_210mg5d_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_64mg3d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg6h_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
alprazolam_115mg1d_fc	1
alprazolam_115mg3d_fc	1
alprazolam_115mg5d_fc	1
glimepiride_2500mg1d_fc	1
glimepiride_2500mg3d_fc	1
glimepiride_2500mg5d_fc	1
glipizide_2500mg1d_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
mefenamicAcid_93mg6h_fc	1

Table CXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates (Continued)

Sample	Label
melatonin_2g6h_fc	1
metronidazole_50mg1d_fc	1
metronidazole_50mg6h_fc	1
metronidazole_1500mg1d_fc	1
metronidazole_1500mg3d_fc	1
nevirapine_29mg5d_fc	1
nevirapine_200mg5d_fc	1
phenacetin_619mg3d_fc	1
phenacetin_619mg5d_fc	1
phenacetin_619mg6h_fc	1
phenobarbital_25mg1d_fc	1
phenobarbital_25mg6h_fc	1
phenobarbital_54mg1d_fc	1
pioglitazone_3mg6h_fc	1
pioglitazone_300mg1d_fc	1
sildenafil_300mg5d_fc	1
sulfadiazine_1170mg5d_fc	1
terbinafine_2g1d_fc	1
terbinafine_2g5d_fc	1
troglitazone_1200mg3d_fc	1
zidovudine_1540mg1d_fc	1
zidovudine_1540mg3d_fc	1
zidovudine_1540mg5d_fc	1
zidovudine_1540mg6h_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg3d_fc	1
zopiclone_414mg6h_fc	1
Cluster 19	
Exemplar: indomethacin_5mg1d_fc	
Sample	Label
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg5d_fc	0
torsemide_3mg3d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
artemether_74mg1d_fc	1
artemether_74mg5d_fc	1
aspirin_35mg3d_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_500mg1d_fc	1
aspirin_500mg3d_fc	1
bupropion_895mg5d_fc	1
diclofenac_3_5mg1d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg6h_fc	1
fluvastatin_5mg1d_fc	1
fluvastatin_5mg3d_fc	1
fluvastatin_5mg5d_fc	1

Table CXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates (Continued)

Sample	Label
fluvastatin_94mg6h_fc	1
glimepiride_2500mg6h_fc	1
glipizide_2500mg3d_fc	1
ifosfamide_17mg6h_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg5d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_4500ug3d_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
leflunomide_30mg5d_fc	1
leflunomide_60mg3d_fc	1
meloxicam_33mg5d_fc	1
meloxicam_600ug5d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg1d_fc	1
pioglitazone_300mg3d_fc	1
rofecoxib_3mg3d_fc	1
rofecoxib_3mg5d_fc	1
rofecoxib_3mg6h_fc	1
rosiglitazone_10mg6h_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
sildenafil_14600ug5d_fc	1
sulfadiazine_1170mg1d_fc	1
sulfadiazine_1170mg3d_fc	1
thalidomide_113mg5d_fc	1
tretinoin_7mg1d_fc	1
tretinoin_7mg5d_fc	1
troglitazone_100mg1d_fc	1
troglitazone_100mg5d_fc	1
troglitazone_1200mg1d_fc	1
troglitazone_1200mg5d_fc	1
valproicAcid_235mg6h_fc	1
valproicAcid_1340mg5d_fc	1
valproicAcid_1500mg3d_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug5d_fc	1
zileuton_450mg6h_fc	1
Cluster 47 **Exemplar: pioglitazone_1500mg1d_fc**	
Sample	Label
fluoxetine_52mg1d_fc	0
sertraline_210mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg6h_fc	0
acetaminophen_100mg1d_fc	1

Table CXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C9 Substrates (Continued)

Sample	Label
acetaminophen_100mg3d_fc	1
acetaminophen_100mg5d_fc	1
acetaminophen_100mg6h_fc	1
artemether_74mg3d_fc	1
aspirin_375mg1d_fc	1
aspirin_375mg3d_fc	1
aspirin_375mg5d_fc	1
bupropion_895mg3d_fc	1
celecoxib_400mg1d_fc	1
celecoxib_400mg3d_fc	1
diclofenac_3_5mg5d_fc	1
diclofenac_10mg1d_fc	1
etodolac_24mg1d_fc	1
glipizide_2500mg5d_fc	1
ifosfamide_143mg3d_fc	1
imatinib_150mg3d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug6h_fc	1
leflunomide_30mg1d_fc	1
leflunomide_60mg1d_fc	1
nevirapine_29mg6h_fc	1
nevirapine_200mg6h_fc	1
omeprazole_415mg3d_fc	1
phenobarbital_54mg3d_fc	1
phenobarbital_54mg5d_fc	1
phenobarbital_80mg1d_fc	1
phenobarbital_80mg3d_fc	1
phenobarbital_80mg5d_fc	1
pioglitazone_3mg1d_fc	1
pioglitazone_1500mg1d_fc	1
pioglitazone_1500mg3d_fc	1
pioglitazone_1500mg5d_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug6h_fc	1
rofecoxib_775mg6h_fc	1
rofecoxib_1550mg1d_fc	1
sildenafil_300mg1d_fc	1
sildenafil_300mg6h_fc	1
sildenafil_14600ug6h_fc	1
testosterone_375mg1d_fc	1
testosterone_375mg3d_fc	1
testosterone_375mg5d_fc	1
thalidomide_113mg1d_fc	1
thalidomide_113mg3d_fc	1
troglitazone_100mg3d_fc	1
valproicAcid_235mg1d_fc	1
valproicAcid_1500mg1d_fc	1

Cytochrome P-450 CYP2C19 Inhibitors

Number of Samples = 255

Number of Clusters = 61

No "All QT" clusters were found. Cluster 1 was comprised of approximately ¼ QT samples. Cluster 2

was approximately ½ QT samples. Cluster 34 was approximately ½ QT samples. Cluster 44 was

approximately 1/5 QT samples. Cluster 50 was approximately 1/6 QT samples.

Table CXVII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors

Cluster 1 Exemplar: ketoconazole_25mg6h_fc	
Sample	**Label**
citalopram_40mg6h_fc	0
clarithromycin_56mg6h_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
torsemide_110mg3d_fc	0
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
cerivastatin_50ug6h_fc	1
clotrimazole_52mg1d_fc	1
clotrimazole_52mg3d_fc	1
clotrimazole_178mg3d_fc	1
clotrimazole_178mg6h_fc	1
fluvastatin_94mg6h_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug6h_fc	1
methimazole_28mg6h_fc	1
miconazole_200mg6h_fc	1
modafinil_325mg1d_fc	1
olanzapine_23mg3d_fc	1
omeprazole_30mg6h_fc	1
pioglitazone_3mg1d_fc	1
pioglitazone_3mg6h_fc	1
rosiglitazone_10mg5d_fc	1
rosiglitazone_10mg6h_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg6h_fc	1

Table CXVII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors (Continued)

Cluster 2	
Exemplar: torsemide_3mg3d_fc	
Sample	**Label**
citalopram_40mg5d_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0
sertraline_210mg1d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
carbamazepine_490mg1d_fc	1
cholecalciferol_8mg1d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_89mg3d_fc	1
clotrimazole_89mg5d_fc	1
cyclosporin_350mg3d_fc	1
isoniazid_50mg1d_fc	1
isoniazid_79mg3d_fc	1
methimazole_28mg1d_fc	1
methimazole_100mg3d_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_920mg1d_fc	1
miconazole_920mg6h_fc	1
modafinil_325mg5d_fc	1

Table CXVII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors (Continued)

Sample	Label
modafinil_17500ug5d_fc	1
olanzapine_23mg1d_fc	1
oxymetholone_1170mg1d_fc	1
oxymetholone_1170mg3d_fc	1
oxymetholone_1170mg5d_fc	1
progesterone_164mg3d_fc	1
progesterone_164mg5d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_14600ug5d_fc	1
ticlopidine_223mg1d_fc	1
ticlopidine_223mg3d_fc	1
ticlopidine_223mg5d_fc	1
valproicAcid_850mg5d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg6h_fc	1
warfarin_250ug5d_fc	1

Cluster 34
Exemplar: indomethacin_4500ug5d_fc

Sample	Label
citalopram_90mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_2274mg3d_fc	0
indomethacin_4500ug5d_fc	1
indomethacin_9600ug1d_fc	1
modafinil_325mg3d_fc	1

Cluster 44
Exemplar: omeprazole_415mg1d_fc

Sample	Label
fluconazole_394mg5d_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
sertraline_210mg5d_fc	0
carbamazepine_490mg3d_fc	1
clotrimazole_52mg5d_fc	1
cyclosporin_70mg6h_fc	1
diazepam_710mg3d_fc	1
diazepam_710mg5d_fc	1
gemfibrozil_100mg6h_fc	1
lansoprazole_600mg1d_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
lovastatin_450mg6h_fc	1
lovastatin_1500mg6h_fc	1
methimazole_100mg1d_fc	1
omeprazole_30mg1d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
omeprazole_415mg6h_fc	1

Table CXVII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Inhibitors (Continued)

Sample	Label
pioglitazone_300mg1d_fc	1
pioglitazone_1500mg1d_fc	1
progesterone_164mg1d_fc	1
progesterone_164mg6h_fc	1
rabeprazole_1024mg1d_fc	1
rabeprazole_1024mg3d_fc	1
rabeprazole_1024mg5d_fc	1
rosiglitazone_10mg1d_fc	1
rosiglitazone_10mg3d_fc	1
rosiglitazone_1800mg6h_fc	1
sildenafil_300mg3d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_100mg5d_fc	1
valproicAcid_235mg6h_fc	1
Cluster 50 **Exemplar: sildenafil_2500ug3d_fc**	
Sample	Label
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
clarithromycin_476mg5d_fc	0
fluconazole_10mg3d_fc	0
indomethacin_9600ug6h_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg5d_fc	1
miconazole_200mg5d_fc	1
modafinil_17500ug1d_fc	1
modafinil_17500ug3d_fc	1
modafinil_17500ug6h_fc	1
omeprazole_30mg3d_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug5d_fc	1
progesterone_11300ug6h_fc	1
sildenafil_300mg1d_fc	1
sildenafil_300mg6h_fc	1
sildenafil_420mg6h_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug3d_fc	1
sildenafil_14600ug6h_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_850mg3d_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug3d_fc	1

Cytochrome P-450 CYP2C19 Substrates

Number of Samples = 201

Number of Clusters = 46

No "All QT" clusters were found. Cluster 1 contained all but 2 QT samples. Cluster 4 contained

approximately 2/3 QT clusters. Cluster 5 contained 3 QT samples.

Table CXVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
promazine_100mg5d_fc	0
sertraline_210mg1d_fc	0
ifosfamide_17mg1d_fc	1
ifosfamide_143mg3d_fc	1
Cluster 4 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
citalopram_40mg1d_fc	0
citalopram_40mg6h_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
promazine_100mg3d_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0

Table CXVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates (Continued)

Sample	Label
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
diazepam_710mg3d_fc	1
diclofenac_3_5mg5d_fc	1
diclofenac_10mg1d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
progesterone_164mg3d_fc	1
progesterone_164mg5d_fc	1
progesterone_164mg6h_fc	1
terbinafine_2g1d_fc	1
troglitazone_100mg1d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_100mg5d_fc	1
zidovudine_1540mg6h_fc	1
Cluster 5	
Exemplar: amoxicillin_1100mg1d_fc	
Sample	Label
citalopram_40mg5d_fc	0
citalopram_90mg3d_fc	0
tamoxifen_64mg6h_fc	0
amoxicillin_1100mg1d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
imatinib_150mg5d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug6h_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
melatonin_2g6h_fc	1
omeprazole_415mg1d_fc	1
pentobarbital_70mg5d_fc	1
phenacetin_619mg5d_fc	1
phenacetin_619mg6h_fc	1
phenobarbital_54mg5d_fc	1
phenobarbital_80mg5d_fc	1
primidone_750mg1d_fc	1
primidone_750mg5d_fc	1
progesterone_164mg1d_fc	1
progesterone_11300ug3d_fc	1
ticlopidine_223mg1d_fc	1

Table CXVIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2C19 Substrates (Continued)

Sample	Label
troglitazone_1200mg3d_fc	1
valproicAcid_235mg3d_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_850mg5d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg3d_fc	1
valproicAcid_1340mg5d_fc	1
valproicAcid_1340mg6h_fc	1
valproicAcid_1500mg3d_fc	1

Cytochrome P-450 CYP2D6 Inhibitors

Number of Samples = 296

Number of Clusters = 70

Cluster 1 was slightly more than ½ QT samples. Cluster 3 was an "All QT" cluster. Cluster 4 was

approximately 1/5 QT samples. Clusters 5 and 6 were "All QT". Cluster 7 contained all but 1 QT sample.

Cluster 8 contained approximately ½ QT samples. Cluster 9 was "All QT". Cluster 10 was approximately

1/3 QT samples. Cluster 52 was slightly less than ½ QT samples.

Table CXIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
sertraline_210mg1d_fc	0
cyclosporin_350mg1d_fc	1
pioglitazone_1500mg5d_fc	1
simvastatin_15mg1d_fc	1
terbinafine_2g1d_fc	1
Cluster 3 Exemplar: itraconazole_1093mg1d_fc	
Sample	**Label**
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_114mg1d_fc	0
venlafaxine_320mg3d_fc	0
Cluster 4 Exemplar: ketoconazole_25mg6h_fc	
Sample	**Label**
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0

Table CXIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors (Continued)

Sample	Label
tamoxifen_2_5mg6h_fc	0
tamoxifen_64mg6h_fc	0
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
cerivastatin_50ug6h_fc	1
cyclosporin_70mg6h_fc	1
fluphenazine_22mg6h_fc	1
hydroxyurea_59mg5d_fc	1
lomustine_8750ug1d_fc	1
lomustine_8750ug6h_fc	1
lovastatin_450mg6h_fc	1
lovastatin_1500mg6h_fc	1
mifepristone_3mg1d_fc	1
mifepristone_3mg6h_fc	1
omeprazole_30mg6h_fc	1
pioglitazone_3mg6h_fc	1
pioglitazone_300mg1d_fc	1
rosiglitazone_10mg5d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1

Cluster 5
Exemplar: ketoconazole_114mg3d_fc

Sample	Label
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0

Cluster 6
Exemplar: ketoconazole_2274mg1d_fc

Sample	Label
ketoconazole_2274mg1d_fc	0

Cluster 7
Exemplar: promethazine_113mg3d_fc

Sample	Label
clomipramine_115mg5d_fc	0
ketoconazole_114mg6h_fc	0
promethazine_113mg3d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
niacin_2625mg6h_fc	1

Cluster 8
Exemplar: promethazine_2300ug1d_fc

Sample	Label
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
citalopram_40mg5d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
clomipramine_115mg1d_fc	0
fluoxetine_52mg3d_fc	0

Table CXIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors (Continued)

Sample	Label
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
primaquine_45mg1d_fc	0
promethazine_113mg1d_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug6h_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg5d_fc	0
amlodipine_19mg6h_fc	1
amlodipine_200ug6h_fc	1
clotrimazole_52mg6h_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug5d_fc	1
hydroxyurea_59mg1d_fc	1
hydroxyurea_400mg5d_fc	1
isoniazid_79mg5d_fc	1
miconazole_920mg6h_fc	1
nevirapine_29mg5d_fc	1
niacin_2625mg3d_fc	1
niacin_2625mg5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg5d_fc	1
pergolide_1100ug1d_fc	1
perhexiline_325mg1d_fc	1
rosiglitazone_10mg6h_fc	1
sildenafil_300mg5d_fc	1
sildenafil_14600ug5d_fc	1
vinorelbine_1500ug1d_fc	1

Cluster 9	
Exemplar: sertraline_210mg5d_fc	
Sample	**Label**
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0

Cluster 10	
Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
granisetron_175mg1d_fc	0
granisetron_175mg6h_fc	0
ketoconazole_25mg5d_fc	0
primaquine_45mg3d_fc	0
promethazine_113mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
atorvastatin_2500ug3d_fc	1

Table CXIX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Inhibitors (Continued)

Sample	Label
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
cholecalciferol_8mg1d_fc	1
cholecalciferol_8mg3d_fc	1
clotrimazole_52mg5d_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_89mg6h_fc	1
doxorubicin_3mg5d_fc	1
imatinib_150mg1d_fc	1
lomustine_4200ug5d_fc	1
lomustine_8750ug5d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg5d_fc	1
mifepristone_3mg3d_fc	1
mifepristone_300mg6h_fc	1
nevirapine_29mg1d_fc	1
nevirapine_200mg1d_fc	1
nevirapine_200mg3d_fc	1
nevirapine_200mg5d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg5d_fc	1
rosiglitazone_10mg1d_fc	1
sildenafil_300mg1d_fc	1
sildenafil_420mg5d_fc	1
sildenafil_2500ug5d_fc	1
sildenafil_14600ug1d_fc	1
vinorelbine_1500ug3d_fc	1
vinorelbine_1500ug5d_fc	1
Cluster 52	
Exemplar: oxymetholone_1170mg3d_fc	
Sample	Label
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_73mg6h_fc	0
clomipramine_115mg3d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg5d_fc	0
promethazine_113mg6h_fc	0
cholecalciferol_8mg5d_fc	1
isoniazid_79mg3d_fc	1
lansoprazole_600mg3d_fc	1
oxymetholone_1170mg1d_fc	1
oxymetholone_1170mg3d_fc	1
oxymetholone_1170mg5d_fc	1
rosiglitazone_1800mg6h_fc	1
sulfaphenazole_1695mg6h_fc	1
ticlopidine_223mg5d_fc	1

Cytochrome P-450 CYP2D6 Substrates

Number of Samples = 168

Number of Clusters = 26

Cluster 1 contained all but 2 QT samples. Cluster 2 was approximately 2/3 QT samples. Cluster 3 was an

"All QT" cluster. Cluster 4 was approximately ½ QT samples. Cluster 14 was approximately 1/3 QT

samples.

Table CXX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Substrates

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
clomipramine_115mg5d_fc	0
fluoxetine_52mg1d_fc	0
promethazine_113mg5d_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
sertraline_210mg1d_fc	0
doxorubicin_3mg5d_fc	1
sildenafil_300mg5d_fc	1
Cluster 2 Exemplar: promethazine_2300ug1d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_73mg1d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
fluoxetine_52mg5d_fc	0
granisetron_175mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
tamoxifen_32mg5d_fc	0
venlafaxine_320mg1d_fc	0

Table CXX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Substrates (Continued)

Sample	Label
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_650ug5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg5d_fc	1
progesterone_164mg5d_fc	1

Cluster 3 Exemplar: sertraline_210mg3d_fc	
Sample	Label
quetiapine_500mg5d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0

Cluster 4 Exemplar: tamoxifen_32mg1d_fc	
Sample	Label
granisetron_175mg3d_fc	0
granisetron_175mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
artemether_74mg3d_fc	1
doxorubicin_3mg6h_fc	1
fluphenazine_22mg6h_fc	1
fluvastatin_5mg5d_fc	1
phenacetin_619mg5d_fc	1
phenacetin_619mg6h_fc	1
progesterone_164mg3d_fc	1
progesterone_11300ug5d_fc	1
sildenafil_420mg5d_fc	1
ticlopidine_223mg3d_fc	1

Cluster 14 Exemplar: perhexiline_325mg3d_fc	
Sample	Label
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
citalopram_40mg5d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
fluoxetine_52mg3d_fc	0
artemether_74mg1d_fc	1
artemether_74mg5d_fc	1
bupropion_895mg1d_fc	1

Table CXX: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2D6 Substrates (Continued)

Sample	Label
imatinib_150mg5d_fc	1
nevirapine_29mg5d_fc	1
nevirapine_200mg5d_fc	1
olanzapine_23mg3d_fc	1
perhexiline_325mg3d_fc	1
perhexiline_325mg5d_fc	1
phenacetin_619mg1d_fc	1
sildenafil_14600ug5d_fc	1
ticlopidine_223mg5d_fc	1
vinorelbine_1500ug1d_fc	1

Cytochrome P-450 CYP2E1 Inhibitors

Number of Samples = 114

Number of Clusters = 21

No "All QT" clusters were found. Cluster 1 contained slightly more than ½ QT samples.

Table CXXI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Inhibitors

Cluster 1 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
itraconazole_1093mg6h_fc	0
clomiphene_250mg1d_fc	1
clomiphene_250mg5d_fc	1
disulfiram_100mg6h_fc	1
fluphenazine_22mg3d_fc	1
fluphenazine_22mg5d_fc	1
isoniazid_50mg1d_fc	1
isoniazid_79mg3d_fc	1
nitrazepam_310mg3d_fc	1

APPENDIX B (continued)

Cytochrome P-450 CYP2E1 Substrates

Number of Samples = 85

Number of Clusters = 16

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples. Cluster 2

contained approximately 2/3 QT samples.

Table CXXII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP2E1 Substrates

Cluster 1 Exemplar: citalopram_40mg6h_fc	
Sample	**Label**
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
citalopram_90mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
acetaminophen_100mg5d_fc	1
chlorzoxazone_763mg3d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg6h_fc	1
sildenafil_300mg1d_fc	1
sildenafil_2500ug5d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
thalidomide_113mg5d_fc	1
Cluster 2 Exemplar: tamoxifen_32mg3d_fc	
Sample	**Label**
citalopram_90mg1d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
acetaminophen_100mg1d_fc	1
acetaminophen_100mg3d_fc	1
etoposide_100mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1

Cytochrome P-450 CYP3A4 Substrates

Number of Samples = 566

Number of Clusters = 135

No "All QT" clusters except for those having only one sample were found. Cluster 1 contained slightly more than ½ QT samples. Cluster 2 contained slightly less than ½ QT samples. Cluster 3 contained approximately 1/3 QT samples. Cluster 5 contained all but one QT sample. Cluster 8 contained slightly less than 1/3 QT samples. Cluster 9 contained approximately 1/3 QT samples. Cluster 88 contained approximately ¼ QT samples. Cluster 107 contained approximately ¼ QT samples. Cluster 116 contained approximately ¼ QT samples. Cluster 119 contained approximately 1/3 QT samples.

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates

Cluster 1 Exemplar: amiodarone_147mg3d_fc	
Sample	Label
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
naloxone_76mg3d_fc	1
simvastatin_15mg1d_fc	1
terbinafine_2g1d_fc	1
Cluster 2 Exemplar: azithromycin_225mg1d_fc	
Sample	Label
azithromycin_50mg1d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg6h_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg6h_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clomipramine_115mg5d_fc	0
fluoxetine_52mg3d_fc	0
itraconazole_1093mg1d_fc	0

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Sample	Label
itraconazole_1093mg3d_fc	0
ketoconazole_25mg1d_fc	0
amlodipine_200ug6h_fc	1
cholecalciferol_8mg5d_fc	1
cyclosporin_350mg5d_fc	1
daunorubicin_3_25mg1d_fc	1
daunorubicin_3_25mg5d_fc	1
ergocalciferol_15mg3d_fc	1
ergocalciferol_15mg5d_fc	1
etoposide_100mg5d_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg5d_fc	1
meloxicam_33mg5d_fc	1
meloxicam_600ug5d_fc	1
nevirapine_29mg6h_fc	1
nisoldipine_15mg5d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg3d_fc	1
perhexiline_325mg1d_fc	1
perhexiline_325mg3d_fc	1
perhexiline_325mg5d_fc	1
raloxifene_650mg5de2_fc	1
vinorelbine_1500ug1d_fc	1
zomepirac_11mg6h_fc	1
Cluster 3	
Exemplar: clomipramine_115mg1d_fc	
Sample	Label
amiodarone_147mg1d_fc	0
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg6h_fc	0
citalopram_40mg5d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg5d_fc	0
clarithromycin_56mg1d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg5d_fc	0
ketoconazole_2274mg6h_fc	0
primaquine_45mg1d_fc	0
primaquine_45mg3d_fc	0
primaquine_45mg5d_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
roxithromycin_312mg5d_fc	0
tamoxifen_32mg5d_fc	0
venlafaxine_320mg1d_fc	0
albendazole_62mg6h_fc	1

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Sample	Label
alprazolam_115mg3d_fc	1
amlodipine_19mg6h_fc	1
amlodipine_200ug1d_fc	1
bupropion_895mg5d_fc	1
busulfan_9mg5d_fc	1
chlorzoxazone_763mg3d_fc	1
cholecalciferol_8mg3d_fc	1
etoposide_100mg3d_fc	1
famciclovir_112mg5d_fc	1
hydrocortisone_56mg3d_fc	1
ifosfamide_143mg1d_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg5d_fc	1
ivermectin_7500ug1d_fc	1
ivermectin_7500ug3d_fc	1
ivermectin_7500ug5d_fc	1
lansoprazole_600mg3d_fc	1
metronidazole_50mg6h_fc	1
modafinil_325mg5d_fc	1
modafinil_17500ug5d_fc	1
naloxone_76mg1d_fc	1
nevirapine_29mg5d_fc	1
nevirapine_200mg5d_fc	1
nisoldipine_15mg1d_fc	1
omeprazole_30mg5d_fc	1
pergolide_1100ug1d_fc	1
pergolide_1100ug5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
pyrazinamide_1500mg1d_fc	1
pyrazinamide_1500mg3d_fc	1
pyrazinamide_1500mg5d_fc	1
raloxifene_6500ug3d_fc	1
sildenafil_300mg6h_fc	1
sulfadiazine_1170mg1d_fc	1
sulfadiazine_1170mg3d_fc	1
sulfadiazine_1170mg5d_fc	1
tetracycline_1500mg5d_fc	1
tretinoin_7mg1d_fc	1
tretinoin_7mg3d_fc	1
tretinoin_7mg5d_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug5d_fc	1
Cluster 5 **Exemplar: ketoconazole_114mg3d_fc**	
Sample	Label
itraconazole_1093mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
dexamethasone_150mg1d_fc	1

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Cluster 8	
Exemplar: pantoprazole_1100mg3d_fc	
Sample	**Label**
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
diazepam_710mg3d_fc	1
diazepam_710mg5d_fc	1
omeprazole_415mg3d_fc	1
rabeprazole_1024mg1d_fc	1
rabeprazole_1024mg3d_fc	1
Cluster 9	
Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
citalopram_90mg3d_fc	0
erythromycin_1500mg5d_fc	0
granisetron_175mg6h_fc	0
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
ketoconazole_25mg5d_fc	0
sertraline_210mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug5d_fc	1
busulfan_3mg5d_fc	1
diclofenac_10mg3d_fc	1
doxorubicin_3mg3d_fc	1
etoposide_100mg6h_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
glipizide_2500mg5d_fc	1
ifosfamide_17mg3d_fc	1
ifosfamide_17mg6h_fc	1
ifosfamide_143mg3d_fc	1
meloxicam_33mg3d_fc	1
miconazole_200mg5d_fc	1
mifepristone_300mg6h_fc	1
modafinil_17500ug3d_fc	1
nevirapine_29mg3d_fc	1
nevirapine_200mg3d_fc	1
nisoldipine_15mg6h_fc	1
omeprazole_30mg3d_fc	1
omeprazole_415mg5d_fc	1
progesterone_11300ug5d_fc	1
rofecoxib_3mg5d_fc	1
rofecoxib_775mg3d_fc	1
rofecoxib_775mg5d_fc	1
sildenafil_420mg1d_fc	1
sildenafil_420mg5d_fc	1
sildenafil_2500ug6h_fc	1

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Cluster 88	
Exemplar: letrozole_250mg1d_fc	
Sample	**Label**
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
albendazole_62mg1d_fc	1
albendazole_62mg5d_fc	1
clonazepam_2500mg1d_fc	1
clonazepam_2500mg6h_fc	1
glipizide_2500mg1d_fc	1
glipizide_2500mg3d_fc	1
lansoprazole_600mg5d_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg5d_fc	1
mebendazole_50mg6h_fc	1
mebendazole_714mg1d_fc	1
metronidazole_50mg1d_fc	1
metronidazole_1500mg1d_fc	1
nisoldipine_15mg3d_fc	1
nisoldipine_1125mg1d_fc	1
phenacetin_619mg3d_fc	1
prednisolone_184mg5d_fc	1
progesterone_164mg3d_fc	1
zaleplon_100mg3d_fc	1
zaleplon_100mg5d_fc	1
zidovudine_1540mg1d_fc	1
zidovudine_1540mg5d_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg6h_fc	1
Cluster 107	
Exemplar: omeprazole_30mg6h_fc	
Sample	**Label**
citalopram_40mg6h_fc	0
citalopram_90mg6h_fc	0
ketoconazole_25mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_64mg6h_fc	0
acetaminophen_100mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug6h_fc	1
busulfan_3mg6h_fc	1
busulfan_9mg6h_fc	1
busulfan_36mg6h_fc	1
cerivastatin_50ug6h_fc	1
cyclosporin_70mg6h_fc	1
etoposide_188mg6h_fc	1

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Sample	Label
lansoprazole_600mg1d_fc	1
lovastatin_450mg6h_fc	1
meloxicam_33mg6h_fc	1
meloxicam_600ug6h_fc	1
modafinil_17500ug6h_fc	1
nevirapine_200mg6h_fc	1
omeprazole_30mg6h_fc	1
omeprazole_415mg6h_fc	1
pioglitazone_3mg6h_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug6h_fc	1
raloxifene_650mg6h_fc	1
rofecoxib_3mg6h_fc	1
rofecoxib_775mg6h_fc	1
sildenafil_420mg6h_fc	1
simvastatin_1200mg6h_fc	1
zidovudine_1540mg6h_fc	1
Cluster 116	
Exemplar: sildenafil_300mg3d_fc	
Sample	Label
chlorpromazine_73mg1d_fc	0
ketoconazole_2274mg3d_fc	0
quetiapine_500mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
acetaminophen_100mg1d_fc	1
busulfan_3mg1d_fc	1
busulfan_9mg1d_fc	1
carvedilol_2g1d_fc	1
cerivastatin_50ug1d_fc	1
diazepam_710mg1d_fc	1
digoxin_260ug1d_fc	1
etoposide_188mg5d_fc	1
fluvastatin_5mg1d_fc	1
fluvastatin_5mg6h_fc	1
meloxicam_600ug1d_fc	1
nitrazepam_310mg5d_fc	1
norethindrone_80ug6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
rifabutin_1500mg1d_fc	1
rofecoxib_250mg1d_fc	1
rofecoxib_800mg1d_fc	1
sildenafil_300mg3d_fc	1
simvastatin_15mg6h_fc	1
tetracycline_1500mg3d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_1200mg3d_fc	1

Table CXXIII: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A4 Substrates (Continued)

Cluster 119	
Exemplar: sildenafil_14600ug1d_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_225mg5d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_73mg5d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
clarithromycin_476mg5d_fc	0
itraconazole_1093mg5d_fc	0
acetaminophen_100mg5d_fc	1
busulfan_36mg1d_fc	1
diclofenac_3_5mg1d_fc	1
diclofenac_3_5mg5d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg1d_fc	1
digoxin_11mg1d_fc	1
digoxin_11mg3d_fc	1
digoxin_11mg6h_fc	1
digoxin_260ug6h_fc	1
disulfiram_100mg6h_fc	1
famciclovir_112mg1d_fc	1
famciclovir_112mg3d_fc	1
famciclovir_1200mg1d_fc	1
famciclovir_1200mg3d_fc	1
finasteride_25mg3d_fc	1
fluvastatin_94mg6h_fc	1
mifepristone_3mg6h_fc	1
modafinil_17500ug1d_fc	1
nevirapine_29mg1d_fc	1
nisoldipine_1125mg3d_fc	1
raloxifene_6500ug5d_fc	1
rofecoxib_3mg3d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug3d_fc	1
sildenafil_14600ug5d_fc	1

Cytochrome P-450 CYP3A Inducers

Number of Samples = 214

Number of Clusters = 49

No "All QT" clusters were found. Cluster 1 contained slightly less than ½ QT samples.

Table CXXIV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inducers

Cluster 1	
Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
ifosfamide_143mg5d_fc	1
ifosfamide_143mg6h_fc	1
modafinil_325mg1d_fc	1
modafinil_325mg6h_fc	1
modafinil_17500ug1d_fc	1
modafinil_17500ug6h_fc	1
nevirapine_29mg1d_fc	1
nevirapine_29mg6h_fc	1
nevirapine_200mg6h_fc	1
omeprazole_30mg1d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1

Table CXXIV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inducers (Continued)

Sample	Label
omeprazole_30mg6h_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
omeprazole_415mg6h_fc	1
pioglitazone_1500mg5d_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug6h_fc	1
rofecoxib_3mg1d_fc	1
rofecoxib_3mg3d_fc	1
rofecoxib_3mg6h_fc	1
terbinafine_2g1d_fc	1

Cytochrome P-450 CYP3A Inhibitors

Number of Samples = 403

Number of Clusters = 87

No "All QT" clusters were found except for one cluster containing only one sample. Cluster 1 contained

approximately ½ QT samples. Cluster 5 contained 2 out of 3 QT samples. Cluster 6 contained slightly less

than ½ QT samples. Cluster 26 contained 2 out of 5 QT samples. Cluster 30 contained approximately 1/3

QT samples. Cluster 53 contained approximately ¼ QT samples.

Table CXXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors

Cluster 1 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg5d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg5d_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg5d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
itraconazole_1093mg1d_fc	0
primaquine_45mg1d_fc	0
primaquine_45mg3d_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
roxithromycin_312mg5d_fc	0
clomiphene_250mg1d_fc	1
clotrimazole_52mg6h_fc	1
daunorubicin_3_25mg1d_fc	1
etoposide_188mg3d_fc	1
hydrocortisone_56mg1d_fc	1
ifosfamide_17mg1d_fc	1

Table CXXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors (Continued)

Sample	Label
ifosfamide_17mg5d_fc	1
imatinib_150mg1d_fc	1
isoniazid_50mg1d_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg3d_fc	1
lomustine_8750ug3d_fc	1
miconazole_920mg6h_fc	1
modafinil_17500ug5d_fc	1
modafinil_17500ug6h_fc	1
nevirapine_29mg1d_fc	1
nevirapine_29mg6h_fc	1
nisoldipine_15mg5d_fc	1
nisoldipine_15mg6h_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug5d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug6h_fc	1
valproicAcid_235mg5d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg3d_fc	1
valproicAcid_1340mg6h_fc	1
vinblastine_300ug1d_fc	1
vinorelbine_1500ug1d_fc	1
vinorelbine_1500ug3d_fc	1
Cluster 5	
Exemplar: sertraline_210mg5d_fc	
Sample	Label
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
cerivastatin_50ug1d_fc	1
Cluster 6	
Exemplar: venlafaxine_320mg5d_fc	
Sample	Label
amiodarone_147mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg5d_fc	0
acetaminophen_100mg5d_fc	1
acetazolamide_47mg6h_fc	1

Table CXXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors (Continued)

Sample	Label
capsaicin_35mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
dexamethasone_1mg1d_fc	1
dexamethasone_1mg3d_fc	1
dexamethasone_1mg5d_fc	1
etoposide_100mg3d_fc	1
hydrocortisone_56mg5d_fc	1
ifosfamide_17mg6h_fc	1
mifepristone_3mg6h_fc	1
nevirapine_29mg5d_fc	1
nisoldipine_15mg1d_fc	1
nisoldipine_15mg3d_fc	1
nisoldipine_1125mg3d_fc	1
nisoldipine_1125mg5d_fc	1
nisoldipine_1125mg6h_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg3d_fc.1	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug5d_fc	1
valproicAcid_850mg5d_fc	1
Cluster 26 **Exemplar: dexamethasone_150mg6h_fc**	
Sample	Label
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
dexamethasone_150mg1d_fc	1
dexamethasone_150mg6h_fc	1
olanzapine_23mg5d_fc	1
Cluster 30 **Exemplar: doxorubicin_650ug3d_fc**	
Sample	Label
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
azithromycin_50mg1d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg6h_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg6h_fc	0
erythromycin_1500mg1d_fc	0
fluconazole_394mg6h_fc	0
tamoxifen_32mg1d_fc	0
acetazolamide_250mg6h_fc	1
atorvastatin_2500ug6h_fc	1
cerivastatin_50ug6h_fc	1
clomiphene_250mg5d_fc	1
clotrimazole_89mg6h_fc	1

Table CXXV: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 CYP3A Inhibitors (Continued)

Sample	Label
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug3d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
etoposide_100mg6h_fc	1
ifosfamide_143mg3d_fc	1
ifosfamide_143mg5d_fc	1
ifosfamide_143mg6h_fc	1
isoniazid_79mg5d_fc	1
raloxifene_650mg5de2_fc	1
valproicAcid_850mg3d_fc	1
valproicAcid_850mg6h_fc	1
Cluster 53	
Exemplar: lomustine_8750ug6h_fc	
Sample	Label
ciprofloxacin_450mg3d_fc	0
clarithromycin_56mg6h_fc	0
fluconazole_10mg6h_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_25mg6h_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_64mg6h_fc	0
acetaminophen_100mg6h_fc	1
atorvastatin_2500ug1d_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg5d_fc	1
dexamethasone_1mg6h_fc	1
econazole_334mg6h_fc	1
etoposide_188mg6h_fc	1
lansoprazole_600mg3d_fc	1
lomustine_4200ug3d_fc	1
lomustine_4200ug6h_fc	1
lomustine_8750ug6h_fc	1
nevirapine_200mg6h_fc	1
omeprazole_30mg6h_fc	1
omeprazole_415mg6h_fc	1
omeprazole_30mg6h_fc.1	1
omeprazole_415mg6h_fc.1	1
progesterone_11300ug6h_fc	1
raloxifene_650mg6h_fc	1
sildenafil_420mg6h_fc	1

Cytochrome P-450 Enzyme Inhibitors

Number of Samples = 97

Number of Clusters = 16

Cluster 1 contained all but 1 QT sample. Clusters 5 and 6 were "All QT" samples. Cluster 7 contained all

but 1 QT sample. Cluster 9 contained approximately ¼ QT samples. Cluster 13 contained slightly more

than ¼ QT samples.

Table CXXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 Enzyme Inhibitors

Cluster 1 Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg1d_fc	0
fluconazole_10mg6h_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
bupropion_895mg1d_fc	1
Cluster 5 Exemplar: itraconazole_30mg3d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0

Table CXXVI: Representative Clusters using Drugs Classified in DrugBank as Cytochrome P-450 Enzyme Inhibitors (Continued)

Sample	Label
Cluster 6 **Exemplar: itraconazole_30mg6h_fc**	
Sample	**Label**
fluconazole_394mg6h_fc	0
itraconazole_30mg6h_fc	0
Cluster 7 **Exemplar: itraconazole_1093mg5d_fc**	
Sample	**Label**
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_114mg5d_fc	0
enoxacin_100mg3d_fc	1
Cluster 9 **Exemplar: ketoconazole_25mg3d_fc**	
Sample	**Label**
fluconazole_394mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_2274mg6h_fc	0
clotrimazole_89mg1d_fc	1
econazole_43mg1d_fc	1
econazole_43mg3d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg1d_fc	1
enoxacin_750mg1d_fc	1
enoxacin_750mg3d_fc	1
enoxacin_750mg5d_fc	1
gemfibrozil_100mg1d_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
Cluster 13 **Exemplar: clotrimazole_52mg6h_fc**	
Sample	**Label**
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
bupropion_895mg5d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg6h_fc	1
clotrimazole_178mg6h_fc	1
econazole_334mg6h_fc	1
enoxacin_100mg1d_fc	1
enoxacin_100mg5d_fc	1
enoxacin_100mg6h_fc	1
enoxacin_750mg6h_fc	1
gemfibrozil_100mg6h_fc	1
gemfibrozil_700mg6h_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1

Dermatologicals
Number of Samples = 130

Number of Clusters = 21

No "All QT" clusters were found. Cluster 2 contained slightly less than ½ QT samples. Cluster 3

contained approximately 2/3 QT samples.

Table CXXVII: Representative Clusters using Drugs Classified in DrugBank as Dermatologicals

Cluster 2 Exemplar: ketoconazole_25mg6h_fc	
Sample	**Label**
fluconazole_394mg1d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
ketoconazole_2274mg6h_fc	0
clotrimazole_52mg1d_fc	1
clotrimazole_52mg3d_fc	1
dexamethasone_1mg6h_fc	1
diclofenac_10mg1d_fc	1
diclofenac_10mg3d_fc	1
diclofenac_10mg5d_fc	1
econazole_43mg1d_fc	1
finasteride_25mg6h_fc	1
finasteride_800mg5d_fc	1
hydrocortisone_56mg3d_fc	1
Cluster 3 Exemplar: promethazine_113mg5d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg5d_fc	0
fluconazole_394mg6h_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0

Table CXXVII: Representative Clusters using Drugs Classified in DrugBank as Dermatologicals (Continued)

Sample	Label
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
clotrimazole_89mg6h_fc	1
clotrimazole_178mg1d_fc	1
dexamethasone_150mg1d_fc	1
dexamethasone_150mg6h_fc	1
sulconazole_1200mg1d_fc	1

APPENDIX B (continued)

Drugs for Acid Related Disorders

Number of Samples = 38

Number of Clusters = 8

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was comprised of ½

QT samples.

Table CXXVIII: Representative Clusters using Drugs Classified in DrugBank as Drugs for Acid Related Disorders

Cluster 1 Exemplar: clarithromycin_56mg3d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
tetracycline_1500mg1d_fc	1
Cluster 2 Exemplar: pantoprazole_1100mg5d_fc	
Sample	**Label**
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
omeprazole_415mg5d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1

Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

Number of Samples = 38

Number of Clusters = 8

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was comprised of ½

QT samples.

Table CXXIX: Representative Clusters using Drugs Classified in DrugBank as Drugs for Peptic Ulcer and Gastro-Oesophageal Reflux Disease (GORD)

Cluster 1 Exemplar: clarithromycin_56mg3d_fc	
Sample	**Label**
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
tetracycline_1500mg1d_fc	1
Cluster 2 **Exemplar: pantoprazole_1100mg5d_fc**	
Sample	**Label**
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
omeprazole_415mg5d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1

Enzyme Inhibitors

Number of Samples = 399

Number of Clusters = 83

Cluster 1 was comprised of approximately 1/3 QT samples. Cluster 2 was comprised of approximately 2/3 QT samples. Cluster 3 was comprised of approximately 2/3 QT samples. Cluster 4 was comprised of approximately 1/10 QT samples. Cluster 5 was an "All QT" cluster. Cluster 6 contained 2 out of 3 QT samples.

Table CXXX: Representative Clusters using Drugs Classified in DrugBank as Enzyme Inhibitors

| Cluster 1 | |
| Exemplar: amiodarone_147mg1d_fc | |
Sample	Label
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
clarithromycin_476mg3d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
erythromycin_1500mg5d_fc	0
fluconazole_10mg6h_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
ketoconazole_114mg5d_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
aspirin_375mg6h_fc	1
bupropion_895mg5d_fc	1
cerivastatin_50ug6h_fc	1
clotrimazole_89mg5d_fc	1
clotrimazole_89mg6h_fc	1
cyclosporin_350mg3d_fc	1
daunorubicin_3_25mg1d_fc	1
dipyridamole_750mg1d_fc	1
dipyridamole_750mg5d_fc	1
disulfiram_500mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1

Table CXXX: Representative Clusters using Drugs Classified in DrugBank as Enzyme Inhibitors (Continued)

Sample	Label
econazole_334mg5d_fc	1
epirubicin_2700ug1d_fc	1
etoposide_100mg6h_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg6h_fc	1
finasteride_800mg5d_fc	1
gemfibrozil_100mg6h_fc	1
genistein_20mg3d_fc	1
genistein_20mg6h_fc	1
genistein_375mg1d_fc	1
genistein_375mg3d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
lamivudine_35mg1d_fc	1
lamivudine_1300mg1d_fc	1
lansoprazole_600mg1d_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
lomefloxacin_2g5d_fc	1
mefenamicAcid_93mg6h_fc	1
meloxicam_33mg6h_fc	1
methotrexate_27mg1d_fc	1
methotrexate_300ug1d_fc	1
miconazole_920mg6h_fc	1
mitomycinC_500ug3d_fc	1
mitomycinC_1700ug1d_fc	1
mitomycinC_1700ug3d_fc	1
neostigmine_11mg6h_fc	1
nevirapine_29mg6h_fc	1
omeprazole_30mg6h_fc	1
sildenafil_420mg1d_fc	1
sildenafil_2500ug1d_fc	1
sulindac_23mg5d_fc	1
tacrine_24mg1d_fc	1
tacrine_24mg3d_fc	1
tacrine_24mg5d_fc	1
terbinafine_2g1d_fc	1
terbinafine_2g5d_fc	1
tetracycline_1500mg5d_fc	1
Cluster 2	
Exemplar: clarithromycin_56mg1d_fc	
Sample	Label
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0

Table CXXX: Representative Clusters using Drugs Classified in DrugBank as Enzyme Inhibitors (Continued)

Sample	Label
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
diclofenac_10mg6h_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
omeprazole_415mg6h_fc	1

Cluster 3
Exemplar: fluconazole_10mg5d_fc

Sample	Label
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_30mg3d_fc	0
itraconazole_30mg6h_fc	0
itraconazole_1093mg1d_fc	0
ketoconazole_114mg3d_fc	0
atorvastatin_2500ug3d_fc	1
methotrexate_300ug3d_fc	1
naproxen_10mg5d_fc	1
naproxen_10mg6h_fc	1

Cluster 4
Exemplar: fluconazole_394mg1d_fc

Sample	Label
fluconazole_10mg1d_fc	0
fluconazole_394mg1d_fc	0
itraconazole_1093mg3d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
anastrozole_400mg1d_fc	1
anastrozole_400mg3d_fc	1
anastrozole_400mg5d_fc	1
aspirin_375mg1d_fc	1
aspirin_375mg3d_fc	1
aspirin_375mg5d_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
clotrimazole_52mg1d_fc	1
clotrimazole_52mg3d_fc	1

Table CXXX: Representative Clusters using Drugs Classified in DrugBank as Enzyme Inhibitors (Continued)

Sample	Label
clotrimazole_52mg5d_fc	1
cyclosporin_70mg6h_fc	1
daunorubicin_3_25mg3d_fc	1
econazole_43mg5d_fc	1
econazole_334mg1d_fc	1
econazole_334mg3d_fc	1
econazole_334mg6h_fc	1
enoxacin_750mg3d_fc	1
epirubicin_2700ug3d_fc	1
etodolac_24mg1d_fc	1
etoposide_188mg1d_fc	1
genistein_375mg6h_fc	1
hydroxyurea_59mg1d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug6h_fc	1
leflunomide_30mg1d_fc	1
leflunomide_30mg5d_fc	1
leflunomide_60mg3d_fc	1
letrozole_250mg3d_fc	1
letrozole_250mg5d_fc	1
lovastatin_1500mg6h_fc	1
meloxicam_600ug3d_fc	1
meloxicam_600ug6h_fc	1
methotrexate_27mg6h_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg5d_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg1d_fc	1
miconazole_920mg3d_fc	1
naproxen_10mg3d_fc	1
rabeprazole_1024mg1d_fc	1
rabeprazole_1024mg3d_fc	1
rabeprazole_1024mg5d_fc	1
rofecoxib_775mg1d_fc	1
rofecoxib_775mg6h_fc	1
sildenafil_420mg3d_fc	1
simvastatin_15mg6h_fc	1
sulindac_23mg1d_fc	1
sulindac_132mg6h_fc	1
temafloxacin_1000mg5d_fc	1
Cluster 5 **Exemplar: itraconazole_30mg1d_fc**	
Sample	Label
fluconazole_10mg3d_fc	0
fluconazole_394mg5d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_1093mg6h_fc	0

Table CXXX: Representative Clusters using Drugs Classified in DrugBank as Enzyme Inhibitors (Continued)

Cluster 6 Exemplar: ketoconazole_114mg6h_fc	
Sample	**Label**
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0
methotrexate_300ug6h_fc	1

Estrogen Antagonists

Number of Sampels = 37

Number of Clusters = 5

No "All QT" clusters were found. Cluster 1 was comprised of approximately ½ QT samples.

Table CXXXI: Representative Clusters using Drugs Classified in DrugBank as Estrogen Antagonists

Cluster 1 Exemplar: tamoxifen_32mg5d_fc	
Sample	**Label**
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
clomiphene_250mg1d_fc	1
clomiphene_250mg3d_fc	1
clomiphene_250mg5d_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg3d_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1

Fluoroquinolones

Number of Samples = 32

Number of Clusters = 3

Cluster 1 was an "All QT" cluster.

Table CXXXII: Representative Clusters using Drugs Classified in DrugBank as Fluoroquinolones

Cluster 1 Exemplar: sparfloxacin_450mg1d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0

Gastrointestinal Agents

Number of Samples = 51

Number of Clusters = 10

Cluster 1 was an "All QT" cluster. Cluster 2 was comprised of all but 2 QT samples. Cluster 7 was ½

comprised of QT samples.

Table CXXXIII: Representative Clusters using Drugs Classified in DrugBank as Gastrointestinal Agents

Cluster 1 Exemplar: chlorpromazine_18mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
promazine_100mg1d_fc	0
Cluster 2 **Exemplar: granisetron_175mg5d_fc**	
Sample	**Label**
erythromycin_1500mg5d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
dimenhydrinate_165mg1d_fc	1
olanzapine_23mg5d_fc	1
Cluster 7 **Exemplar: dimenhydrinate_165mg3d_fc**	
Sample	**Label**
chlorpromazine_73mg6h_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg5d_fc	0
diazepam_710mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1

Heterocyclic Compounds

Number of Samples = 553

Number of Clusters = 107

No "All QT" clusters were found. Cluster 2 contained 3 out of 5 QT samples. Cluster 4 was approximately 1/5 comprised of QT samples. Cluster 5 contained all but 1 QT sample. Cluster 6 was 1/3 comprised of QT samples. Cluster 10 was approximately ¼ comprised of QT samples. Cluster 16 was approximately ½ comprised of QT samples. Cluster 38 contained 4 QT samples of 53 total. Cluster 74 was approximately ¾ comprised of QT samples. Cluster 77 was approximately ¼ comprised of QT samples.

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds

Cluster 2 Exemplar: fluconazole_10mg3d_fc	
Sample	**Label**
fluconazole_10mg3d_fc	0
itraconazole_30mg6h_fc	0
ketoconazole_114mg3d_fc	0
albendazole_62mg5d_fc	1
fluvastatin_5mg6h_fc	1
Cluster 4 Exemplar: granisetron_175mg5d_fc	
Sample	**Label**
citalopram_40mg5d_fc	0
citalopram_90mg5d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
acetazolamide_250mg5d_fc	1
amlodipine_200ug5d_fc	1
enoxacin_100mg1d_fc	1
enoxacin_100mg6h_fc	1
famciclovir_112mg5d_fc	1
lamivudine_35mg6h_fc	1
letrozole_250mg6h_fc	1
lomefloxacin_2g3d_fc	1
lomefloxacin_2g5d_fc	1
mebendazole_50mg1d_fc	1
mebendazole_50mg6h_fc	1

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds (Continued)

Sample	Label
mebendazole_714mg1d_fc	1
mebendazole_714mg3d_fc	1
metronidazole_1500mg1d_fc	1
niacin_2625mg1d_fc	1
niacin_2625mg3d_fc	1
niacin_2625mg5d_fc	1
niacin_2625mg6h_fc	1
olanzapine_23mg5d_fc	1
oxymetazoline_500ug3d_fc	1
oxymetazoline_500ug5d_fc	1
troglitazone_100mg5d_fc	1
zaleplon_100mg5d_fc	1
zidovudine_1540mg1d_fc	1
zidovudine_1540mg3d_fc	1
zidovudine_1540mg6h_fc	1
zopiclone_414mg6h_fc	1

Cluster 5
Exemplar: ketoconazole_114mg1d_fc

Sample	Label
itraconazole_30mg1d_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
methotrexate_300ug3d_fc	1

Cluster 6
Exemplar: pantoprazole_1100mg3d_fc

Sample	Label
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
econazole_334mg5d_fc	1
omeprazole_415mg3d_fc	1
rabeprazole_1024mg3d_fc	1
zopiclone_414mg5d_fc	1

Cluster 10
Exemplar: amoxicillin_1100mg5d_fc

Sample	Label
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg3d_fc	0
citalopram_90mg3d_fc	0
clomipramine_115mg3d_fc	0
fluconazole_10mg5d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg5d_fc	0
amlodipine_200ug3d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
capsaicin_35mg5d_fc	1
cerivastatin_50ug6h_fc	1

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds (Continued)

Sample	Label
dimenhydrinate_165mg5d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
isoniazid_79mg1d_fc	1
isoniazid_79mg3d_fc	1
lamivudine_1300mg3d_fc	1
leflunomide_30mg5d_fc	1
melatonin_2g6h_fc	1
methotrexate_27mg1d_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg5d_fc	1
nisoldipine_15mg5d_fc	1
nitrofurantoin_76mg1d_fc	1
nitrofurantoin_76mg3d_fc	1
oxymetazoline_500ug6h_fc	1
sildenafil_14600ug5d_fc	1
tacrine_24mg1d_fc	1
tacrine_24mg3d_fc	1
tacrine_24mg5d_fc	1
vinorelbine_1500ug1d_fc	1
warfarin_250ug5d_fc	1
zomepirac_11mg3d_fc	1
zomepirac_2800ug3d_fc	1
zomepirac_2800ug5d_fc	1
Cluster 16	
Exemplar: atorvastatin_2500ug5d_fc	
Sample	Label
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg5d_fc	0
fluconazole_10mg1d_fc	0
fluconazole_394mg1d_fc	0
fluconazole_394mg6h_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
primaquine_45mg5d_fc	0
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug3d_fc	1
atorvastatin_2500ug5d_fc	1
atorvastatin_2500ug6h_fc	1
atropine_2300ug6h_fc	1
econazole_43mg5d_fc	1
econazole_334mg6h_fc	1
enoxacin_750mg1d_fc	1
indomethacin_4500ug1d_fc	1
leflunomide_60mg3d_fc	1
miconazole_200mg3d_fc	1
nevirapine_200mg3d_fc	1
omeprazole_30mg1d_fc	1
rofecoxib_3mg3d_fc	1

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds (Continued)

Sample	Label
rofecoxib_3mg6h_fc	1
Cluster 38 **Exemplar: famciclovir_1200mg6h_fc**	
Sample	**Label**
chlorpromazine_73mg3d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
clotrimazole_89mg6h_fc	1
famciclovir_112mg3d_fc	1
famciclovir_112mg6h_fc	1
famciclovir_1200mg1d_fc	1
famciclovir_1200mg3d_fc	1
famciclovir_1200mg5d_fc	1
famciclovir_1200mg6h_fc	1
fluphenazine_2500ug1d_fc	1
fluphenazine_2500ug3d_fc	1
fluphenazine_2500ug6h_fc	1
fluvastatin_94mg6h_fc	1
ifosfamide_17mg3d_fc	1
ifosfamide_17mg5d_fc	1
ifosfamide_17mg6h_fc	1
ifosfamide_143mg5d_fc	1
indomethacin_4500ug6h_fc	1
isoniazid_50mg1d_fc	1
lamivudine_35mg1d_fc	1
leflunomide_30mg6h_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug3d_fc	1
meloxicam_600ug6h_fc	1
methotrexate_27mg6h_fc	1
methotrexate_300ug1d_fc	1
miconazole_920mg6h_fc	1
mitomycinC_500ug6h_fc	1
mitomycinC_1700ug6h_fc	1
naloxone_76mg3d_fc	1
nevirapine_29mg6h_fc	1
nevirapine_200mg5d_fc	1
nisoldipine_15mg1d_fc	1
nisoldipine_15mg3d_fc	1
nisoldipine_15mg6h_fc	1
nisoldipine_1125mg3d_fc	1
nisoldipine_1125mg6h_fc	1
pentobarbital_70mg5d_fc	1
pioglitazone_3mg1d_fc	1
rosiglitazone_10mg6h_fc	1
sildenafil_300mg3d_fc	1
sildenafil_300mg6h_fc	1
sildenafil_420mg6h_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds (Continued)

Sample	Label
sildenafil_14600ug1d_fc	1
sildenafil_14600ug3d_fc	1
sildenafil_14600ug6h_fc	1
trovafloxacin_600mg1d_fc	1
vinblastine_300ug1d_fc	1
vinorelbine_1500ug3d_fc	1
Cluster 74	
Exemplar: omeprazole_30mg3d_fc	
Sample	Label
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg6h_fc	0
ketoconazole_2274mg6h_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
enoxacin_750mg6h_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg1d_fc	1
Cluster 77	
Exemplar: perhexiline_325mg3d_fc	
Sample	Label
amiodarone_147mg1d_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg6h_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_450mg1d_fc	0
clomipramine_115mg1d_fc	0
fluconazole_10mg6h_fc	0
itraconazole_1093mg1d_fc	0
primaquine_45mg1d_fc	0
promethazine_2300ug1d_fc	0
amlodipine_19mg3d_fc	1
amlodipine_19mg6h_fc	1
amlodipine_200ug1d_fc	1
amoxicillin_1100mg1d_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg3d_fc	1
dipyridamole_750mg5d_fc	1

Table CXXXIV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds (Continued)

Sample	Label
fluphenazine_22mg3d_fc	1
imatinib_150mg1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_9600ug6h_fc	1
isoniazid_50mg5d_fc	1
isoniazid_79mg5d_fc	1
lansoprazole_600mg3d_fc	1
leflunomide_30mg3d_fc	1
leflunomide_60mg6h_fc	1
metronidazole_50mg1d_fc	1
pergolide_1100ug1d_fc	1
pergolide_1100ug3d_fc	1
perhexiline_325mg1d_fc	1
perhexiline_325mg3d_fc	1
perhexiline_325mg5d_fc	1
pioglitazone_3mg6h_fc	1
rifabutin_1500mg1d_fc	1
secobarbital_70mg5d_fc	1
temafloxacin_1000mg1d_fc	1
temafloxacin_1000mg3d_fc	1
temafloxacin_1000mg5d_fc	1
troglitazone_100mg3d_fc	1
trovafloxacin_600mg3d_fc	1
trovafloxacin_600mg5d_fc	1
warfarin_250ug1d_fc	1
warfarin_250ug3d_fc	1
zomepirac_11mg6h_fc	1
zomepirac_2800ug1d_fc	1
zomepirac_2800ug6h_fc	1

Heterocyclic Compounds – 1 Ring

Number of Samples = 362

Number of Clusters = 64

Cluster 1 was ½ comprised of QT samples. Clusters 2 and 3 were "All QT" clusters. Cluster 4 was

approximately ¼ comprised of QT samples. Cluster 9 was approximately 1/3 comprised of QT samples.

Cluster 10 was approximately ¼ comprised of QT samples. Cluster 57 was approximately 1/8 comprised

of QT samples.

**Table CXXXV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds –
1 Ring**

Cluster 1 Exemplar: fluconazole_10mg5d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg6h_fc	0
atorvastatin_2500ug3d_fc	1
troglitazone_100mg1d_fc	1
Cluster 2 Exemplar: fluconazole_394mg3d_fc	
Sample	**Label**
fluconazole_394mg3d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg6h_fc	0
Cluster 3 Exemplar: fluconazole_394mg5d_fc	
Sample	**Label**
fluconazole_10mg3d_fc	0
fluconazole_394mg5d_fc	0
itraconazole_30mg1d_fc	0
Cluster 4 Exemplar: granisetron_175mg5d_fc	
Sample	**Label**
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
clotrimazole_52mg1d_fc	1
clotrimazole_89mg5d_fc	1
hydralazine_280mg1d_fc	1

Table CXXXV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds – 1 Ring (Continued)

Sample	Label
letrozole_250mg1d_fc	1
letrozole_250mg6h_fc	1
methimazole_28mg6h_fc	1
metronidazole_1500mg3d_fc	1
niacin_2625mg1d_fc	1
niacin_2625mg6h_fc	1
oxymetazoline_500ug1d_fc	1
thiabendazole_92mg3d_fc	1
zidovudine_1540mg1d_fc	1
Cluster 9 **Exemplar: pantoprazole_1100mg5d_fc**	
Sample	Label
fluconazole_10mg1d_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
amlodipine_19mg5d_fc	1
anastrozole_400mg3d_fc	1
anastrozole_400mg5d_fc	1
atorvastatin_300mg1d_fc	1
carbimazole_400mg3d_fc	1
econazole_334mg5d_fc	1
methimazole_100mg1d_fc	1
rifabutin_1500mg3d_fc	1
rosiglitazone_1800mg3d_fc	1
sulfathiazole_2629mg1d_fc	1
ticlopidine_223mg1d_fc	1
troglitazone_100mg3d_fc	1
zopiclone_414mg3d_fc	1
zopiclone_414mg5d_fc	1
Cluster 10 **Exemplar: quetiapine_500mg1d_fc**	
Sample	Label
fluconazole_10mg6h_fc	0
fluconazole_394mg1d_fc	0
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
carbimazole_400mg1d_fc	1
carbimazole_400mg5d_fc	1
clotrimazole_52mg3d_fc	1
clotrimazole_52mg5d_fc	1
econazole_334mg3d_fc	1
leflunomide_60mg3d_fc	1
miconazole_200mg5d_fc	1
miconazole_920mg1d_fc	1
pioglitazone_3mg1d_fc	1
primidone_750mg3d_fc	1
rofecoxib_3mg3d_fc	1

**Table CXXXV: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds –
1 Ring (Continued)**

Sample	Label
rosiglitazone_1800mg1d_fc	1
rosiglitazone_1800mg5d_fc	1
Cluster 57 **Exemplar: sildenafil_2500ug3d_fc**	
Sample	**Label**
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
cerivastatin_7mg3d_fc	1
dipyridamole_750mg1d_fc	1
econazole_43mg5d_fc	1
econazole_334mg6h_fc	1
genistein_20mg5d_fc	1
genistein_375mg1d_fc	1
ifosfamide_143mg3d_fc	1
isoniazid_79mg5d_fc	1
lamivudine_35mg1d_fc	1
lamivudine_1300mg1d_fc	1
leflunomide_60mg6h_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug3d_fc	1
mitomycinC_500ug3d_fc	1
mitomycinC_500ug6h_fc	1
mitomycinC_1700ug3d_fc	1
mitomycinC_1700ug6h_fc	1
nevirapine_29mg1d_fc	1
nevirapine_29mg3d_fc	1
nevirapine_29mg6h_fc	1
nisoldipine_1125mg3d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_415mg5d_fc	1
sildenafil_300mg1d_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug6h_fc	1

Heterocyclic Compounds – 2 Ring

Number of Samples = 225

Number of Clusters = 54

Cluster 2 was comprised of slightly less than ½ QT samples. Cluster 4 was comprised of slightly more

than ½ QT samples. Cluster 50 was approximately 1/7 comprised of QT samples.

Table CXXXVI: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring

Cluster 2 Exemplar: granisetron_175mg5d_fc	
Sample	**Label**
ciprofloxacin_72mg6h_fc	0
citalopram_90mg3d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
pantoprazole_1100mg5d_fc	0
primaquine_45mg1d_fc	0
albendazole_62mg1d_fc	1
albendazole_62mg6h_fc	1
alprazolam_115mg3d_fc	1
enoxacin_100mg1d_fc	1
famciclovir_112mg5d_fc	1
lomefloxacin_2g5d_fc	1
mebendazole_50mg6h_fc	1
mebendazole_714mg1d_fc	1
melatonin_2g6h_fc	1
thiabendazole_92mg3d_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg6h_fc	1
Cluster 4 Exemplar: sparfloxacin_29mg1d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
pantoprazole_1100mg1d_fc	0
pantoprazole_1100mg3d_fc	0

Table CXXXVI: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring (Continued)

Sample	Label
primaquine_45mg5d_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
atropine_2300ug1d_fc	1
enoxacin_750mg1d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_4500ug6h_fc	1
omeprazole_30mg1d_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_30mg6h_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
omeprazole_415mg6h_fc	1
ticlopidine_223mg1d_fc	1

| **Cluster 50** | |
| **Exemplar: sildenafil_14600ug1d_fc** | |
Sample	Label
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
atropine_2300ug6h_fc	1
diazepam_710mg3d_fc	1
enoxacin_100mg6h_fc	1
famciclovir_112mg1d_fc	1
famciclovir_112mg6h_fc	1
famciclovir_1200mg1d_fc	1
famciclovir_1200mg3d_fc	1
famciclovir_1200mg6h_fc	1
fluvastatin_94mg6h_fc	1
genistein_20mg5d_fc	1
genistein_375mg5d_fc	1
genistein_375mg6h_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_9600ug6h_fc	1
lansoprazole_600mg1d_fc	1
lomefloxacin_2g3d_fc	1
methotrexate_27mg6h_fc	1
mitomycinC_500ug3d_fc	1
mitomycinC_500ug6h_fc	1
mitomycinC_1700ug6h_fc	1

Table CXXXVI: Representative Clusters using Drugs Classified in DrugBank as Heterocyclic Compounds – 2 Ring (Continued)

Sample	Label
nitrazepam_310mg1d_fc	1
nitrazepam_310mg3d_fc	1
nitrazepam_310mg5d_fc	1
sildenafil_300mg1d_fc	1
sildenafil_300mg3d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_300mg6h_fc	1
sildenafil_420mg1d_fc	1
sildenafil_420mg6h_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug5d_fc	1
sildenafil_14600ug6h_fc	1
temafloxacin_1000mg1d_fc	1
temafloxacin_1000mg3d_fc	1
temafloxacin_1000mg5d_fc	1
thiabendazole_10mg6h_fc	1
thiabendazole_92mg1d_fc	1
ticlopidine_223mg5d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_100mg5d_fc	1
troglitazone_1200mg1d_fc	1
troglitazone_1200mg3d_fc	1
trovafloxacin_600mg5d_fc	1
vinblastine_300ug1d_fc	1
vinorelbine_1500ug5d_fc	1
warfarin_250ug1d_fc	1

Hormone Antagonists

Number of Samples = 117

Number of Clusters = 19

Clusters 2 and 3 were "All QT" clusters. Cluster 4 was approximately ½ comprised of QT samples.

Table CXXXVII: Representative Clusters using Drugs Classified in DrugBank as Hormone Antagonists

Cluster 2 Exemplar: itraconazole_30mg1d_fc	
Sample	**Label**
fluconazole_10mg3d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_1093mg6h_fc	0
Cluster 3 Exemplar: itraconazole_30mg3d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_30mg3d_fc	0
itraconazole_30mg6h_fc	0
itraconazole_1093mg1d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg6h_fc	0
Cluster 4 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_2274mg6h_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0

Table CXXXVII: Representative Clusters using Drugs Classified in DrugBank as Hormone Antagonists (Continued)

Sample	Label
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
clomiphene_250mg1d_fc	1
clomiphene_250mg3d_fc	1
clomiphene_250mg5d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_89mg6h_fc	1
clotrimazole_178mg6h_fc	1
econazole_43mg1d_fc	1
econazole_43mg3d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg1d_fc	1
econazole_334mg6h_fc	1
finasteride_25mg1d_fc	1
finasteride_25mg3d_fc	1
finasteride_25mg5d_fc	1
finasteride_800mg3d_fc	1
finasteride_800mg5d_fc	1
finasteride_800mg6h_fc	1
letrozole_250mg1d_fc	1
methimazole_28mg1d_fc	1
methimazole_28mg6h_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1
mifepristone_3mg1d_fc	1
mifepristone_3mg3d_fc	1
mifepristone_3mg5d_fc	1
mifepristone_3mg6h_fc	1
mifepristone_300mg6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_6500ug3d_fc	1

Hormones, Hormone Substitutes, and Hormone Antagonists

Number of Samples = 196

Number of Clusters = 32

No "All QT" clusters were found. Cluster 1 was 1/3 comprised of QT samples. Cluster 2 was

approximately ½ comprised of QT samples.

Table CXXXVIII: Representative Clusters using Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists

Cluster 1 Exemplar: itraconazole_30mg6h_fc	
Sample	**Label**
fluconazole_394mg5d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_30mg6h_fc	0
51 diethylstilbestrol_280mg1d_fc	1
diethylstilbestrol_280mg6h_fc	1
estriol_313mg1d_fc	1
norethindrone_125mg1d_fc	1
norethindrone_375mg5d_fc	1
norethindrone_375mg6h_fc	1
Cluster 2 Exemplar: ketoconazole_25mg3d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_10mg5d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg1d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg6h_fc	0

Table CXXXVIII: Representative Clusters using Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists (Continued)

Sample	Label
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
clomiphene_250mg1d_fc	1
clomiphene_250mg3d_fc	1
clomiphene_250mg5d_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_89mg6h_fc	1
clotrimazole_178mg6h_fc	1
dexamethasone_150mg1d_fc	1
dexamethasone_150mg3d_fc	1
dexamethasone_150mg6h_fc	1
diethylstilbestrol_2800ug6h_fc	1
econazole_43mg1d_fc	1
econazole_43mg3d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg1d_fc	1
econazole_334mg6h_fc	1
finasteride_25mg1d_fc	1
finasteride_25mg3d_fc	1
finasteride_25mg5d_fc	1
finasteride_800mg3d_fc	1
finasteride_800mg5d_fc	1
finasteride_800mg6h_fc	1
genistein_20mg1d_fc	1
genistein_20mg3d_fc	1
genistein_20mg5d_fc	1
genistein_20mg6h_fc	1
genistein_375mg1d_fc	1
genistein_375mg3d_fc	1
genistein_375mg5d_fc	1
genistein_375mg6h_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg3d_fc	1
hydrocortisone_56mg5d_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg3d_fc	1
melatonin_2g6h_fc	1
methimazole_28mg1d_fc	1
methimazole_28mg6h_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1

Table CXXXVIII: Representative Clusters using Drugs Classified in DrugBank as Hormones, Hormone Substitutes, and Hormone Antagonists (Continued)

Sample	Label
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1
mifepristone_3mg1d_fc	1
mifepristone_3mg3d_fc	1
mifepristone_3mg5d_fc	1
mifepristone_3mg6h_fc	1
mifepristone_300mg6h_fc	1
norethindrone_75mg1d_fc	1
norethindrone_80ug1d_fc	1
norethindrone_80ug3d_fc	1
norethindrone_80ug5d_fc	1
norethindrone_80ug6h_fc	1
oxymetholone_1170mg1d_fc	1
oxymetholone_1170mg3d_fc	1
oxymetholone_1170mg5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
progesterone_164mg1d_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug5d_fc	1
progesterone_11300ug6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de1_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de1_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_650mg6h_fc	1
raloxifene_6500ug1d_fc	1
raloxifene_6500ug3d_fc	1
raloxifene_6500ug5d_fc	1
raloxifene_6500ug6h_fc	1
testosterone_375mg1d_fc	1
testosterone_375mg3d_fc	1
testosterone_375mg5d_fc	1
zileuton_450mg6h_fc	1

Hydrocarbons

Number of Samples = 251

Number of Clusters = 48

No "All QT" clusters were found. Cluster 3 was approximately 1/7 comprised of QT samples.

Table CXXXIX: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons

Cluster 3	
Exemplar: aspirin_500mg1d_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	1
amoxicillin_1100mg1d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
artemether_74mg1d_fc	1
artemether_74mg3d_fc	1
artemether_74mg5d_fc	1
aspirin_35mg1d_fc	1
aspirin_35mg3d_fc	1
aspirin_35mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg3d_fc	1
aspirin_500mg1d_fc	1

Table CXXXIX: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons (Continued)

Sample	Label
aspirin_500mg3d_fc	1
atropine_94mg3d_fc	1
atropine_94mg6h_fc	1
atropine_2300ug1d_fc	1
atropine_2300ug3d_fc	1
atropine_2300ug5d_fc	1
atropine_2300ug6h_fc	1
benzocaine_1100mg1d_fc	1
benzocaine_1100mg3d_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
busulfan_3mg1d_fc	1
busulfan_3mg3d_fc	1
busulfan_3mg5d_fc	1
busulfan_9mg3d_fc	1
busulfan_9mg5d_fc	1
busulfan_9mg6h_fc	1
busulfan_36mg1d_fc	1
busulfan_36mg6h_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg3d_fc	1
capsaicin_35mg5d_fc	1
chlorambucil_600ug1d_fc	1
chlorambucil_600ug5d_fc	1
chlorambucil_600ug6h_fc	1
chlorambucil_4500ug1d_fc	1
chlorambucil_4500ug3d_fc	1
chlorambucil_4500ug5d_fc	1
chlorambucil_4500ug6h_fc	1
clofibrate_130mg1d_fc	1
clomiphene_250mg1d_fc	1
clomiphene_250mg5d_fc	1
daunorubicin_3_25mg1d_fc	1
daunorubicin_3_25mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
diethylstilbestrol_280mg6h_fc	1
diethylstilbestrol_2800ug6h_fc	1
dimenhydrinate_165mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
doxycycline_1g1d_fc	1
doxycycline_1g3d_fc	1
doxycycline_14mg1d_fc	1
doxycycline_14mg6h_fc	1
epirubicin_2700ug1d_fc	1

Table CXXXIX: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons (Continued)

epirubicin_2700ug3d_fc	1
etoposide_100mg1d_fc	1
etoposide_100mg3d_fc	1
etoposide_100mg5d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
gemfibrozil_100mg1d_fc	1
gemfibrozil_100mg6h_fc	1
ifosfamide_17mg1d_fc	1
ifosfamide_17mg6h_fc	1
ifosfamide_143mg6h_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
mefenamicAcid_93mg6h_fc	1
mevastatin_1200mg1d_fc	1
mevastatin_1200mg3d_fc	1
mevastatin_1200mg5d_fc	1
modafinil_325mg3d_fc	1
modafinil_325mg5d_fc	1
modafinil_325mg6h_fc	1
modafinil_17500ug3d_fc	1
modafinil_17500ug5d_fc	1
modafinil_17500ug6h_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg3d_fc	1
naloxone_76mg5d_fc	1
naproxen_10mg1d_fc	1
naproxen_10mg3d_fc	1
naproxen_10mg5d_fc	1
naproxen_10mg6h_fc	1
oxytetracycline_1500mg1d_fc	1
oxytetracycline_1500mg3d_fc	1
oxytetracycline_1500mg5d_fc	1
procarbazine_27mg5d_fc	1
procarbazine_27mg6h_fc	1
procarbazine_54mg3d_fc	1
procarbazine_54mg5d_fc	1
procarbazine_54mg6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_650mg6h_fc	1
raloxifene_6500ug3d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1

Table CXXXIX: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons (Continued)

simvastatin_15mg1d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1
sulindac_23mg1d_fc	1
sulindac_23mg5d_fc	1
terbinafine_2g1d_fc	1
tetracycline_1500mg1d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1
tretinoin_7mg1d_fc	1
tretinoin_7mg3d_fc	1
tretinoin_7mg5d_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg3d_fc	1
zopiclone_414mg5d_fc	1
zopiclone_414mg6h_fc	1

Hydrocarbons, Aromatic

Number of Samples = 193

Number of Clusters = 32

No "All QT" clusters were found. Cluster 4 was approximately 1/10 comprised of QT samples.

Table CXL: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Aromatic

Cluster 4 Exemplar: aspirin_500mg1d_fc	
Sample	**Label**
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
aspirin_35mg1d_fc	1
aspirin_35mg3d_fc	1
aspirin_35mg5d_fc	1
aspirin_35mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg3d_fc	1
aspirin_500mg1d_fc	1
aspirin_500mg3d_fc	1
benzocaine_1100mg1d_fc	1
benzocaine_1100mg3d_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg3d_fc	1
capsaicin_35mg5d_fc	1
clofibrate_130mg1d_fc	1
clomiphene_250mg1d_fc	1
clomiphene_250mg3d_fc	1
clomiphene_250mg5d_fc	1
daunorubicin_3_25mg1d_fc	1
daunorubicin_3_25mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
diethylstilbestrol_280mg6h_fc	1

Table CXL: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Aromatic (Continued)

Sample	Label
diethylstilbestrol_2800ug6h_fc	1
dimenhydrinate_165mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
doxycycline_1g1d_fc	1
doxycycline_1g3d_fc	1
doxycycline_14mg1d_fc	1
doxycycline_14mg6h_fc	1
epirubicin_2700ug1d_fc	1
epirubicin_2700ug3d_fc	1
epirubicin_2700ug5d_fc	1
etoposide_100mg1d_fc	1
etoposide_100mg3d_fc	1
etoposide_100mg5d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
gemfibrozil_100mg1d_fc	1
gemfibrozil_100mg6h_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
lovastatin_450mg1d_fc	1
lovastatin_1500mg1d_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
mefenamicAcid_93mg6h_fc	1
mevastatin_1200mg1d_fc	1
mevastatin_1200mg3d_fc	1
mevastatin_1200mg5d_fc	1
modafinil_325mg1d_fc	1
modafinil_325mg3d_fc	1
modafinil_325mg5d_fc	1
modafinil_325mg6h_fc	1
modafinil_17500ug1d_fc	1
modafinil_17500ug3d_fc	1
modafinil_17500ug5d_fc	1
modafinil_17500ug6h_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg3d_fc	1
naloxone_76mg5d_fc	1
naproxen_10mg1d_fc	1

Table CXL: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Aromatic (Continued)

Sample	Label
naproxen_10mg3d_fc	1
naproxen_10mg5d_fc	1
naproxen_10mg6h_fc	1
naproxen_134mg1d_fc	1
naproxen_134mg6h_fc	1
oxytetracycline_1500mg1d_fc	1
oxytetracycline_1500mg3d_fc	1
oxytetracycline_1500mg5d_fc	1
procarbazine_27mg5d_fc	1
procarbazine_27mg6h_fc	1
procarbazine_54mg1d_fc	1
procarbazine_54mg3d_fc	1
procarbazine_54mg5d_fc	1
procarbazine_54mg6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_650mg6h_fc	1
raloxifene_6500ug3d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
simvastatin_15mg1d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1
sulindac_23mg1d_fc	1
sulindac_23mg3d_fc	1
sulindac_23mg5d_fc	1
sulindac_64mg1d_fc	1
sulindac_64mg3d_fc	1
terbinafine_2g1d_fc	1
tetracycline_1500mg1d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1

Hydrocarbons, Cyclic

Number of Samples = 222

Number of Clusters = 39

No "All QT" clusters were found. Cluster 3 was approximately 1/6 comprised of QT samples.

Table CXLI: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Cyclic

Cluster 3 Exemplar: aspirin_500mg1d_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg5d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
amoxicillin_1100mg1d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
aspirin_35mg1d_fc	1
aspirin_35mg3d_fc	1
aspirin_35mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg3d_fc	1
aspirin_500mg1d_fc	1
aspirin_500mg3d_fc	1
atropine_94mg3d_fc	1
atropine_94mg6h_fc	1

Table CXLI: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Cyclic (Continued)

Sample	Label
atropine_2300ug1d_fc	1
atropine_2300ug3d_fc	1
atropine_2300ug5d_fc	1
atropine_2300ug6h_fc	1
benzocaine_1100mg1d_fc	1
benzocaine_1100mg3d_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg3d_fc	1
capsaicin_35mg5d_fc	1
clofibrate_130mg1d_fc	1
clomiphene_250mg1d_fc	1
clomiphene_250mg5d_fc	1
daunorubicin_3_25mg1d_fc	1
daunorubicin_3_25mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
diethylstilbestrol_280mg6h_fc	1
diethylstilbestrol_2800ug6h_fc	1
dimenhydrinate_165mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg5d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
doxycycline_1g1d_fc	1
doxycycline_1g3d_fc	1
doxycycline_14mg1d_fc	1
doxycycline_14mg6h_fc	1
epirubicin_2700ug1d_fc	1
epirubicin_2700ug3d_fc	1
etoposide_100mg1d_fc	1
etoposide_100mg3d_fc	1
etoposide_100mg5d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
etoposide_188mg6h_fc	1
gemfibrozil_100mg1d_fc	1
gemfibrozil_100mg6h_fc	1
gemfibrozil_700mg6h_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1

Table CXLI: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Cyclic (Continued)

Sample	Label
mefenamicAcid_93mg6h_fc	1
mevastatin_1200mg1d_fc	1
mevastatin_1200mg3d_fc	1
mevastatin_1200mg5d_fc	1
modafinil_325mg1d_fc	1
modafinil_325mg3d_fc	1
modafinil_325mg5d_fc	1
modafinil_325mg6h_fc	1
modafinil_17500ug1d_fc	1
modafinil_17500ug3d_fc	1
modafinil_17500ug5d_fc	1
modafinil_17500ug6h_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg3d_fc	1
naloxone_76mg5d_fc	1
naproxen_10mg1d_fc	1
naproxen_10mg3d_fc	1
naproxen_10mg5d_fc	1
naproxen_10mg6h_fc	1
oxytetracycline_1500mg1d_fc	1
oxytetracycline_1500mg3d_fc	1
oxytetracycline_1500mg5d_fc	1
procarbazine_27mg5d_fc	1
procarbazine_27mg6h_fc	1
procarbazine_54mg1d_fc	1
procarbazine_54mg3d_fc	1
procarbazine_54mg5d_fc	1
procarbazine_54mg6h_fc	1
raloxifene_650mg1de2_fc	1
raloxifene_650mg3de2_fc	1
raloxifene_650mg5de2_fc	1
raloxifene_650mg6h_fc	1
raloxifene_6500ug3d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
simvastatin_15mg1d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1
sulindac_23mg1d_fc	1
sulindac_23mg5d_fc	1
terbinafine_2g1d_fc	1
tetracycline_1500mg1d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1
tretinoin_7mg1d_fc	1
tretinoin_7mg3d_fc	1

Table CXLI: Representative Clusters using Drugs Classified in DrugBank as Hydrocarbons, Cyclic (Continued)

Sample	Label
tretinoin_7mg5d_fc	1
zopiclone_414mg1d_fc	1
zopiclone_414mg3d_fc	1
zopiclone_414mg5d_fc	1
zopiclone_414mg6h_fc	1

Hyperglycemia-Associated Agents

Number of Samples = 74

Number of Clusters = 12

No "All QT" clusters were found. Cluster 1 was approximately ¼ comprised of QT samples.

Table CXLII: Representative Clusters using Drugs Classified in DrugBank as Hyperglycemia-Associated Agents

Cluster 1 Exemplar: quetiapine_500mg1d_fc	
Sample	**Label**
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
cyproteroneAcetate_2500mg1d_fc	1
cyproteroneAcetate_2500mg3d_fc	1
cyproteroneAcetate_2500mg5d_fc	1
cyproteroneAcetate_2500mg6h_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg3d_fc	1
hydrocortisone_56mg5d_fc	1
megestrolAcetate_132mg1d_fc	1
megestrolAcetate_132mg3d_fc	1
megestrolAcetate_132mg5d_fc	1
niacin_2625mg1d_fc	1
niacin_2625mg3d_fc	1
niacin_2625mg5d_fc	1
niacin_2625mg6h_fc	1
norethindrone_75mg1d_fc	1
norethindrone_80ug1d_fc	1
norethindrone_80ug3d_fc	1
norethindrone_80ug5d_fc	1
norethindrone_80ug6h_fc	1
olanzapine_23mg5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
prednisolone_184mg5d_fc	1
progesterone_164mg1d_fc	1

Table CXLII: Representative Clusters using Drugs Classified in DrugBank as Hyperglycemia-Associated Agents (Continued)

Sample	Label
progesterone_164mg3d_fc	1
progesterone_164mg5d_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug1d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug5d_fc	1
progesterone_11300ug6h_fc	1

Hypotensive Agents

Number of Samples = 67

Number of Clusters = 10

No "All QT" clusters were found. Cluster 1 contained all but 1 QT sample. Cluster 2 was 1/3 comprised of

QT samples.

Table CXLIII: Representative Clusters using Drugs Classified in DrugBank as Hypotensive Agents

Cluster 1 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
clomipramine_115mg5d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
nisoldipine_1125mg3d_fc	1
Cluster 2 Exemplar: torsemide_3mg3d_fc	
Sample	**Label**
amiodarone_147mg1d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
chlorpromazine_18mg3d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
quetiapine_500mg1d_fc	0
sotalol_2g1d_fc	0
sotalol_2g3d_fc	0
sotalol_2g5d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg6h_fc	0
acetazolamide_47mg5d_fc	1
amlodipine_200ug1d_fc	1

Table CXLIII: Representative Clusters using Drugs Classified in DrugBank as Hypotensive Agents (Continued)

Sample	Label
amlodipine_200ug5d_fc	1
amlodipine_200ug6h_fc	1
dipyridamole_750mg5d_fc	1
thalidomide_113mg3d_fc	1
thalidomide_113mg5d_fc	1
tretinoin_7mg3d_fc	1

Imidazole Derivatives

Number of Samples = 48

Number of Clusters = 6

No "All QT" clusters were found. Cluster 1 was approximately ½ comprised of QT samples.

Table CXLIV: Representative Clusters using Drugs Classified in DrugBank as Imidazole Derivatives

Cluster 1 Exemplar: ketoconazole_114mg3d_fc	
Sample	**Label**
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
ketoconazole_2274mg6h_fc	0
clotrimazole_52mg6h_fc	1
econazole_43mg1d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg6h_fc	1
metronidazole_50mg1d_fc	1
metronidazole_50mg6h_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_920mg6h_fc	1

Inorganic Chemicals

Number of Samples = 203

Number of Clusters = 38

No "All QT" clusters were found. Cluster 1 contained all but 2 QT samples. Cluster 2 contained all but 2

QT samples. Cluster 3 was approximately 1/5 comprised of QT samples.

Table CXLV: Representative Clusters using Drugs Classified in DrugBank as Inorganic Chemicals

Cluster 1 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
quetiapine_500mg5d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
glipizide_2500mg6h_fc	1
ifosfamide_17mg6h_fc	1
Cluster 2 Exemplar: promethazine_113mg1d_fc	
Sample	**Label**
pantoprazole_1100mg5d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
quetiapine_500mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
rosiglitazone_10mg6h_fc	1
sulfaphenazole_1695mg6h_fc	1

Table CXLV: Representative Clusters using Drugs Classified in DrugBank as Inorganic Chemicals (Continued)

Cluster 3 Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
promazine_100mg1d_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
torsemide_3mg1d_fc	0
amoxicillin_1100mg1d_fc	1
busulfan_36mg6h_fc	1
celecoxib_400mg3d_fc	1
celecoxib_400mg5d_fc	1
cisplatin_2mg6h_fc	1
disulfiram_100mg6h_fc	1
disulfiram_500mg1d_fc	1
glimepiride_2500mg1d_fc	1
glimepiride_2500mg3d_fc	1
glipizide_2500mg1d_fc	1
glipizide_2500mg3d_fc	1
methimazole_28mg1d_fc	1
methimazole_28mg6h_fc	1
methimazole_100mg3d_fc	1
neostigmine_11mg6h_fc	1
neostigmine_40mg3d_fc	1
pioglitazone_3mg6h_fc	1
pioglitazone_300mg3d_fc	1
rofecoxib_1550mg3d_fc	1
rofecoxib_1550mg5d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_14600ug5d_fc	1
sulfadiazine_1170mg3d_fc	1
sulfathiazole_31mg6h_fc	1
thiabendazole_10mg1d_fc	1
thiabendazole_92mg3d_fc	1

Nervous System

Number of Samples = 171

Number of Clusters = 33

No "All QT" clusters were found. Cluster 1 was approximately 1/3 comprised of QT samples. Cluster 2

was comprised of slightly less than ½ QT samples. Cluster 24 was slightly more than 1/3 comprised of QT

samples. Cluster 28 was comprised of slightly less than 1/3 QT samples.

Table CXLVI: Representative Clusters using Drugs Classified in DrugBank as Nervous System

Cluster 1 Exemplar: chlorpromazine_18mg1d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg5d_fc	0
clomipramine_115mg3d_fc	0
clomipramine_115mg5d_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
promazine_100mg5d_fc	0
venlafaxine_320mg1d_fc	0
pergolide_1100ug1d_fc	1
secobarbital_70mg5d_fc	1
valproicAcid_235mg1d_fc	1
valproicAcid_850mg5d_fc	1
valproicAcid_1340mg1d_fc	1
zaleplon_100mg5d_fc	1
Cluster 2 Exemplar: quetiapine_500mg5d_fc	
Sample	**Label**
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
aspirin_375mg5d_fc	1

Table CXLVI: Representative Clusters using Drugs Classified in DrugBank as Nervous System (Continued)

Sample	Label
fluphenazine_22mg5d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg3d_fc	1
nitrazepam_310mg5d_fc	1
olanzapine_23mg5d_fc	1
primidone_750mg3d_fc	1
zopiclone_414mg1d_fc	1
Cluster 24	
Exemplar: neostigmine_40mg3d_fc	
Sample	**Label**
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
citalopram_90mg6h_fc	0
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
alprazolam_115mg1d_fc	1
alprazolam_115mg5d_fc	1
aspirin_35mg5d_fc	1
clonazepam_2500mg1d_fc	1
clonazepam_2500mg6h_fc	1
neostigmine_11mg1d_fc	1
neostigmine_11mg6h_fc	1
neostigmine_40mg3d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
secobarbital_70mg3d_fc	1
valproicAcid_235mg6h_fc	1
zaleplon_100mg1d_fc	1
zaleplon_100mg3d_fc	1
Cluster 28	
Exemplar: salicylicAcid_223mg3d_fc	
Sample	**Label**
chlorpromazine_73mg6h_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg6h_fc	0
acetaminophen_100mg5d_fc	1
bupropion_895mg1d_fc	1
disulfiram_100mg6h_fc	1
fluphenazine_22mg3d_fc	1
pentobarbital_70mg5d_fc	1
phenobarbital_54mg5d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
valproicAcid_1340mg5d_fc	1

Neurotransmitter Agents
Number of Samples = 154

Number of Clusters = 25

Cluster 1 was approximately 4/5 comprised of QT samples. Cluster 2 was 2/3 comprised of QT samples.

Cluster 3 contained all but 1 QT sample. Cluster 4 was an "All QT" cluster. Cluster 15 was approximately

1/5 comprised of QT samples. Cluster 25 was approximately ¼ comprised of QT samples.

Table CXLVII: Representative Clusters using Drugs Classified in DrugBank as Neurotransmitter Agents

Cluster 1 Exemplar: citalopram_90mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
citalopram_40mg1d_fc	0
citalopram_40mg3d_fc	0
citalopram_40mg5d_fc	0
citalopram_40mg6h_fc	0
citalopram_90mg1d_fc	0
citalopram_90mg3d_fc	0
clomipramine_115mg1d_fc	0
fluoxetine_52mg3d_fc	0
fluoxetine_52mg5d_fc	0
isoproterenol_15mg1d_fc	0
isoproterenol_15mg3d_fc	0
promethazine_113mg1d_fc	0
promethazine_2300ug1d_fc	0
sertraline_210mg1d_fc	0
alprazolam_115mg3d_fc	1
atropine_2300ug1d_fc	1
secobarbital_70mg3d_fc	1
valproicAcid_1340mg1d_fc	1
valproicAcid_1340mg6h_fc	1
Cluster 2 Exemplar: granisetron_175mg5d_fc	
Sample	**Label**
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
citalopram_90mg5d_fc	0

Table CXLVII: Representative Clusters using Drugs Classified in DrugBank as Neurotransmitter Agents (Continued)

Sample	Label
clomipramine_115mg3d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
promazine_100mg3d_fc	0
venlafaxine_320mg5d_fc	0
clonazepam_2500mg6h_fc	1
oxymetazoline_500ug3d_fc	1
oxymetazoline_500ug5d_fc	1
oxymetazoline_500ug6h_fc	1
valproicAcid_235mg6h_fc	1

Cluster 3	
Exemplar: promethazine_2300ug5d_fc	
Sample	Label
citalopram_90mg6h_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
venlafaxine_320mg3d_fc	0
pergolide_1100ug1d_fc	1

Cluster 4	
Exemplar: sotalol_2g3d_fc	
Sample	Label
clomipramine_115mg5d_fc	0
isoproterenol_15mg5d_fc	0
sotalol_2g3d_fc	0
sotalol_2g5d_fc	0

Cluster 15	
Exemplar: dimenhydrinate_165mg3d_fc	
Sample	Label
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
fluoxetine_52mg1d_fc	0
sertraline_210mg5d_fc	0
alprazolam_115mg5d_fc	1
bupropion_895mg5d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
fluphenazine_22mg5d_fc	1
fluphenazine_22mg6h_fc	1
neostigmine_11mg1d_fc	1
neostigmine_40mg1d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg3d_fc	1
nitrazepam_310mg5d_fc	1
olanzapine_23mg5d_fc	1
pergolide_1100ug3d_fc	1

Table CXLVII: Representative Clusters using Drugs Classified in DrugBank as Neurotransmitter Agents (Continued)

Sample	Label
pergolide_1100ug5d_fc	1
secobarbital_20mg6h_fc	1
valproicAcid_850mg3d_fc	1
valproicAcid_850mg5d_fc	1
Cluster 25 **Exemplar: zaleplon_100mg1d_fc**	
Sample	Label
promazine_100mg1d_fc	0
promazine_100mg5d_fc	0
venlafaxine_320mg1d_fc	0
alprazolam_115mg1d_fc	1
clonazepam_2500mg1d_fc	1
neostigmine_11mg6h_fc	1
neostigmine_40mg3d_fc	1
oxymetazoline_500ug1d_fc	1
zaleplon_100mg1d_fc	1
zaleplon_100mg3d_fc	1

Ophthalmologicals

Number of Samples = 115

Number of Clusters = 28

Cluster 1 was an "All QT" cluster. Cluster 2 was slightly more than ½ comprised of QT samples. Cluster

23 was ½ comprised of QT samples.

Table CXLVIII: Representative Clusters using Drugs Classified in DrugBank as Ophthalmologicals

Cluster 1	
Exemplar: ciprofloxacin_72mg5d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
Cluster 2	
Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
azithromycin_50mg6h_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg1d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
erythromycin_1500mg5d_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
diclofenac_10mg6h_fc	1
famciclovir_112mg1d_fc	1
famciclovir_1200mg6h_fc	1
indomethacin_5mg1d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
tetracycline_1500mg3d_fc	1
tetracycline_1500mg5d_fc	1
Cluster 23	
Exemplar: indomethacin_4500ug5d_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0

Table CXLVIII: Representative Clusters using Drugs Classified in DrugBank as Ophthalmologicals (Continued)

Sample	Label
azithromycin_225mg6h_fc	0
cyclosporin_70mg6h_fc	1
cyclosporin_350mg5d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug5d_fc	1
indomethacin_4500ug6h_fc	1

Peripheral Nervous System Agents

Number of Samples = 187

Number of Clusters = 48

No "All QT" clusters were found. Cluster 1 contained 2 QT samples of 5 total samples. Cluster 2 was

approximately 1/8 comprised of QT samples. Cluster 29 was approximately 1/3 comprised of QT

samples.

Table CXLIX: Representative Clusters using Drugs Classified in DrugBank as Peripheral Nervous System Agents

Cluster 1	
Exemplar: isoproterenol_15mg5d_fc	
Sample	**Label**
isoproterenol_15mg1d_fc	0
isoproterenol_15mg5d_fc	0
indomethacin_4500ug5d_fc	1
oxymetazoline_500ug1d_fc	1
rofecoxib_1550mg5d_fc	1
Cluster 2	
Exemplar: aspirin_167mg3d_fc	
Sample	**Label**
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
isoproterenol_15mg3d_fc	0
sotalol_2g1d_fc	0
acetaminophen_100mg1d_fc	1
acetaminophen_100mg5d_fc	1
acetaminophen_100mg6h_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg1d_fc	1
aspirin_375mg3d_fc	1
aspirin_375mg6h_fc	1
aspirin_500mg1d_fc	1
aspirin_500mg3d_fc	1
atropine_2300ug1d_fc	1
atropine_2300ug6h_fc	1
capsaicin_35mg1d_fc	1
capsaicin_35mg3d_fc	1

Table CXLIX: Representative Clusters using Drugs Classified in DrugBank as Peripheral Nervous System Agents (Continued)

Sample	Label
capsaicin_35mg5d_fc	1
carbamazepine_490mg1d_fc	1
celecoxib_400mg1d_fc	1
celecoxib_400mg3d_fc	1
chlorzoxazone_763mg1d_fc	1
chlorzoxazone_763mg3d_fc	1
diazepam_710mg1d_fc	1
diclofenac_3_5mg1d_fc	1
diclofenac_3_5mg5d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg1d_fc	1
diclofenac_10mg6h_fc	1
dimenhydrinate_165mg1d_fc	1
dimenhydrinate_165mg3d_fc	1
dimenhydrinate_165mg5d_fc	1
etodolac_24mg1d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug6h_fc	1
indomethacin_9600ug6h_fc	1
meloxicam_33mg5d_fc	1
meloxicam_600ug1d_fc	1
meloxicam_600ug3d_fc	1
meloxicam_600ug5d_fc	1
meloxicam_600ug6h_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg5d_fc	1
naproxen_10mg3d_fc	1
naproxen_10mg5d_fc	1
neostigmine_40mg5d_fc	1
rofecoxib_3mg3d_fc	1
rofecoxib_3mg5d_fc	1
rofecoxib_3mg6h_fc	1
rofecoxib_1550mg1d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
sulindac_23mg1d_fc	1
sulindac_23mg5d_fc	1
sulindac_23mg6h_fc	1
sulindac_64mg6h_fc	1
tacrine_24mg1d_fc	1
tacrine_24mg3d_fc	1
tacrine_24mg5d_fc	1
zileuton_450mg5d_fc	1
zileuton_450mg6h_fc	1
zomepirac_11mg3d_fc	1
zomepirac_11mg6h_fc	1
zomepirac_2800ug1d_fc	1
zomepirac_2800ug6h_fc	1

Table CXLIX: Representative Clusters using Drugs Classified in DrugBank as Peripheral Nervous System Agents (Continued)

Cluster 29 Exemplar: mefenamicAcid_93mg5d_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
amantadine_220mg3d_fc	0
chlorpromazine_18mg1d_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
benzocaine_1100mg1d_fc	1
benzocaine_1100mg3d_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
mefenamicAcid_93mg1d_fc	1
mefenamicAcid_93mg3d_fc	1
mefenamicAcid_93mg5d_fc	1
mefenamicAcid_93mg6h_fc	1
neostigmine_11mg1d_fc	1
neostigmine_11mg6h_fc	1
neostigmine_40mg1d_fc	1
neostigmine_40mg3d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
olanzapine_23mg5d_fc	1
oxymetazoline_500ug3d_fc	1
oxymetazoline_500ug5d_fc	1
oxymetazoline_500ug6h_fc	1
phenacetin_619mg1d_fc	1
phenacetin_619mg3d_fc	1
phenacetin_619mg5d_fc	1
phenacetin_619mg6h_fc	1

P-Glycoprotein/ABCB1 Inducers

Number of Samples = 86

Number of Clusters = 16

No "All QT" clusters were found. Cluster 1 was slightly more than 1/3 comprised of QT samples.

Table CL: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inducers

Cluster 1	
Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
phenacetin_619mg6h_fc	1
procarbazine_27mg5d_fc	1
procarbazine_54mg5d_fc	1
sildenafil_300mg5d_fc	1
sildenafil_420mg5d_fc	1
sildenafil_14600ug5d_fc	1
sulfaphenazole_1695mg6h_fc	1
sulfathiazole_31mg6h_fc	1
tocainide_67mg1d_fc	1
tocainide_67mg3d_fc	1
tocainide_67mg5d_fc	1
tocainide_67mg6h_fc	1
tocainide_224mg1d_fc	1
tocainide_224mg3d_fc	1
tocainide_224mg5d_fc	1
tocainide_224mg6h_fc	1
zaleplon_100mg1d_fc	1
zaleplon_100mg3d_fc	1
zaleplon_100mg5d_fc	1

P-Glycoprotein/ABCB1 Inhibitors

Number of Samples = 338

Number of Clusters = 69

No "All QT" clusters were found. Cluster 2 was approximately 2/3 comprised of QT samples. Cluster 3 contained 2 QT samples of 3 total. Cluster 5 was approximately 4/5 comprised of QT samples. Cluster 6 was slightly more than ½ comprised of QT samples. Cluster 8 contained 5 QT samples out of 7 total. Cluster 12 contained 3 QT samples of 4 total. Cluster 14 was slightly less than 1/3 comprised of QT samples. Cluster 37 was approximately 1/6 comprised of QT samples. Cluster 38 was 1/3 comprised of QT samples. Cluster 47 was slightly more than ½ comprised of QT samples. Cluster 56 was slightly more than ¼ comprised of QT samples. Cluster 64 was slightly less than 1/3 comprised of QT samples.

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors

Cluster 2 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
azithromycin_50mg1d_fc	0
azithromycin_50mg3d_fc	0
azithromycin_50mg6h_fc	0
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
fluconazole_10mg5d_fc	0
fluconazole_10mg6h_fc	0
fluoxetine_52mg1d_fc	0
fluoxetine_52mg3d_fc	0
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg5d_fc	0
atorvastatin_2500ug3d_fc	1
dexamethasone_1mg1d_fc	1
doxorubicin_650ug5d_fc	1
hydrocortisone_56mg3d_fc	1

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors (Continued)

Sample	Label
miconazole_920mg6h_fc	1
nisoldipine_15mg5d_fc	1
simvastatin_15mg1d_fc	1
vinorelbine_1500ug1d_fc	1
Cluster 3 **Exemplar: ciprofloxacin_72mg5d_fc**	
Sample	Label
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
omeprazole_30mg3d_fc	1
Cluster 5 **Exemplar: clarithromycin_56mg1d_fc**	
Sample	Label
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg6h_fc	0
citalopram_40mg5d_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
fluconazole_10mg1d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg5d_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug6h_fc	0
amlodipine_200ug1d_fc	1
dipyridamole_750mg5d_fc	1
omeprazole_30mg6h_fc	1
Cluster 6 **Exemplar: erythromycin_1500mg1d_fc**	
Sample	Label
amantadine_220mg3d_fc	0
amiodarone_147mg3d_fc	0
amiodarone_147mg5d_fc	0
clomipramine_115mg1d_fc	0
clomipramine_115mg3d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
erythromycin_1500mg5d_fc	0
fluoxetine_52mg5d_fc	0
sertraline_210mg5d_fc	0
tamoxifen_32mg5d_fc	0
venlafaxine_320mg3d_fc	0
amlodipine_19mg6h_fc	1
cyclosporin_350mg3d_fc	1
digoxin_11mg5d_fc	1
etoposide_100mg5d_fc	1
fluphenazine_22mg5d_fc	1
lansoprazole_600mg3d_fc	1
nitrazepam_310mg1d_fc	1

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors (Continued)

Sample	Label
tacrine_24mg5d_fc	1
Cluster 8	
Exemplar: ketoconazole_114mg1d_fc	

Sample	Label
itraconazole_30mg6h_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
dexamethasone_150mg1d_fc	1
dexamethasone_150mg6h_fc	1
Cluster 12	
Exemplar: promethazine_113mg3d_fc	

Sample	Label
promethazine_113mg3d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
digoxin_11mg6h_fc	1
Cluster 14	
Exemplar: tamoxifen_64mg3d_fc	

Sample	Label
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amiodarone_147mg1d_fc	0
azithromycin_50mg5d_fc	0
ciprofloxacin_450mg3d_fc	0
citalopram_40mg1d_fc	0
citalopram_90mg5d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
fluconazole_10mg3d_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_25mg3d_fc	0
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
venlafaxine_320mg5d_fc	0
albendazole_62mg1d_fc	1
amlodipine_19mg5d_fc	1
atorvastatin_2500ug1d_fc	1
atorvastatin_2500ug5d_fc	1
clotrimazole_52mg3d_fc	1
clotrimazole_52mg5d_fc	1
clotrimazole_89mg3d_fc	1
clotrimazole_89mg5d_fc	1
clotrimazole_89mg6h_fc	1
daunorubicin_3_25mg5d_fc	1

535

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors (Continued)

Sample	Label
diclofenac_3_5mg5d_fc	1
digoxin_260ug1d_fc	1
dipyridamole_750mg1d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_650ug1d_fc	1
etoposide_100mg3d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
genistein_375mg6h_fc	1
imatinib_150mg3d_fc	1
ivermectin_7500ug1d_fc	1
ivermectin_7500ug3d_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg5d_fc	1
miconazole_920mg1d_fc	1
mifepristone_3mg6h_fc	1
mitomycinC_500ug1d_fc	1
mitomycinC_1700ug6h_fc	1
nisoldipine_15mg1d_fc	1
nisoldipine_15mg3d_fc	1
nisoldipine_15mg6h_fc	1
nisoldipine_1125mg1d_fc	1
nisoldipine_1125mg3d_fc	1
omeprazole_30mg5d_fc	1
omeprazole_415mg1d_fc	1
omeprazole_415mg3d_fc	1
omeprazole_415mg5d_fc	1
progesterone_164mg5d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug5d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
testosterone_375mg5d_fc	1
vinblastine_300ug1d_fc	1
Cluster 37	
Exemplar: imatinib_150mg1d_fc	
Sample	Label
citalopram_40mg3d_fc	0
citalopram_90mg3d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg6h_fc	0
acetaminophen_100mg6h_fc	1
amlodipine_200ug6h_fc	1
clotrimazole_52mg6h_fc	1
clotrimazole_89mg1d_fc	1
clotrimazole_178mg6h_fc	1
daunorubicin_3_25mg1d_fc	1
diclofenac_3_5mg1d_fc	1
diclofenac_3_5mg6h_fc	1
diclofenac_10mg1d_fc	1

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors (Continued)

Sample	Label
digoxin_11mg1d_fc	1
digoxin_11mg3d_fc	1
digoxin_260ug6h_fc	1
fluphenazine_22mg3d_fc	1
imatinib_150mg1d_fc	1
imatinib_150mg5d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug6h_fc	1
megestrolAcetate_132mg1d_fc	1
miconazole_200mg6h_fc	1
mifepristone_300mg6h_fc	1
nitrazepam_310mg3d_fc	1
tacrine_24mg1d_fc	1

Cluster 38
Exemplar: indomethacin_5mg1d_fc

Sample	Label
chlorpromazine_73mg1d_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_450mg1d_fc	0
sertraline_210mg3d_fc	0
tamoxifen_32mg1d_fc	0
amlodipine_19mg1d_fc	1
benzocaine_1100mg1d_fc	1
carvedilol_2g1d_fc	1
cyclosporin_70mg1d_fc	1
cyclosporin_350mg5d_fc	1
etoposide_100mg1d_fc	1
etoposide_188mg5d_fc	1
indomethacin_5mg1d_fc	1
neostigmine_40mg5d_fc	1
nitrazepam_310mg5d_fc	1

Cluster 47
Exemplar: indomethacin_4500ug3d_fc

Sample	Label
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg6h_fc	0
chlorpromazine_18mg5d_fc	0
clomipramine_115mg5d_fc	0
fluconazole_394mg6h_fc	0
itraconazole_1093mg3d_fc	0
promethazine_113mg6h_fc	0
dexamethasone_1mg6h_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg5d_fc	1
indomethacin_4500ug3d_fc	1
megestrolAcetate_132mg3d_fc	1
megestrolAcetate_132mg5d_fc	1
tacrine_24mg3d_fc	1

Table CLI: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Inhibitors (Continued)

Cluster 56 Exemplar: mebendazole_50mg6h_fc	
Sample	**Label**
amantadine_220mg1d_fc	0
citalopram_90mg6h_fc	0
fluconazole_394mg3d_fc	0
ketoconazole_2274mg6h_fc	0
venlafaxine_320mg1d_fc	0
albendazole_62mg6h_fc	1
atorvastatin_300mg6h_fc	1
atorvastatin_2500ug6h_fc	1
benzocaine_1100mg5d_fc	1
benzocaine_1100mg6h_fc	1
diclofenac_10mg6h_fc	1
ivermectin_7500ug5d_fc	1
lovastatin_1500mg6h_fc	1
mebendazole_50mg6h_fc	1
mebendazole_714mg1d_fc	1
neostigmine_11mg1d_fc	1
neostigmine_11mg6h_fc	1
neostigmine_40mg3d_fc	1
Cluster 64 Exemplar: omeprazole_415mg6h_fc	
Sample	**Label**
citalopram_40mg6h_fc	0
clarithromycin_56mg6h_fc	0
sertraline_210mg1d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_64mg6h_fc	0
carbamazepine_490mg1d_fc	1
doxorubicin_650ug6h_fc	1
etoposide_188mg6h_fc	1
indomethacin_9600ug6h_fc	1
lansoprazole_600mg1d_fc	1
mitomycinC_500ug6h_fc	1
omeprazole_415mg6h_fc	1
progesterone_164mg6h_fc	1
progesterone_11300ug6h_fc	1
simvastatin_15mg6h_fc	1
simvastatin_1200mg6h_fc	1

P-Glycoprotein/ABCB1 Substrates

Number of Samples = 244

Number of Clusters = 62

Cluster 1 was an "All QT" cluster. Cluster 6 was approximately ¾ comprised of QT samples. Cluster 7

was slightly less than ½ comprised of QT samples. Cluster 9 was slightly more than 1/3 comprised of QT

samples. Cluster 58 was approximately 1/10 comprised of QT samples.

Table CLII: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates

Cluster 1 Exemplar: ciprofloxacin_72mg5d_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg6h_fc	0
Cluster 6 Exemplar: sparfloxacin_29mg3d_fc	
Sample	**Label**
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
citalopram_40mg3d_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg6h_fc	0
ketoconazole_2274mg6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
digoxin_260ug3d_fc	1
doxorubicin_3mg5d_fc	1
etoposide_188mg6h_fc	1
indomethacin_9600ug6h_fc	1
Cluster 7 Exemplar: tamoxifen_64mg3d_fc	
Sample	**Label**
citalopram_40mg1d_fc	0

Table CLII: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates (Continued)

Sample	Label
citalopram_40mg6h_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
tamoxifen_2_5mg1d_fc	0
tamoxifen_2_5mg3d_fc	0
tamoxifen_2_5mg6h_fc	0
tamoxifen_64mg1d_fc	0
tamoxifen_64mg3d_fc	0
tamoxifen_64mg6h_fc	0
venlafaxine_320mg1d_fc	0
cisplatin_2mg3d_fc	1
cisplatin_2mg6h_fc	1
cisplatin_1170ug3d_fc	1
cisplatin_1170ug6h_fc	1
clomiphene_250mg5d_fc	1
dexamethasone_150mg6h_fc	1
digoxin_11mg5d_fc	1
digoxin_260ug1d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg5d_fc	1
Cluster 9 **Exemplar: aspirin_167mg1d_fc**	
Sample	Label
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
ciprofloxacin_72mg6h_fc	0
citalopram_40mg5d_fc	0
citalopram_90mg3d_fc	0
citalopram_90mg5d_fc	0
citalopram_90mg6h_fc	0
clarithromycin_56mg5d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
erythromycin_1500mg5d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg1d_fc	0
tamoxifen_32mg1d_fc	0
tamoxifen_32mg3d_fc	0
tamoxifen_32mg5d_fc	0
venlafaxine_320mg3d_fc	0
venlafaxine_320mg5d_fc	0
acetaminophen_100mg1d_fc	1

Table CLII: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates (Continued)

Sample	Label
acetaminophen_100mg3d_fc	1
acetaminophen_100mg6h_fc	1
aspirin_35mg1d_fc	1
aspirin_35mg5d_fc	1
aspirin_167mg1d_fc	1
aspirin_167mg3d_fc	1
aspirin_375mg1d_fc	1
aspirin_375mg5d_fc	1
aspirin_500mg1d_fc	1
aspirin_500mg3d_fc	1
cisplatin_1170ug1d_fc	1
clomiphene_250mg1d_fc	1
cyclosporin_70mg6h_fc	1
daunorubicin_3_25mg1d_fc	1
daunorubicin_3_25mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
digoxin_260ug6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
etoposide_100mg1d_fc	1
imatinib_150mg1d_fc	1
indomethacin_5mg1d_fc	1
indomethacin_4500ug1d_fc	1
indomethacin_4500ug3d_fc	1
indomethacin_4500ug6h_fc	1
lamivudine_35mg6h_fc	1
lamivudine_1300mg3d_fc	1
methotrexate_27mg1d_fc	1
naloxone_76mg3d_fc	1
naloxone_76mg5d_fc	1
phenobarbital_54mg5d_fc	1
progesterone_11300ug5d_fc	1
salicylicAcid_223mg1d_fc	1
salicylicAcid_223mg3d_fc	1
salicylicAcid_223mg5d_fc	1
vinblastine_300ug1d_fc	1
zidovudine_1540mg6h_fc	1
Cluster 58	
Exemplar: phenobarbital_80mg5d_fc	
Sample	Label
quetiapine_500mg1d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
tamoxifen_2_5mg5d_fc	0
acetaminophen_100mg5d_fc	1
aspirin_375mg3d_fc	1
carbamazepine_490mg1d_fc	1
cerivastatin_7mg1d_fc	1
cerivastatin_7mg3d_fc	1
cerivastatin_50ug1d_fc	1

Table CLII: Representative Clusters using Drugs Classified in DrugBank as P-Glycoprotein/ABCB1 Substrates (Continued)

Sample	Label
cerivastatin_50ug6h_fc	1
cisplatin_2mg1d_fc	1
cisplatin_2mg5d_fc	1
diazepam_710mg1d_fc	1
digoxin_11mg1d_fc	1
digoxin_11mg3d_fc	1
digoxin_11mg6h_fc	1
dipyridamole_750mg1d_fc	1
dipyridamole_750mg3d_fc	1
dipyridamole_750mg5d_fc	1
hydrocortisone_56mg1d_fc	1
hydrocortisone_56mg3d_fc	1
hydrocortisone_56mg5d_fc	1
imatinib_150mg3d_fc	1
imatinib_150mg5d_fc	1
ivermectin_7500ug3d_fc	1
ivermectin_7500ug5d_fc	1
lamivudine_1300mg1d_fc	1
lansoprazole_600mg1d_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
naloxone_76mg1d_fc	1
phenobarbital_80mg1d_fc	1
phenobarbital_80mg3d_fc	1
phenobarbital_80mg5d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
prednisolone_184mg5d_fc	1
progesterone_164mg1d_fc	1
progesterone_11300ug3d_fc	1
vinblastine_300ug3d_fc	1
zidovudine_1540mg1d_fc	1

Piperazines

Number of Samples = 40

Number of Clusters = 6

Clusters 1, 2, and 3, respectively, were "All QT" clusters.

Table CLIII: Representative Clusters using Drugs Classified in DrugBank as Piperazines

Cluster 1 Exemplar: itraconazole_30mg6h_fc	
Sample	**Label**
itraconazole_30mg6h_fc	0
itraconazole_1093mg6h_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_114mg1d_fc	0
Cluster 2 Exemplar: itraconazole_1093mg1d_fc	
Sample	**Label**
itraconazole_30mg1d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_114mg6h_fc	0
ketoconazole_2274mg1d_fc	0
ketoconazole_2274mg3d_fc	0
ketoconazole_2274mg6h_fc	0
Cluster 3 Exemplar: ketoconazole_114mg3d_fc	
Sample	**Label**
itraconazole_1093mg5d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0

Polycyclic Compounds

Number of Samples = 240

Number of Clusters = 57

No "All QT" clusters were found. Cluster 1 was slightly more than 1/3 comprised of QT samples. Cluster

2 was comprised of slightly more than 1/6 of QT samples.

Table CLIV: Representative Clusters using Drugs Classified in DrugBank as Polycyclic Compounds

Cluster 1	
Exemplar: clarithromycin_56mg1d_fc	
Sample	**Label**
amantadine_58mg1d_fc	0
amantadine_58mg6h_fc	0
amantadine_220mg1d_fc	0
azithromycin_50mg1d_fc	0
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
azithromycin_225mg5d_fc	0
azithromycin_225mg6h_fc	0
clarithromycin_56mg1d_fc	0
clarithromycin_56mg3d_fc	0
clarithromycin_56mg5d_fc	0
clarithromycin_56mg6h_fc	0
clarithromycin_476mg1d_fc	0
clarithromycin_476mg3d_fc	0
clarithromycin_476mg5d_fc	0
clarithromycin_476mg6h_fc	0
granisetron_175mg1d_fc	0
granisetron_175mg3d_fc	0
granisetron_175mg5d_fc	0
granisetron_175mg6h_fc	0
roxithromycin_312mg1d_fc	0
roxithromycin_312mg3d_fc	0
venlafaxine_320mg1d_fc	0
venlafaxine_320mg5d_fc	0
atropine_94mg1d_fc	1
atropine_94mg3d_fc	1
atropine_94mg5d_fc	1
atropine_94mg6h_fc	1
atropine_2300ug1d_fc	1
atropine_2300ug3d_fc	1
atropine_2300ug5d_fc	1

Table CLIV: Representative Clusters using Drugs Classified in DrugBank as Polycyclic Compounds (Continued)

Sample	Label
atropine_2300ug6h_fc	1
cholecalciferol_8mg1d_fc	1
cholecalciferol_8mg5d_fc	1
cholicAcid_1402mg1d_fc	1
cholicAcid_1402mg5d_fc	1
daunorubicin_3_25mg1d_fc	1
digoxin_11mg3d_fc	1
digoxin_11mg5d_fc	1
digoxin_11mg6h_fc	1
digoxin_260ug1d_fc	1
digoxin_260ug3d_fc	1
doxorubicin_3mg3d_fc	1
doxorubicin_3mg6h_fc	1
doxorubicin_650ug1d_fc	1
doxorubicin_650ug3d_fc	1
doxorubicin_650ug5d_fc	1
doxorubicin_650ug6h_fc	1
doxycycline_1g1d_fc	1
doxycycline_14mg1d_fc	1
epirubicin_2700ug1d_fc	1
etoposide_188mg1d_fc	1
etoposide_188mg3d_fc	1
etoposide_188mg6h_fc	1
finasteride_25mg3d_fc	1
hydrocortisone_56mg1d_fc	1
ivermectin_7500ug3d_fc	1
ivermectin_7500ug5d_fc	1
mevastatin_1200mg1d_fc	1
mifepristone_3mg6h_fc	1
naproxen_134mg1d_fc	1
naproxen_134mg6h_fc	1
norethindrone_80ug1d_fc	1
norethindrone_80ug5d_fc	1
oxymetholone_1170mg1d_fc	1
oxymetholone_1170mg3d_fc	1
oxymetholone_1170mg5d_fc	1
oxytetracycline_1500mg1d_fc	1
oxytetracycline_1500mg5d_fc	1
sulindac_64mg3d_fc	1
sulindac_64mg5d_fc	1
testosterone_375mg3d_fc	1
tetracycline_1500mg5d_fc	1
tretinoin_7mg1d_fc	1
tretinoin_7mg3d_fc	1
zopiclone_414mg6h_fc	1
Cluster 2 **Exemplar: erythromycin_1500mg3d_fc**	
Sample	**Label**
amantadine_220mg3d_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0

Table CLIV: Representative Clusters using Drugs Classified in DrugBank as Polycyclic Compounds (Continued)

Sample	Label
erythromycin_1500mg5d_fc	0
roxithromycin_312mg5d_fc	0
sertraline_210mg1d_fc	0
sertraline_210mg3d_fc	0
sertraline_210mg5d_fc	0
venlafaxine_320mg3d_fc	0
amoxicillin_1100mg1d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
cholecalciferol_8mg3d_fc	1
cholicAcid_1402mg3d_fc	1
cyproteroneAcetate_2500mg5d_fc	1
cyproteroneAcetate_2500mg6h_fc	1
daunorubicin_3_25mg3d_fc	1
daunorubicin_3_25mg5d_fc	1
digoxin_11mg1d_fc	1
doxorubicin_3mg1d_fc	1
doxorubicin_3mg5d_fc	1
epirubicin_2700ug3d_fc	1
epirubicin_2700ug5d_fc	1
ergocalciferol_15mg1d_fc	1
ergocalciferol_15mg3d_fc	1
ergocalciferol_15mg5d_fc	1
etoposide_188mg5d_fc	1
ivermectin_7500ug1d_fc	1
megestrolAcetate_132mg1d_fc	1
megestrolAcetate_132mg3d_fc	1
megestrolAcetate_132mg5d_fc	1
mevastatin_1200mg3d_fc	1
mevastatin_1200mg5d_fc	1
naloxone_76mg1d_fc	1
naloxone_76mg5d_fc	1
naproxen_10mg3d_fc	1
oxytetracycline_1500mg3d_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
progesterone_164mg5d_fc	1
progesterone_11300ug3d_fc	1
progesterone_11300ug5d_fc	1
rifabutin_1500mg1d_fc	1
rifabutin_1500mg3d_fc	1
simvastatin_15mg3d_fc	1
simvastatin_15mg5d_fc	1
sulindac_23mg3d_fc	1
sulindac_23mg5d_fc	1
sulindac_64mg1d_fc	1
terbinafine_2g1d_fc	1
testosterone_375mg5d_fc	1
zopiclone_414mg1d_fc	1

Psycholeptics

Number of Samples = 55

Number of Clusters = 8

No "All QT" clusters were found. Cluster 1 was comprised of all but 1 QT sample. Cluster 2 was 1/3

comprised of QT samples.

Table CLV: Representative Clusters using Drugs Classified in DrugBank as Psycholeptics

Cluster 1 Exemplar: chlorpromazine_73mg3d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg5d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
chlorpromazine_73mg6h_fc	0
quetiapine_500mg1d_fc	0
nitrazepam_310mg3d_fc	1
Cluster 2 Exemplar: promazine_100mg3d_fc	
Sample	**Label**
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
fluphenazine_22mg5d_fc	1
nitrazepam_310mg1d_fc	1
nitrazepam_310mg5d_fc	1
olanzapine_23mg1d_fc	1
olanzapine_23mg3d_fc	1
olanzapine_23mg5d_fc	1
pentobarbital_70mg1d_fc	1
secobarbital_20mg1d_fc	1
secobarbital_70mg5d_fc	1
zaleplon_100mg5d_fc	1

Respiratory System

Number of Samples = 32

Number of Clusters = 8

Cluster 1 contained 3 QT samples of 4 total. Cluster 2 was an "All QT" cluster.

Table CLVI: Representative Clusters using Drugs Classified in DrugBank as Respiratory System

Cluster 1 Exemplar: isoproterenol_15mg5d_fc	
Sample	**Label**
isoproterenol_15mg1d_fc	0
isoproterenol_15mg3d_fc	0
isoproterenol_15mg5d_fc	0
oxymetazoline_500ug3d_fc	1
Cluster 2 Exemplar: promethazine_113mg1d_fc	
Sample	**Label**
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0

Sensory Organs

Number of Samples = 123

Number of Clusters = 28

No "All QT" clusters were found. Cluster 1 was slightly less than ¾ comprised of QT samples. Cluster 21

was slightly more than 1/3 comprised of QT samples.

Table CLVII: Representative Clusters using Drugs Classified in DrugBank as Sensory Organs

Cluster 1 Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
azithromycin_50mg6h_fc	0
azithromycin_225mg1d_fc	0
azithromycin_225mg3d_fc	0
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_72mg6h_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
erythromycin_1500mg1d_fc	0
erythromycin_1500mg3d_fc	0
erythromycin_1500mg5d_fc	0
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
atropine_2300ug6h_fc	1
diclofenac_10mg6h_fc	1
famciclovir_112mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
prednisolone_184mg1d_fc	1
prednisolone_184mg3d_fc	1
Cluster 21 Exemplar: indomethacin_4500ug5d_fc	
Sample	**Label**
azithromycin_50mg3d_fc	0
azithromycin_50mg5d_fc	0
azithromycin_225mg5d_fc	0
azithromycin_225mg6h_fc	0
cyclosporin_70mg6h_fc	1
cyclosporin_350mg5d_fc	1
indomethacin_4500ug1d_fc	1

Table CLVII: Representative Clusters using Drugs Classified in DrugBank as Sensory Organs (Continued)

Sample	Label
indomethacin_4500ug3d_fc	1
indomethacin_4500ug5d_fc	1
indomethacin_4500ug6h_fc	1
miconazole_200mg5d_fc	1

Steroid Synthesis Inhibitors

Number of Samples = 72

Number of Clusters = 10

Clusters 1, 2, and 3, respectively were "All QT" clusters. Cluster 9 was slightly less than ¼ comprised of

QT samples.

Table CLVIII: Representative Clusters using Drugs Classified in DrugBank as Steroid Synthesis Inhibitors

Cluster 1 Exemplar: fluconazole_10mg3d_fc	
Sample	**Label**
fluconazole_10mg3d_fc	0
fluconazole_394mg5d_fc	0
itraconazole_30mg1d_fc	0
Cluster 2 Exemplar: fluconazole_394mg3d_fc	
Sample	**Label**
fluconazole_10mg5d_fc	0
fluconazole_394mg3d_fc	0
itraconazole_30mg3d_fc	0
itraconazole_1093mg1d_fc	0
itraconazole_1093mg3d_fc	0
itraconazole_1093mg5d_fc	0
ketoconazole_114mg1d_fc	0
ketoconazole_114mg3d_fc	0
ketoconazole_114mg5d_fc	0
ketoconazole_114mg6h_fc	0
Cluster 3 Exemplar: fluconazole_394mg6h_fc	
Sample	**Label**
fluconazole_394mg6h_fc	0
itraconazole_30mg6h_fc	0
Cluster 9 Exemplar: econazole_43mg5d_fc	
Sample	**Label**
fluconazole_10mg1d_fc	0
fluconazole_10mg6h_fc	0
fluconazole_394mg1d_fc	0
ketoconazole_25mg1d_fc	0
ketoconazole_25mg3d_fc	0
ketoconazole_25mg5d_fc	0
ketoconazole_25mg6h_fc	0
ketoconazole_2274mg6h_fc	0
aminoglutethimide_350mg6h_fc	1
clotrimazole_52mg6h_fc	1

Table CLVIII: Representative Clusters using Drugs Classified in DrugBank as Steroid Synthesis Inhibitors (Continued)

Sample	Label
clotrimazole_89mg1d_fc	1
clotrimazole_89mg6h_fc	1
econazole_43mg1d_fc	1
econazole_43mg3d_fc	1
econazole_43mg5d_fc	1
econazole_43mg6h_fc	1
econazole_334mg6h_fc	1
finasteride_25mg1d_fc	1
finasteride_25mg3d_fc	1
finasteride_25mg5d_fc	1
finasteride_800mg3d_fc	1
finasteride_800mg5d_fc	1
finasteride_800mg6h_fc	1
letrozole_250mg1d_fc	1
letrozole_250mg3d_fc	1
letrozole_250mg6h_fc	1
miconazole_200mg1d_fc	1
miconazole_200mg3d_fc	1
miconazole_200mg6h_fc	1
miconazole_920mg6h_fc	1

Sulfonamides

Number of Samples = 41

Number of Clusters = 6

No "All QT" clusters were found. Cluster 1 was ¾ comprised of QT samples.

Table CLIX: Representative Clusters using Drugs Classified in DrugBank as Sulfonamides

Cluster 1 Exemplar: torsemide_3mg3d_fc	
Sample	**Label**
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
torsemide_3mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
sildenafil_300mg5d_fc	1
sildenafil_420mg5d_fc	1
sildenafil_2500ug5d_fc	1
sildenafil_14600ug5d_fc	1

Sulfones

Number of Samples = 49

Number of Clusters = 7

No "All QT" clusters were found. Cluster 1 was ¾ comprised of QT samples. Cluster 3 was slightly more

than ¼ comprised of QT samples.

Table CLX: Representative Clusters using Drugs Classified in DrugBank as Sulfones

Cluster 1 Exemplar: torsemide_110mg3d_fc	
Sample	**Label**
sulfisoxazole_250mg6h_fc	0
sulfisoxazole_2500mg3d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg3d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
sildenafil_300mg5d_fc	1
sildenafil_2500ug5d_fc	1
sildenafil_14600ug5d_fc	1
Cluster 7 Exemplar: sulfathiazole_31mg6h_fc	
Sample	**Label**
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_2500mg1d_fc	0
torsemide_3mg1d_fc	0
glimepiride_2500mg6h_fc	1
glipizide_2500mg6h_fc	1
sildenafil_300mg6h_fc	1
sildenafil_420mg5d_fc	1
sildenafil_2500ug1d_fc	1
sulfaphenazole_1695mg6h_fc	1
sulfathiazole_31mg6h_fc	1
sulfathiazole_2629mg3d_fc	1

Sulfur Compounds

Number of Samples = 179

Number of Clusters = 32

No "All QT" clusters were found. Cluster 1 was more than ¾ comprised of QT samples. Cluster 2 was slightly more than ¼ comprised of QT samples. Cluster 9 was comprised of slightly less than ¼ QT samples. Cluster 23 was comprised of slightly less than 1/6 QT samples. Cluster 32 was comprised of slightly less than 1/6 QT samples.

Table CLXI: Representative Clusters using Drugs Classified in DrugBank as Sulfur Compounds

Cluster 1 Exemplar: promethazine_2300ug1d_fc	
Sample	**Label**
chlorpromazine_18mg1d_fc	0
chlorpromazine_18mg3d_fc	0
chlorpromazine_18mg6h_fc	0
chlorpromazine_73mg1d_fc	0
chlorpromazine_73mg3d_fc	0
chlorpromazine_73mg5d_fc	0
promethazine_113mg1d_fc	0
promethazine_113mg3d_fc	0
promethazine_113mg5d_fc	0
promethazine_113mg6h_fc	0
promethazine_2300ug1d_fc	0
promethazine_2300ug3d_fc	0
promethazine_2300ug5d_fc	0
promethazine_2300ug6h_fc	0
quetiapine_500mg1d_fc	0
torsemide_3mg3d_fc	0
torsemide_3mg5d_fc	0
torsemide_3mg6h_fc	0
torsemide_110mg1d_fc	0
torsemide_110mg5d_fc	0
torsemide_110mg6h_fc	0
rosiglitazone_10mg6h_fc	1
sildenafil_300mg5d_fc	1
sildenafil_14600ug5d_fc	1
ticlopidine_223mg5d_fc	1
Cluster 2 Exemplar: sulfisoxazole_250mg1d_fc	
Sample	**Label**
sulfisoxazole_250mg1d_fc	0
sulfisoxazole_250mg6h_fc	0

Table CLXI: Representative Clusters using Drugs Classified in DrugBank as Sulfur Compounds (Continued)

Sample	Label
sulfisoxazole_2500mg1d_fc	0
sulfisoxazole_2500mg3d_fc	0
acetazolamide_250mg6h_fc	1
disulfiram_100mg6h_fc	1
disulfiram_500mg1d_fc	1
lansoprazole_600mg1d_fc	1
methimazole_28mg1d_fc	1
methimazole_100mg3d_fc	1
pioglitazone_3mg6h_fc	1
pioglitazone_300mg3d_fc	1
rofecoxib_800mg1d_fc	1
rofecoxib_1550mg5d_fc	1
sulfathiazole_31mg6h_fc	1
Cluster 9 **Exemplar: glipizide_2500mg1d_fc**	
Sample	Label
promazine_100mg1d_fc	0
promazine_100mg3d_fc	0
promazine_100mg5d_fc	0
torsemide_3mg1d_fc	0
busulfan_36mg6h_fc	1
glimepiride_2500mg1d_fc	1
glimepiride_2500mg3d_fc	1
glimepiride_2500mg5d_fc	1
glipizide_2500mg1d_fc	1
glipizide_2500mg3d_fc	1
glipizide_2500mg5d_fc	1
glipizide_2500mg6h_fc	1
methimazole_28mg6h_fc	1
sulfaphenazole_1695mg6h_fc	1
thiabendazole_92mg3d_fc	1
Cluster 23 **Exemplar: sildenafil_2500ug3d_fc**	
Sample	Label
chlorpromazine_18mg5d_fc	0
chlorpromazine_73mg6h_fc	0
torsemide_110mg3d_fc	0
busulfan_36mg1d_fc	1
meloxicam_33mg6h_fc	1
meloxicam_600ug6h_fc	1
omeprazole_30mg3d_fc	1
omeprazole_30mg6h_fc	1
rofecoxib_3mg5d_fc	1
sildenafil_300mg3d_fc	1
sildenafil_300mg6h_fc	1
sildenafil_420mg6h_fc	1
sildenafil_2500ug1d_fc	1
sildenafil_2500ug3d_fc	1
sildenafil_2500ug6h_fc	1
sildenafil_14600ug1d_fc	1
sildenafil_14600ug3d_fc	1

Table CLXI: Representative Clusters using Drugs Classified in DrugBank as Sulfur Compounds (Continued)

Sample	Label
sildenafil_14600ug6h_fc	1
troglitazone_100mg5d_fc	1
Cluster 32 **Exemplar: troglitazone_1200mg3d_fc**	
Sample	Label
pantoprazole_1100mg3d_fc	0
pantoprazole_1100mg5d_fc	0
quetiapine_500mg3d_fc	0
quetiapine_500mg5d_fc	0
acetazolamide_250mg5d_fc	1
amoxicillin_1100mg3d_fc	1
amoxicillin_1100mg5d_fc	1
busulfan_9mg6h_fc	1
lansoprazole_600mg3d_fc	1
lansoprazole_600mg5d_fc	1
troglitazone_100mg1d_fc	1
troglitazone_100mg3d_fc	1
troglitazone_1200mg1d_fc	1
troglitazone_1200mg3d_fc	1
troglitazone_1200mg5d_fc	1

Topoisomerase II Inhibitors

Number of Samples = 54

Number of Clusters = 11

No "All QT" clusters were found. Cluster 1 contains all but 1 QT sample.

Table CLXII: Representative Clusters using Drugs Classified in DrugBank as Topoisomerase II Inhibitors

Cluster 1 Exemplar: sparfloxacin_450mg6h_fc	
Sample	**Label**
ciprofloxacin_72mg1d_fc	0
ciprofloxacin_72mg3d_fc	0
ciprofloxacin_72mg5d_fc	0
ciprofloxacin_450mg1d_fc	0
ciprofloxacin_450mg3d_fc	0
ciprofloxacin_450mg6h_fc	0
sparfloxacin_29mg1d_fc	0
sparfloxacin_29mg3d_fc	0
sparfloxacin_29mg5d_fc	0
sparfloxacin_29mg6h_fc	0
sparfloxacin_450mg1d_fc	0
sparfloxacin_450mg3d_fc	0
sparfloxacin_450mg5d_fc	0
sparfloxacin_450mg6h_fc	0
etoposide_188mg6h_fc	1

APPENDIX C

Reprint Permissions

Dear Dr. Abriel,

I am working on my PhD dissertation and I will be presenting my work at an IEEE BIBM conference in Kansas City, Missouri in November. There is an image from one of your manuscripts that I would like to use in my dissertation and in one of the slides I will be presenting at the conference. I will of course reference the paper in both works. I am specifically referring to Figure 2 in "Stereoselective Inhibition of the hERG2 Potassium Channel" from Front. Pharmacol., 22 November 2010 | https://doi.org/10.3389/fphar.2010.00137.
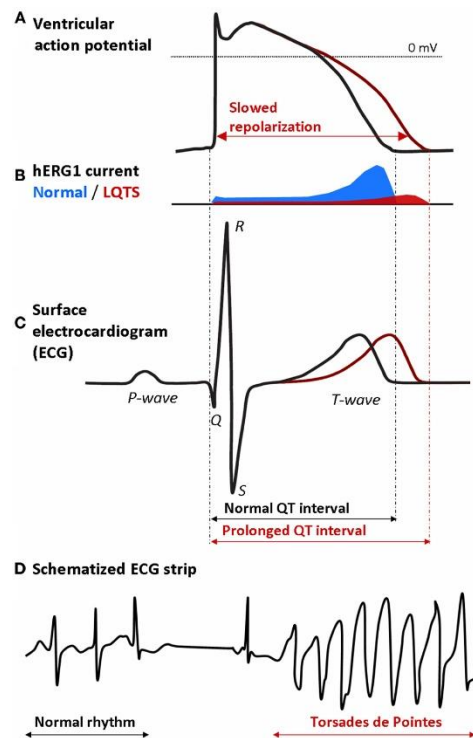
Warm regards,
Dennis Bergau

Abriel, Hugues (IBMM) <Hugues.Abriel@ibmm.unibe.ch>
To Dennis Bergau
Oct 20 at 2:34 AM

Dear Dennis,
Yes, no problem, Hugues
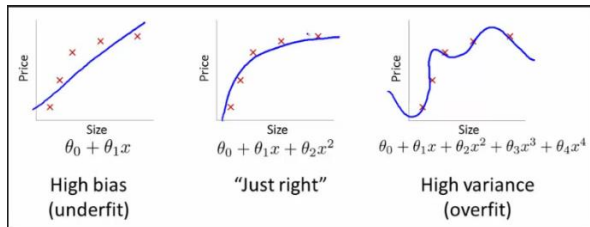
Dennis Bergau <dmbergau@yahoo.com>
To: ang@cs.stanford.edu
 Oct 29 at 12:49 AM

Dear Professor Ng,

I am writing my PhD dissertation and I would like to use the attached image found at this
URL: .10_Advice_for_applying_machine_learning

I will not modify the image, and if permission is granted, please let me know your preferred citation.

Warm regards,
Dennis Bergau

Andrew Y. Ng <ang@cs.stanford.edu>
To: Dennis Bergau
Oct 31 at 2:33 PM

Sure, please feel free to use it.

Andrew

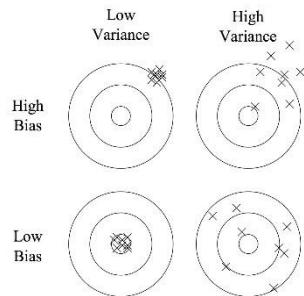Dennis Bergau <dmbergau@yahoo.com>
To: pedrod@cs.washington.edu
Nov 5 at 6:58 PM

Dear Professor Domingos,

I am writing my PhD dissertation and I would like to use the dart and target image (Figure 1) from this
URL: https://homes.cs.washington.edu/~pedrod/papers/cacm12.pdf

I will not alter the image, and please let me know your preferred way of citing it.

Warm regards,
Dennis Bergau

Pedro Domingos <pedrod@cs.washington.edu>
To: Dennis Bergau
CC: Pedro Domingos
Nov 5 at 7:47 PM

Sure. Just cite the CACM paper (see link on my home page for details.)

The paper is copyrighted. The copyright information and proof of purchase is below.

ASSOCIATION FOR COMPUTING MACHINERY, INC. LICENSE
TERMS AND CONDITIONS
Nov 06, 2017

This Agreement between Dennis Bergau ("You") and Association for Computing Machinery, Inc. ("Association for Computing Machinery, Inc.") consists of your license details and the terms and conditions provided by Association for Computing Machinery, Inc. and Copyright Clearance Center. **All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.**
License Number
4223400886967
License date
Nov 06, 2017
Licensed Content Publisher
Association for Computing Machinery, Inc.
Licensed Content Publication
Communications of the ACM
Licensed Content Title
A few useful things to know about machine learning
Licensed Content Author
Pedro Domingos
Licensed Content Date
Oct 1, 2012

Licensed Content Volume
55
Licensed Content Issue
10
Volume number
55
Issue number
10
Type of Use
Thesis/Dissertation
Requestor type
Academic
Format
Print and electronic
Portion
figure/table
Number of figures/tables
1
Will you be translating?
No
Order reference number
Title of your thesis/dissertation
Prediction of Human QT Prolongation Liability Based on Pre-Clinical RNA Expression Profiles
Expected completion date
Jan 2018
Estimated size (pages)
200
Requestor Location
Dennis Bergau
36144 N Springbrook Ln

GURNEE, IL 60031
United States
Attn: Dennis Bergau
Billing Type
Credit Card
Total
8.00 USD

Thank you for your order!

Dear Dennis Bergau,
Thank you for placing your order through Copyright Clearance Center's RightsLink® service.

Order Summary
  Licensee: Dennis Bergau
  Order Date: Nov 6, 2017
  Order Number: 4223400886967
  Publication: Communications of the ACM
  Title: A few useful things to know about machine learning
  Type of Use: Thesis/Dissertation
  Order Total: 8.00 USD

OXFORD UNIVERSITY PRESS LICENSE
TERMS AND CONDITIONS
Feb 13, 2018

This Agreement between Dennis Bergau ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

License Number
4287350608080
License date
Feb 13, 2018
Licensed content publisher
Oxford University Press
Licensed content publication
Bioinformatics
Licensed content title
APCluster: an R package for affinity propagation clustering
Licensed content author
Bodenhofer, Ulrich; Kothmeier, Andreas
Licensed content date
Jul 6, 2011
Type of Use
Thesis/Dissertation
Institution name
Title of your work
Prediction of Human QT Prolongation Liability Based on Pre-Clinical RNA Expression Profiles
Publisher of your work
n/a
Expected publication date
Jan 2018
Permissions cost
0.00 USD
Value added tax
0.00 USD
Total
0.00 USD

STANDARD TERMS AND CONDITIONS FOR REPRODUCTION OF MATERIAL FROM AN OXFORD UNIVERSITY PRESS JOURNAL

1. Use of the material is restricted to the type of use specified in your order details.

2. This permission covers the use of the material in the English language in the following territory: world. If you have requested additional permission to translate this material, the terms and conditions of this reuse will be set out in clause 12.

3. This permission is limited to the particular use authorized in (1) above and does not allow you to sanction its use elsewhere in any other format other than specified above, nor does it apply to quotations, images, artistic works etc that have been reproduced from other sources which may be part of the material to be used.

4. No alteration, omission or addition is made to the material without our written consent. Permission must be re-cleared with Oxford University Press if/when you decide to reprint.

5. The following credit line appears wherever the material is used: author, title, journal, year, volume, issue number, pagination, by permission of Oxford University Press or the sponsoring society if the journal is a society journal. Where a journal is being published on behalf of a learned society, the details of that society must be included in the credit line.

6. For the reproduction of a full article from an Oxford University Press journal for whatever purpose, the corresponding author of the material concerned should be informed of the proposed use. Contact details for the corresponding authors of all Oxford University Press journal contact can be found alongside either the abstract or full text of the article concerned, accessible from www.oxfordjournals.org Should there be a problem clearing these rights, please contact journals.permissions@oup.com

7. If the credit line or acknowledgement in our publication indicates that any of the figures, images or photos was reproduced, drawn or modified from an earlier source it will be necessary for you to clear this permission with the original publisher as well. If this permission has not been obtained, please note that this material cannot be included in your publication/photocopies.

8. While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by Oxford University Press or by Copyright Clearance Center (CCC)) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and Oxford University Press reserves the right to take any and all action to protect its copyright in the materials.

9. This license is personal to you and may not be sublicensed, assigned or transferred by you to any other person without Oxford University Press's written permission.

10. Oxford University Press reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

11. You hereby indemnify and agree to hold harmless Oxford University Press and CCC, and their respective officers, directors, employs and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

12. Other Terms and Conditions:

v1.4

Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.

VITAE

NAME   Dennis Michael Bergau

EDUCATION   B.S., Biology, Northeastern University, Boston, Massachusetts, 1991

                M.A. Physiology, Boston University, Boston, Massachusetts, 1993

ABSTRACTS   Randomized Placebo-Controlled Crossover Study to Evaluate the Effect of Veliparib (ABT-888) on Cardiac Repolarization in Subjects with Relapsed and Refractory Solid Tumors. Wijith Munasinghe, Anthony Tolcher, Emiliano Calvo, Michael Gordon, Mathilde Jalving, Judith de Vos-Geelen, Diane Medina, Dennis Bergau, Silpa Nuthalapati, David Hoffman, Stacie Shepherd, and Hao Xiong. *American Association for Cancer Research – 107th Annual Meeting.* April 2016.

                eECG/ABBIOS: Validation of a Fully Automated QT Evaluation Program. Nada A, Bystricky W, Safer A, Bergau DM, Gintant G, Locke C, Mikhael R, Liden K. *Drug Information Association Cardiovascular Safety, QT, and Arrhythmia in Drug Development.* Bethesda, MD. April 30-May 1, 2009.

                Safety of Radiofrequency Catheter Ablation of Accessory Pathways in Children and Young Adults: Long Term Follow Up. Kamenir SA, Tanel RE, Bergau DM, Walsh EP, Saul JP. *Supplement to Circulation*. October 15, 1996, Vol. 94, No. 8, Abstract 0701.

                Determinants and Usefulness of RF Impedance: Quantitative Effects of Tissue Contact and Frequency. Saul JP, Bergau DM, Weindling SN, Rittman WJ. *Pacing and Clinical Electrophysiology*. April 1994, Vol. 17, No. 4, Part II, Abstract 421.

                Porous Tipped Catheter Produces Larger Radiofrequency Lesions Through Tip Cooling. Bergau DM, Brucker GG, Saul JP. *Supplement to Circulation*. October 1993, Vol. 88, No. 4, Part 2, Abstract 873.

PUBLICATIONS   Prediction of Human QT Prolongation Liability Based on Pre-Clinical RNA Expression Profiles. Bergau D, Liu C, Lu H. *IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. Kansas City, MO (Nov 13-17, 2017). Paper B530. Pp515-518.

                Effect of Veliparib (ABT-888) on Cardiac Repolarization in Patients with Advanced Solid Tumors: A Randomized, Placebo-Controlled Crossover Study. *Cancer Chemother Pharmacol.* 2016 Nov;78(5):1003-1011. Epub 2016 Oct 5.

                Effects of Chronic Heparin Administration on Coronary Vascular Adaptation to Hypertension and Ventricular Hypertrophy in Sheep. Flanagan MF, Aoyagi T, Arnold LW, Maute C, Fujii AM, Currier J, Bergau DM, Warren H, Rakusen K. *Circulation*. 1999 Aug 31; 100(9): 981-7.

PUBLICATIONS
(continued)

A Five-Year Experience with Radiofrequency Catheter Ablation: Implications for Arrhythmia Management in the Pediatric and Young Adult Population. Tanel RE, Walsh EP, Triedman JK, Bergau DM, Saul JP. *Journal of Pediatrics*. December 1997, Vol. 131, No. 6: 878 – 887.

Efficacy of Radiofrequency Ablation for Control of Intraatrial Reentrant Tachycardia in Patients with Congenital Heart Disease. Triedman JK, Bergau DM, Saul JP, Epstein MR, Walsh EP. *Journal of the American College of Cardiology*. October 1997, Vol. 30, No. 4: 1032 – 1038.

Multipolar Endocardial Mapping of the Right Atrium during Cardiac Catheterization: Description of a New Technique. Jenkins KJ, Walsh EP, Colan SD, Bergau DM, Saul JP, Lock JE. *Journal of the American College of Cardiology*. October 1993, Vol. 22, No. 4: 1105 – 1110.

Hemodynamic Changes Associated with Obstructive Sleep Apnea Followed by Arousal in a Porcine Model. Pinto JMB, Garpestad E, Bergau DM, Lown B, Kirby DA. *Journal of Applied Physiology*. October 1993, Vol. 75, No. 4: 1439 – 1443.

Plasma Norepinephrine Changes Following Arousal Were Enhanced in Conscious Pigs With Perinephritic Hypertension. Zhao S, Pinto JMB, Bergau DM, Lown B, Kirby DA. *American Journal of Hypertension*. October 1993, Vol. 6, No. 10: 844 – 850.