Antipsychotic Pharmacogenetics in First Episode Psychosis:

Is There a Role for Glutamate Genes?

BY

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THESIS

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LIST OF ABBREVIATIONS

AIMS	Ancestry informative markers
BPRS	Brief Psychiatric Rating Scale
CPZ	Chlorpromazine
DSM-IV	Fourth Edition, Diagnostic and Statistical Manual of Mental Disorders
GluD2	Glutamate receptor delta 2
HWE	Hardy Weinberg Equilibrium
LD	Linkage disequilibrium
mGlu1	Metabotropic glutamate receptor 1
NMDA	N-methyl-D-aspartic acid
RDoC	Research Domain Criteria
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism

SUMMARY

Symptomatic response to antipsychotic treatment in patients treated for psychotic disorders is highly heterogeneous. The reasons for variable response and tolerability are unclear, but likely multifactorial including biological, environmental, and clinical contributors. Systematically examining these factors is necessary for us to improve current treatment strategies. Biological contributors may involve aberrant glutamate transmission which is thought to contribute to the pathophysiology of psychotic disorders and influence treatment response.

In the present study we examined genetic associations between variants in genes related to glutamate signaling and disposition and performed a genome-wide association study to identify other polymorphisms associated with antipsychotic response in first episode psychosis. We found a significant association between negative symptom response and rs274622 in *GRM3*, which has previously been associated with negative symptom response in schizophrenia. *GRM7* and *SLC38A1*, both previously unstudied in the context of antipsychotic response, showed potential for association although no single SNP in either gene was statistically significant after adjusting for multiple comparisons. Our genome-wide analysis identified two SNPs in *GRID2* significantly associated with antipsychotic response. Recent evidence suggests that GluD2, the product of *GRID2*, interacts with the glutamate neurotransmitter system. Together, our results suggest that genetic polymorphisms related to the glutamate neurotransmitter system may influence antipsychotic response in first episode psychosis.

I. INTRODUCTION

Psychotic disorders are characterized by hallucinations and delusions. Schizophrenia is the most commonly recognized disorder in this category. However, psychotic bipolar disorder and major depressive disorder with psychotic features can also present with psychotic symptoms and require treatment with antipsychotic medications [1]. The National Institute of Mental Health's Research Domain Criteria (RDoC) project aims to study psychiatric illnesses based upon neurobiological markers or observed symptom domains (such as psychosis) that are present across clinically used diagnoses [2]. The concept of trans-diagnostic research is supported by recent evidence that suggests common genetic polymorphisms increase odds of illness across major clinical psychiatric diagnoses [3].

It is well established that treating psychotic illness with antipsychotics improves outcomes and reduces relapse rates [4]. Use of these agents may also decrease risk of all-cause death and suicide [5]. Unfortunately, treatment resistance is a common and severe problem. Up to 50% of patients experiencing their first episode of psychosis have incomplete remission or treatment resistance [6]. Early remission may have prognostic significance for better long-term symptom control and social function [7]. The prospective identification of patients with poor prognosis may help to refine drug selection or dosing and improve treatment algorithms to reduce the amount of time spent inadequately treated.

Response to antipsychotics is a complicated area of study in which clinical, biological, and social factors may contribute. In this study, we aim to identify genetic markers predictive of antipsychotic response in first episode psychosis. Many studies of psychotic disorders are complicated by selection for poorer outcome patients as well as potential confounding by duration of illness and prior treatment [1]. The study of first episode patients helps to control for these factors.

Our genetic approach focused on genes related to the glutamate neurotransmitter system. Aberrant glutamate transmission is a leading hypothesis of the pathophysiology of schizophrenia [8]. Pharmacologic modulation of this system via drugs that act at N-methyl-D-aspartic acid (NMDA) receptors can create animal models that mimic the positive, negative, and cognitive symptoms of psychosis [9]. Glutamate-related polymorphisms have been associated with schizophrenia risk. In addition, glutamate-related genes have been associated with antipsychotic response in schizophrenia [10, 11]. However, these previous studies have focused on only a handful of polymorphisms in a single gene (*GRM3*) related to glutamate signaling. Our study will be the most comprehensive examination of antipsychotic response and its association with glutamate gene polymorphisms. It is also the first examination of glutamate-related genes and antipsychotic response in a first episode psychosis population.

We employed a three-staged approach for genetic analyses in this study involving hypothesis-driven candidate gene and gene set association studies followed by a genome-wide approach. Our hypothesis-driven analyses are designed to test the hypothesis that

polymorphisms in glutamate-related genes can explain variability in symptom response to antipsychotics. To test this hypothesis, first we examined glutamate gene polymorphisms that have previously been associated with antipsychotic response in our relatively unique first-episode population. Next, we searched for associated polymorphisms in genes known to be involved in glutamate transmission. Lastly, we performed a hypothesis-generating genome-wide association study to identify associated polymorphisms or genomic regions for future study.

II. METHODS

A. Ethics Statement

This study was approved by the Institutional Review Boards at both the University of Illinois at Chicago and the University of Pittsburgh. Only individuals who provided informed consent to study evaluations and genetic analyses were included.

B. Study Population

Eighty-nine patients meeting Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, or major depressive disorder with psychotic features according to the Structured Clinical Interview for DSM Disorders [12] along with consensus diagnostic meetings were enrolled from outpatient and inpatient clinics at the University of Illinois at Chicago (n=40) and University of Pittsburgh Western Psychiatric Institute and Clinic (n=58). Participants were either completely drug naïve (n=70) or had received minimal prior antipsychotic exposure (n=18). Those with prior antipsychotic exposure were not assessed unless they were known to be currently untreated for a minimum of three half-lives of medication to ensure washout prior to initiating study procedures. Participants were at least 12 years of age, with no history of head trauma and no currently active substance or alcohol abuse or lifetime history of substance dependence.

C. Treatment Protocol and Outcomes

Consenting individuals were treated with 6 weeks of open-label, flexibly-dosed antipsychotics. Risperidone was the antipsychotic of choice, but physicians could opt for alternative antipsychotic agents where clinically preferred. Chlorpromazine (CPZ) equivalents were calculated to allow for examination of antipsychotic dose across patients treated with different antipsychotic agents [13, 14]. This variable was natural log-transformed to improve normality. Clinical symptoms were evaluated by the Brief Psychiatric Rating Scale (BPRS) [15] administered by a trained clinician. The BPRS contains 18 items evaluating both positive and negative symptoms of psychosis and is validated in the diagnostic groups included in the present study and was therefore selected as the primary outcome measure for the examination of clinical response. Change score on the BPRS was calculated by subtracting the post-treatment score from the baseline score, thus higher numbers represent better clinical improvement. Clinical response is defined a priori as a $\geq$20% change in BPRS total score. Paired t-tests were used to examine pre-post treatment changes in BPRS total scores. Genetic analyses were based upon changes in the total BPRS score, however we examined changes in negative symptom scores in an analysis of a previously identified SNP associated with negative symptom response [10].

D. Genotyping and Quality Control

Genomic DNA was isolated from ethylenediaminetetraacetic acid-treated whole blood using the Gentra Puregene extraction kit (Qiagen Sciences, Germantown, MD), quantified, and quality checked with Picogreen (Invitrogen, Eugene, OR) and Nanodrop assays (Thermo Scientific, Wilmington, DE). Genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, California, USA) which interrogates 908,440 single nucleotide polymorphisms (SNPs). Each well of the 96-well master plates contained 1 ug of genomic DNA. Samples were digested using restriction enzymes and PCR amplification was performed using universal primers. These fragments were labeled with biotinylated nucleotides and hybridized to the microarray. Genotypes were called using Birdseed software.

A minimum call rate of 95% was required for each sample to be included in analyses; all samples met this criterion. The sex of all study samples was inferred using X chromosome heterozygosity. All genetically-inferred sex determinations matched those obtained by self-report. Identity-by-descent analyses were used to identify and exclude duplicated or contaminated samples; no samples were excluded for this reason. The final data set included 88 individuals and 750,347 SNPs that met the following criteria: (1) genotype call rate of $\geq$95%; (2) minor allele frequency $\geq$5%; (3) not on X or Y chromosome (analyses not adjusted for sex). No exclusions were performed based on Hardy-Weinberg equilibrium given admixture of the sample.

E. Glutamate Candidate Gene Panel

A panel of SNPs in glutamate-related genes was compiled, based upon known proteins involved in glutamate signaling [16]. Genes encoding glutamate receptors, downstream signaling components, and enzymes involved in the transport, secretion, and metabolism of glutamate were identified. Fifty-eight genes were identified (see Table 1), and 3,674 SNPs within these genes met the quality control parameters described above.

TABLE I

GLUTAMATE SYSTEM CANDIDATE GENES

Ionotropic Receptors		Metabotropic Receptors	Downstream Signaling		Transport and Secretion		Metabolism
GRIK1	*GRIA3*	*GRM1*	*RGS4*	*GNAQ*	*ADORA1*	*SLC17A8*	*SNCA*
GRIK2	*GRIA4*	*GRM2*	*ADCY7*	*HOMER1*	*ADORA2A*	*SLC1A1*	*ALDH5A1*
GRIK3	*GRIN1*	*GRM3*	*APP*	*HOMER2*	*AVP*	*SLC1A2*	*GAD1*
GRIK4	*GRIN2A*	*GRM4*	*CACNA1A*	*ITPR1*	*BDNF*	*SLC1A3*	*GLS*
GRIA1	*GRIN2B*	*GRM5*	*CDK5R1*	*MAPK1*	*IL1B*	*SLC1A6*	*GLUL*
GRIA2		*GRM6*	*CLN3*	*PLA2G6*	*P2RX7*	*SLC38A1*	*PRODH*
		GRM7	*DLG4*	*PLCB1*	*SLC17A6*	*SLC7A11*	*SRR*
		GRM8	*GNAI1*	*SHANK2*			

F. Glutamate Candidate Gene Panel and Genome-Wide Statistical Analysis

Golden Helix SNP & Variation Suite version 7.7.8 (Golden Helix, Montana, USA) was used to analyze the glutamate gene panel and genome-wide data. Association tests used change in BPRS total score as a quantitative train phenotype. This method modeled BPRS total change score using a linear regression approach whereby SNPs were assessed using an additive model. All analyses were adjusted for race, diagnosis, antipsychotic equivalent dose [13, 14], and baseline BPRS score. Antipsychotic equivalent dose was natural log-transformed to improve normality. Genetic analyses represent changes in F statistic between the reduced model (covariates only) and a full model including the covariates and a single SNP.

Power analyses for the glutamate panel data were conducted with Quanto [17] to examine genotype-phenotype relationships. At a minor allele frequency of 0.25 and assuming an additive inheritance model we were adequately powered (β=0.80, 2-sided type-I error rate=0.05) only to detect genotype variants that explained 28% of the variability in outcomes (r^2=0.28). Genome-wide significance was set at the standard p-value threshold of 5×10^{-8} [18]. Given that our final analyses included 750,347 SNPs, this is slightly more conservative than a Bonferroni adjustment at α=0.05 ($p=6.6 \times 10^{-8}$). GWAPower was used for genome-wide association test power analyses [19]. We were powered (β=0.80, 2-sided type-I error rate=5×10^{-8}) to detect SNPs that explained 21% of the variability in outcomes if they were in strong LD (r^2>0.8) with the causative allele.

G. Correcting for race and ancestry in a racially heterogeneous sample

Samples were genotyped for 105 Ancestry Informative Markers (AIMs) using the Sequenom MassARRAY platform (Sequenom, California, USA) as previously described [20]. Ancestry was determined for each individual for European, West African, and Native American genetic components. Individual ancestry estimates scored from 0-100% for each ancestry group were obtained from the genotype results using the Bayesian Markov Chain Monte Carlo method implemented in the program STRUCTURE 2.1 [21].

In addition to whole group analyses, we also conducted stratified analyses of self-reported race groups to examine effects of population and admixture. In these stratified analyses, association studies were repeated with the additional inclusion of the percent ancestry relevant for the population (e.g. percentage European ancestry in the analysis of white participants, and percentage West African ancestry in the analysis of African American participants) [20].

III. RESULTS

A. Sample Characteristics

Eighty-eight participants that met inclusion/exclusion criteria, completed six weeks of therapy, and consented to genetic analyses were included in analysis. Pre- and post-treatment characteristics of the sample are summarized in Table 1. Symptoms significantly improved after treatment (paired t-test $p<0.001$) with a mean improvement of 9.4 on the BPRS, which represents an approximate 20% decrease in symptoms. There were significant ($p<0.05$) differences between diagnoses in mean pre- and post-treatment scores, but the primary outcome, BPRS total change score, did not significantly differ between diagnoses. Diagnosis, self-identified race, baseline BPRS score, and CPZ equivalents explained 34% of the treatment response variation (See Table 3). Although race indicator variables were not statistically significant in our model, they were forced in because of differing minor allele frequencies and linkage disequilibrium across races.

TABLE II

SAMPLE CHARACTERISTICS BY GENOTYPE

	Full sample (n=88)	Schizophrenia (n=69)	Bipolar Disorder (n=11)	Major depressive disorder (n=8)
Pre-treatment characteristics				
Age (Std Dev)	23.9 (7.0)			
Male (%)	56 (63.6)	47 (68.1)	5 (45.5)	4 (50.0)
Race (%)				
Caucasian	38 (43.2)	33 (47.8)	2 (18.2)	3 (37.5)
African American	36 (40.9)	27 (39.1)	6 (54.5)	3 (37.5)
Asian, Hispanic, or other	14 (15.9)	9 (13.0)	3 (27.3)	2 (25.0)
Antipsychotic naïve (%)	70 (79.5)	56 (81.2)	8 (72.7)	6 (75.0)
BPRS Total Baseline (Std Dev) *	45.7 (9.5)	47.1 (9.3)	37.3 (7.9)	44.4 (7.8)
Post-treatment characteristics				
Treatment agent				
Risperidone	69 (78.4)	51 (73.9)	11 (100)	7 (87.5)
Other second-generation antipsychotic	8 (9.1)	7 (10.1)	0 (0)	1 (12.5)
First-generation antipsychotic	10 (11.4)	10 (14.5)	0 (0)	0 (0)
First- and second-generation antipsychotic	1 (1.1)	1 (1.4)	0 (0)	0 (0)
CPZ Equivalents (Std Dev)	247.0 (172.0)	268.1 (181.4)	180.5 (83.5)	156.8 (131.0)
Taking benztropine (%)	15 (17.0)	15 (21.7)	0 (0)	0 (0)
Taking antidepressant (%)	16 (18.2)	10 (14.5)	0 (0)	6 (75.0)
Taking mood stabilizer (%)	2 (2.3)	1 (1.4)	1 (9.1)	0 (0)
Taking sedative/hypnotic (%)	3 (3.4)	3 (4.3)	0 (0)	0 (0)
BPRS Total End (Std Dev) *	36.3 (9.0)	38.2 (8.5)	27.1 (4.6)	32.9 (8.9)
BPRS Total Change Score (Std Dev)	9.4 (7.9)	9.0 (8.0)	10.2 (9.2)	11.5 (5.8)
BPRS Response (%)	43 (48.9)	31 (44.9)	7 (63.6)	5 (62.5)

*=$p<0.05$ between diagnoses using one-way ANOVA for continuous variables or $\chi 2$ statistic for categorical variables

TABLE III

CLINICAL LINEAR REGRESSION MODEL FOR BPRS CHANGE SCORE

Variable	β	p
Bipolar disorder diagnosis	5.91	0.013
Major depressive disorder diagnosis	2.97	0.251
Caucasian	1.75	0.423
African American	0.29	0.893
Baseline BPRS	0.47	<0.001
ln(CPZ)	-1.79	0.077
Model r^2	0.34	

B. Candidate SNPs Previously Associated with Antipsychotic Response Phenotypes

We are aware of three published studies that identified associations between glutamate system genes and antipsychotic response phenotypes [10, 11, 22]. Of note, none of these studies was conducted in a first episode psychosis population. Bishop et al. (2005) found that 6 SNPs in *GRM3* collectively helped to explain variability in negative symptom improvement in patients treated with olanzapine [10]. Individually, the SNP rs274622 was the most strongly associated with negative symptom improvement (p=0.02). Although *GRM3* polymorphisms helped to explain negative symptom response, they did not help to explain total symptom response as measured by the BPRS in this study.

In our sample, only three of the SNPs examined by Bishop et al. were available (rs274622, rs1468412, and rs1989796). These SNPs were not associated with BPRS change score when added together to our clinical model (p=0.79). When examining BPRS negative symptoms change score as the phenotype and controlling for diagnosis, race, chlorpromazine equivalents, and baseline BPRS negative subscale score, the three SNPs did not improve the model (p=0.13). However, rs274622 alone improved model fit (p=0.03).

Fijal et al. (2009) found an association between the *GRM3* rs724226 G allele and total score change on the Positive and Negative Syndrome Scale in patients treated with 12 weeks of risperidone [11]. This SNP was not available on our array, but rs274622, is in strong LD (r^2>0.8) with this marker. As mentioned above, this SNP was not associated with total response in our sample (p=0.79).

Bishop et al. (2011) found an association between *GRM3* rs1989796 and rs1476455 and treatment refractory symptoms in schizophrenia [22]. Only rs1989796 was available on our array. In our sample, adding this SNP to the clinical model did not improve model fit (p=0.75). Using a recessive model in the same manner as Bishop et al. (CC genotype compared to CT and TT) did not change this finding (p=0.77).

C. Glutamate Candidate Gene Panel Association Study

We examined 3674 SNPs in 58 candidate genes related to glutamate transmission. The ten strongest associations are shown in Table 4. None of the associations retained significance after a Bonferroni correction (threshold p<0.000014).

TABLE IV

STRONGEST ASSOCIATIONS BETWEEN GLUTAMATE CANDIDATE SNPS AND BPRS CHANGE SCORE

Gene	SNP	p
GRM7	rs2069062	0.00014
GRM7	rs2014195	0.00031
SLC38A1	rs7313085	0.00037
SLC38A1	rs4360754	0.00037
SLC38A1	rs11525670	0.00037
PLCB1	rs6140570	0.00046
PLCB1	rs6140566	0.00048
GRM7	rs9877337	0.00060
SLC38A1	rs11525671	0.00074
SLC38A1	rs7294699	0.00085

* All associations reflect analyses adjusted for race, diagnosis, baseline BPRS, and chlorpromazine equivalents

Five of the 20 strongest associations were in *GRM7* and seven were in or flanking *SLC38A1*. The top SNPs from both genes were in Hardy Weinberg Equilibrium (HWE, both p>0.1). We then examined all SNPs from the array in these two genes in an attempt to identify gene regions associated with response (see Figures 1 and 2). Strong *GRM7* associations were primarily localized to an 18kb intronic region. Strong *SLC38A1* associations were downstream from the 3' UTR region of the gene.

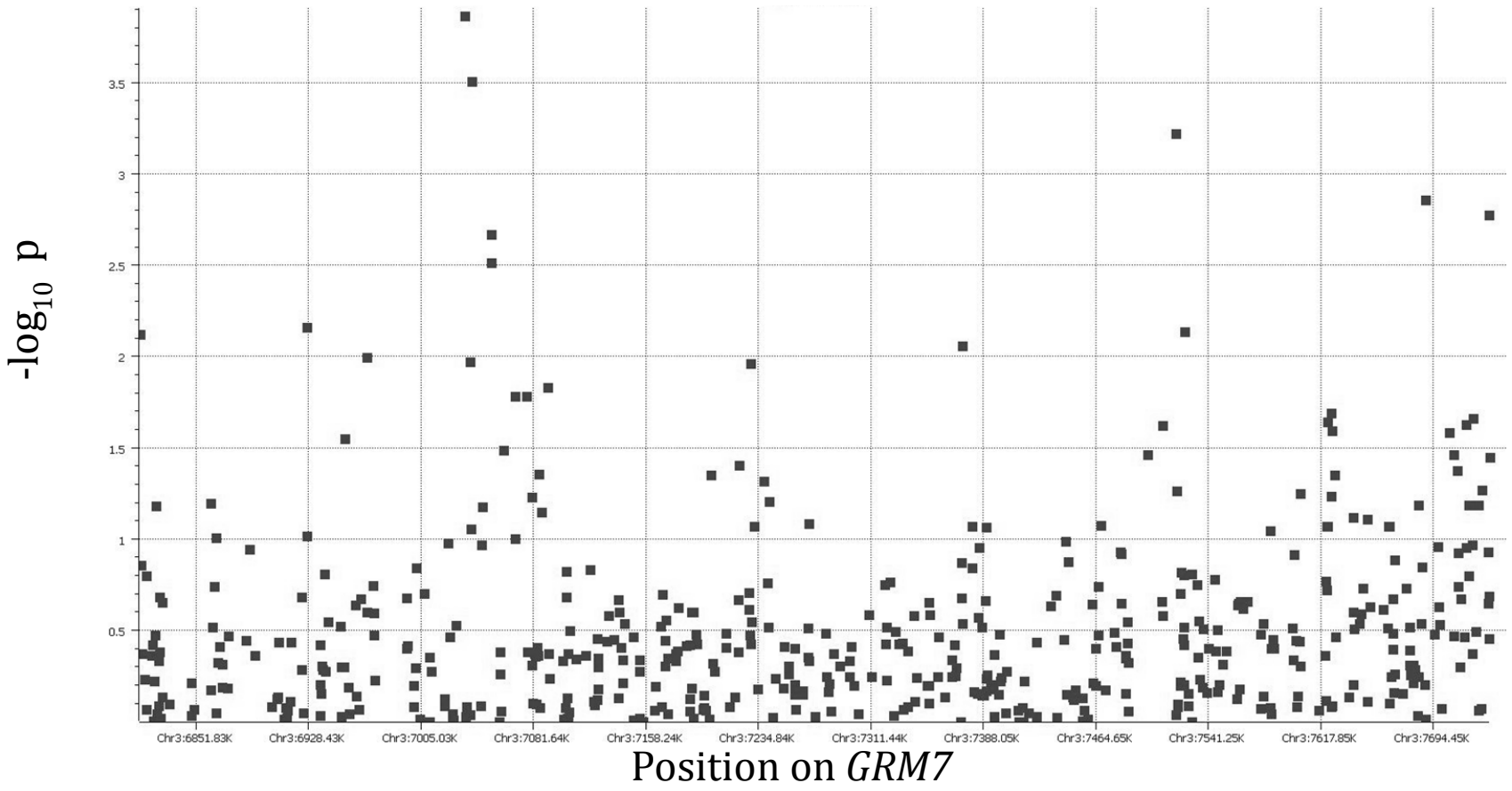

Figure 1. *GRM7* Associations by Gene Position

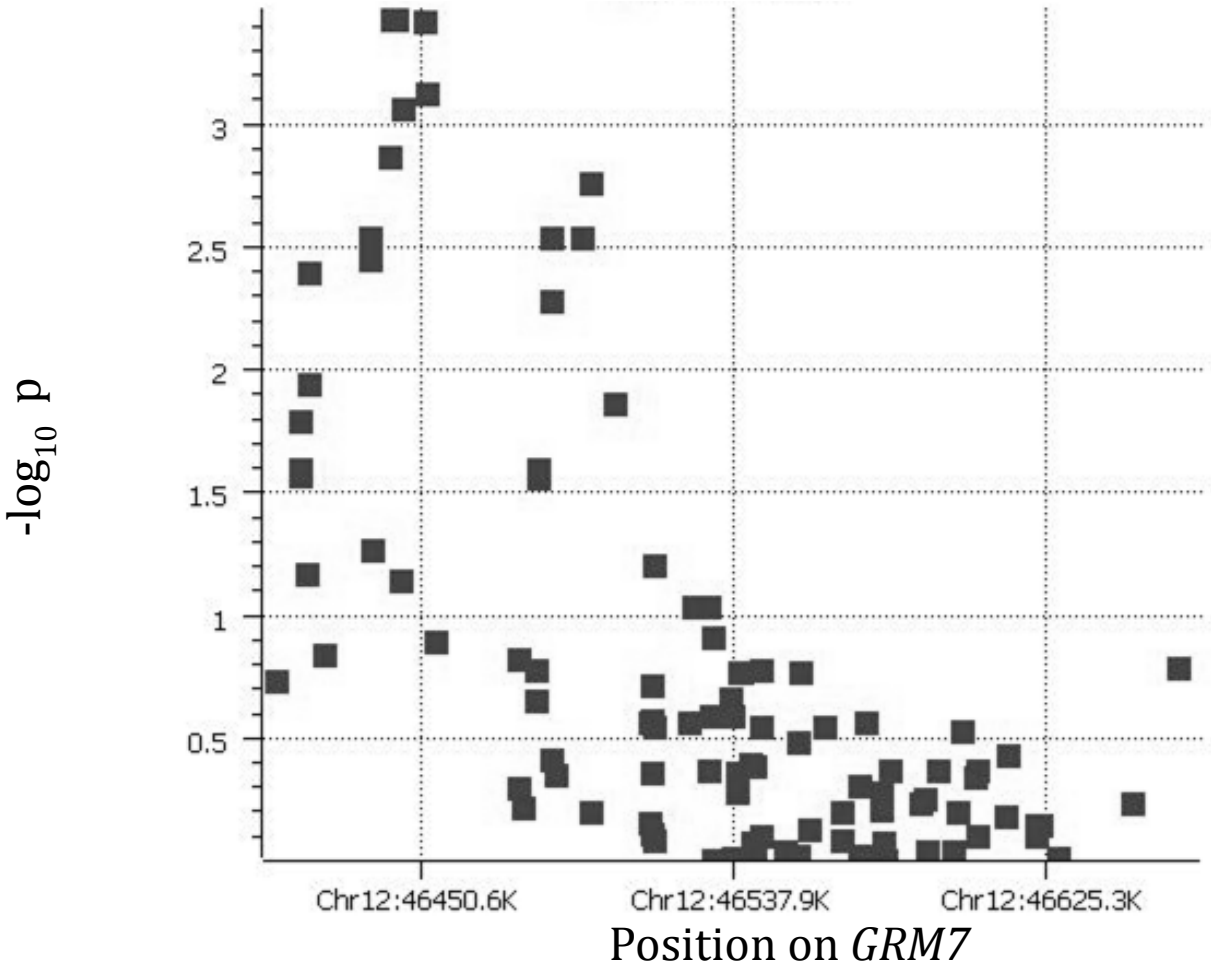

Figure 2. *SLC38A1* Associations by Gene Position

D. Genome-Wide Association Study

Genome-wide association tests controlling for baseline BPRS, diagnosis, race, and medication dose identified a significant association of two *GRID2* variants and symptom response (see Figure 3). The two *GRID2* variants, rs9307122 and rs1875705 were in full LD in the study sample. Both SNPs were in HWE ($p>0.1$). Figure 4 presents a Q-Q plot from adjusted analyses. The adjusted mean BPRS change score by genotype from a generalized linear model is displayed in Figure 5.

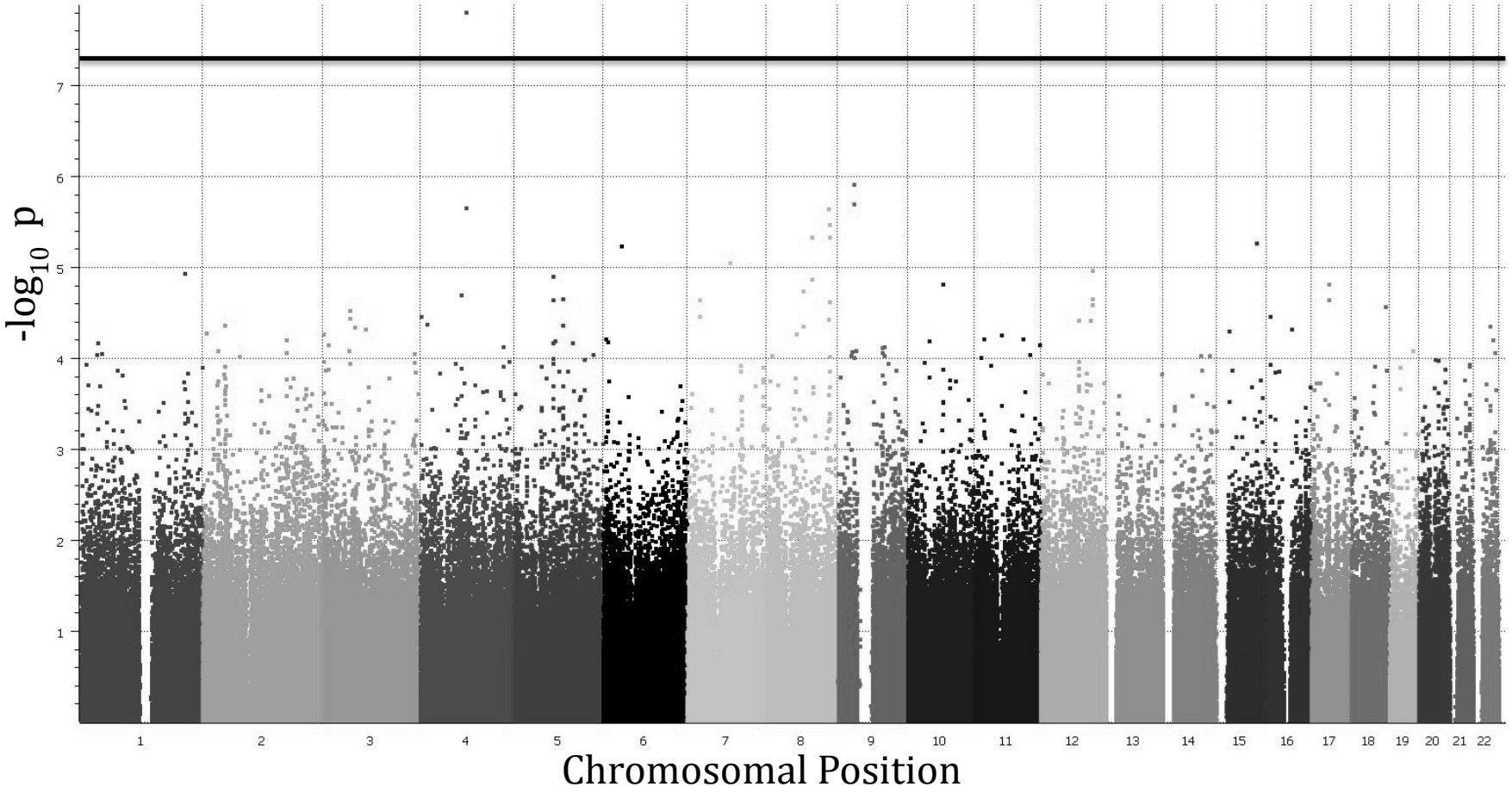

Figure 3. Manhattan plot of BPRS change score adjusted for baseline BPRS, diagnosis, race, and medication dose

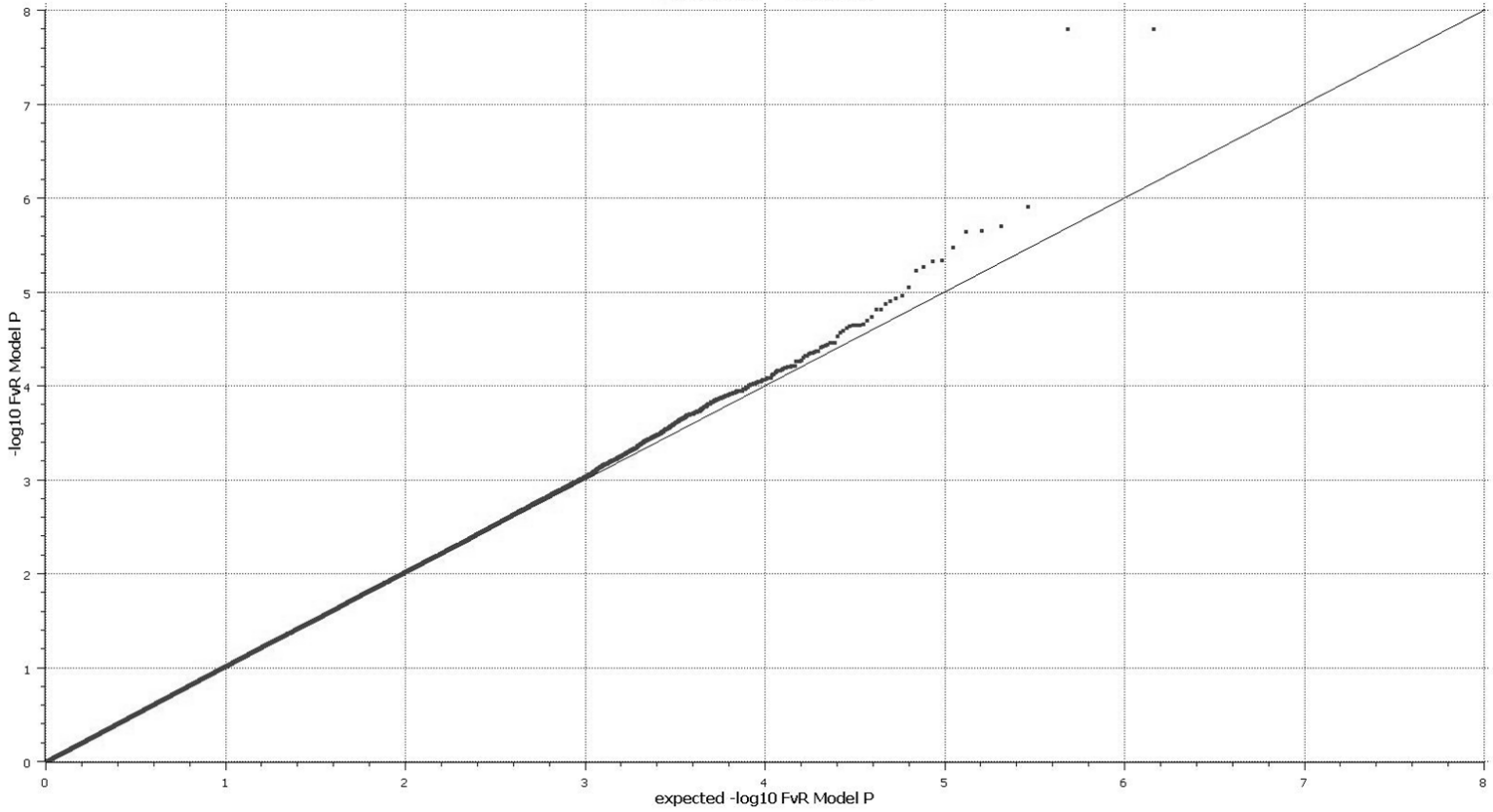

Figure 4. Q-Q plot adjusted for self-identified race, diagnosis, baseline BPRS score, and medication dose

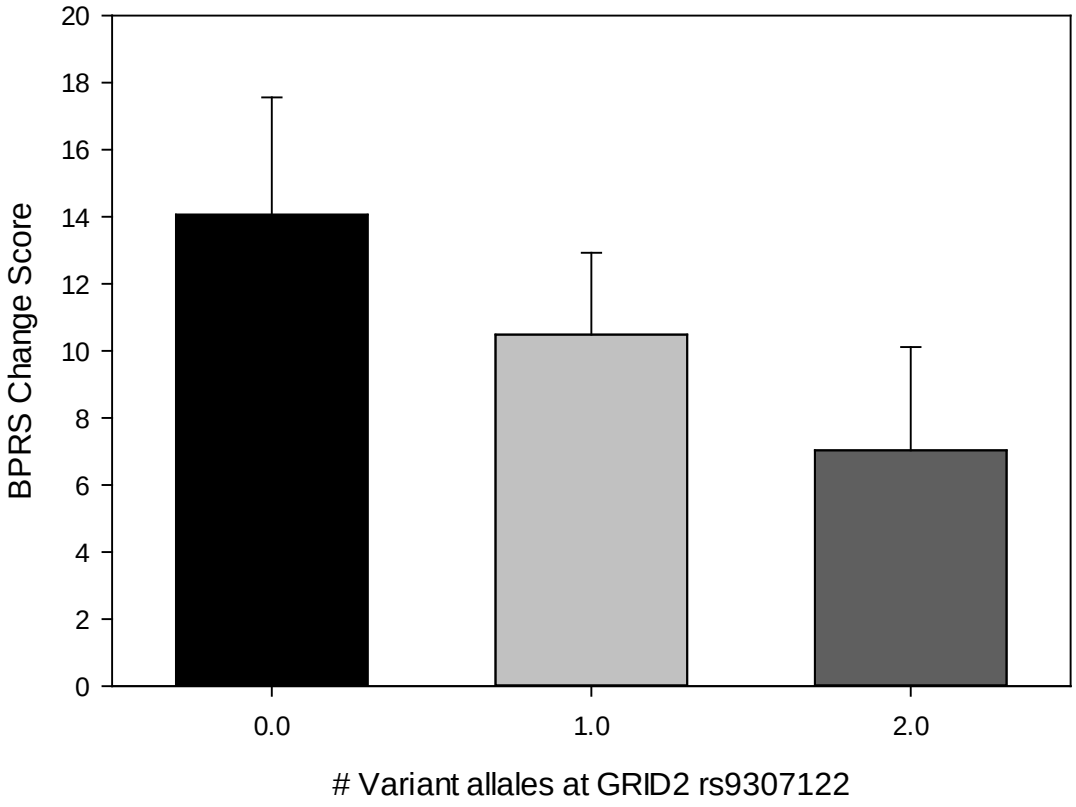

Figure 5. Adjusted mean BPRS change score by *GRID2* rs9307122 genotype (95% confidence interval)

We also performed a genome-wide analysis in a subgroup of patients with schizophrenia only (n=69), adjusting for baseline BPRS, race, and medication dose (see Figure 6). The same two *GRID2* SNPs were also significant in the subgroup of schizophrenia patients. In addition, another SNP (rs687279) in a poorly characterized region of chromosome 8 reached genome-wide significance in this subanalysis. The accompanying Q-Q plot is displayed in Figure 7. This SNP was also in HWE (p=0.67).

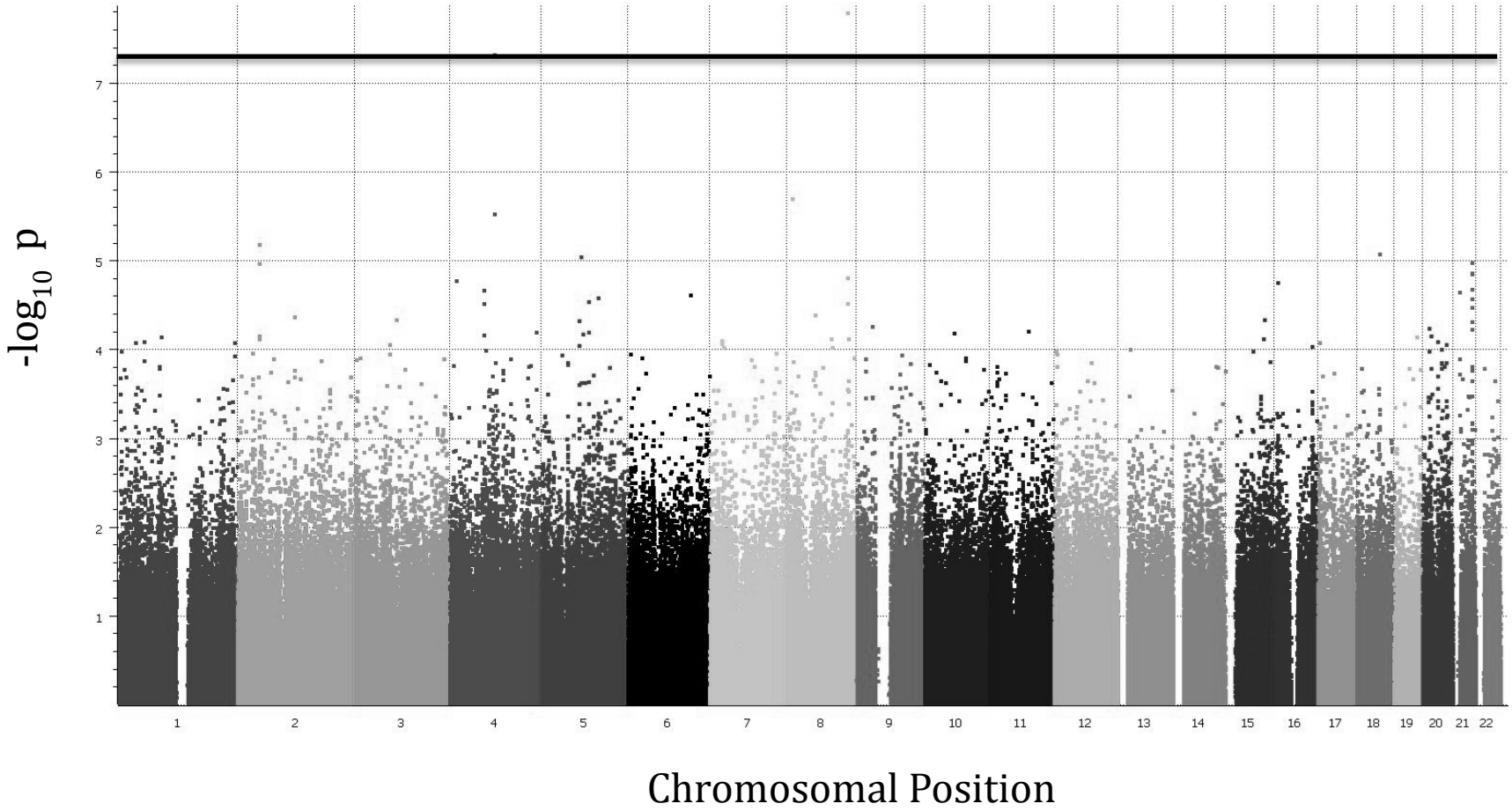

Figure 6. Manhattan plot of BPRS change score in individuals with schizophrenia adjusted for baseline BPRS, race, and medication dose

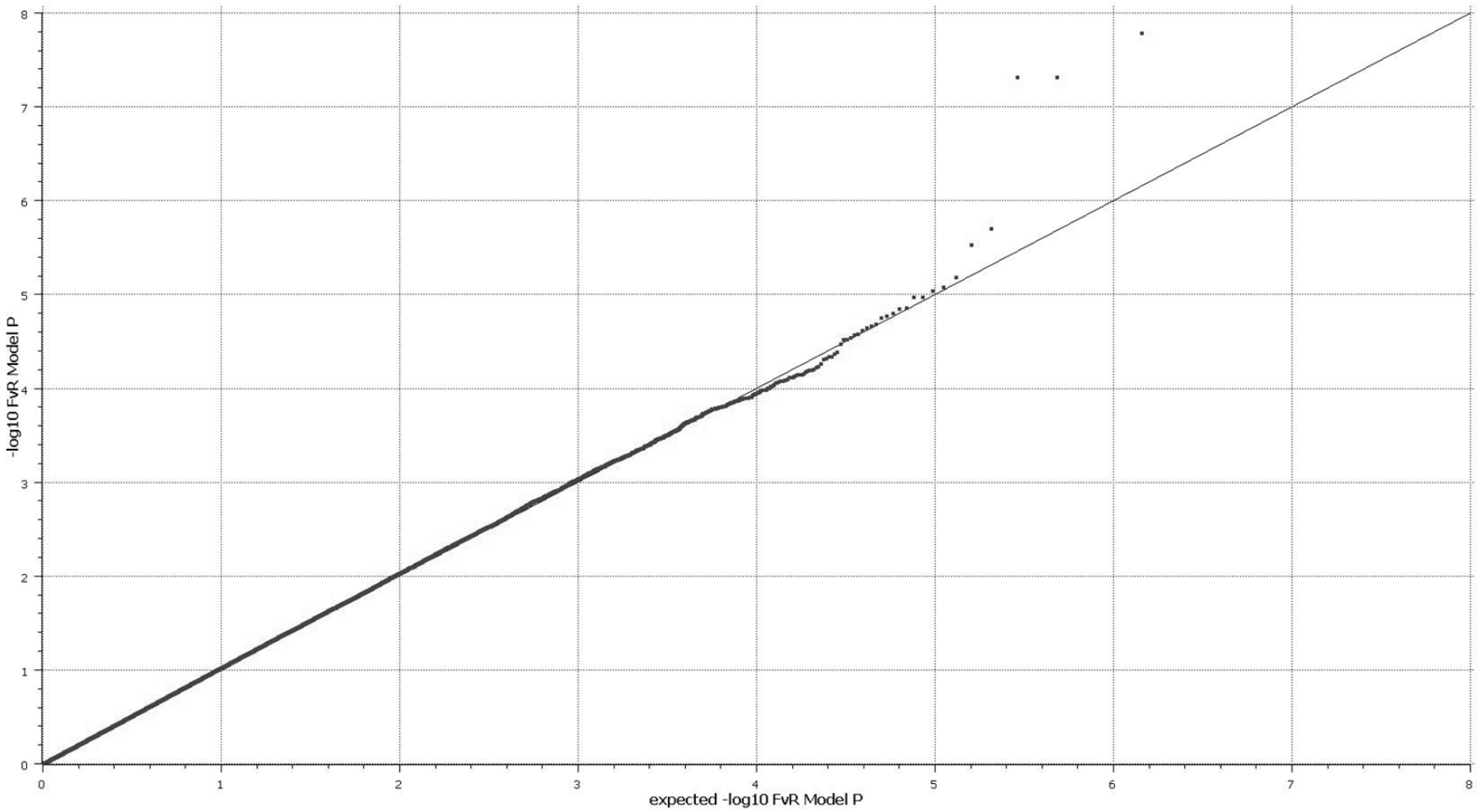

Figure 7. Q-Q plot of schizophrenia subjects only adjusted for self-identified race, baseline BPRS score, and medication dose

E. Race, ancestry and *GRID2* association

The observed minor allele (A) frequency at *GRID2* rs9307122 was 54, 26, and 71% for self-identified Caucasians, African Americans, and Hispanic/Asian/Native Americans, respectively. Because allele frequencies differ with between race groups and LD to a causal genetic variant can differ based on ancestry, analysis of rs9307122 was stratified by self-reported race (See Table 5). Interaction terms for self-identified race X rs9307122 genotype were not significant (p>0.5, data not shown). The effect of ancestry (as measured by AIMs) was examined in each self-identified race stratum (see Table 6).

TABLE V

STRATIFIED ANALYSIS OF *GRID2* rs9307122

	White (n=38)		Black (n=36)		Hispanic/Asian/ Native American (n=14)	
Variable	**β**	**p**	**β**	**p**	**β**	**p**
Bipolar diagnosis	3.92	0.367	8.84	0.003	5.22	0.135
Depression diagnosis	6.63	0.066	-1.02	0.779	10.45	0.021
Baseline BPRS	0.48	<0.001	0.55	<0.001	0.29	0.072
ln(CPZ)	-2.46	0.081	-1.66	0.185	-1.20	0.496
GRID2 rs9307122	-4.87	<0.001	-6.70	<0.001	-5.89	0.009
Model r^2	0.59		0.59		0.68	

TABLE VI

AIMS ADDED TO BPRS CHANGE SCORE MODELS OF *GRID2*

	White (n=38)		Black (n=36)		Hispanic/Asian/ Native American (n=14)	
Variable	β	p	β	p	β	p
Bipolar diagnosis	4.09	0.346	8.99	0.002	5.56	0.142
Depession diagnosis	6.18	0.088	-2.10	0.564	10.90	0.027
Baseline BPRS	0.50	<0.001	0.60	<0.001	0.25	0.164
ln(CPZ)	-2.98	0.048	-1.23	0.330	-0.84	0.674
GRID2 rs9307122	-4.63	0.001	-6.42	<0.001	-5.38	0.033
%European	-22.40	0.300				
%West African			9.47	0.151		
%Native American					2.91	0.616
Model r^2	0.608		0.62		0.69	

IV. DISCUSSION

In our three-staged approach, we first examined *GRM3* SNPs that have previously associated with antipsychotic response phenotypes. In our independent sample, rs274622 was not associated with overall symptom response as seen in Fijal et al. (2009), but was associated with negative symptom response as found in Bishop 2005 [10]. This is especially impressive because the BPRS negative symptom subscale used in our study is a less comprehensive negative symptom evaluation than the Scale for Assessment of Negative Symptoms that was used in the Bishop 2005 study [23]. We were unable to replicate the findings of Bishop (2011) [22], however only one of the two SNPs from that study was available to us and the phenotypes in the two studies (treatment refractory symptoms versus early response to antipsychotics) are related but distinct from one another. These negative findings could be due to the heterogeneous diagnostic groups in our study; previous studies have examined patients with schizophrenia only. In addition, genotypes were not available on our array for many of the previously studied polymorphisms.

The examination of candidate genes in the glutamate system did not yield statistically significant associations after correction for multiple testing, however the candidate gene findings could represent clinically-meaningful differences in treatment outcomes. Adjusted mean BPRS change score by *GRM7* rs2069062 genotype is shown in Figure 8. Response rates were 58, 36, and 0% for individuals with the G/G, G/T, and T/T

genotypes, respectively. Again, the intronic SNP rs2069062 is likely not a causal polymorphism, but could be tagging a functional SNP nearby. The metabotropic glutamate receptor 7 encoded by *GRM7* is known to regulate NMDA receptor trafficking and function [24]. NMDA receptor dysregulation has been strongly associated with the pathophysiology of schizophrenia [25].

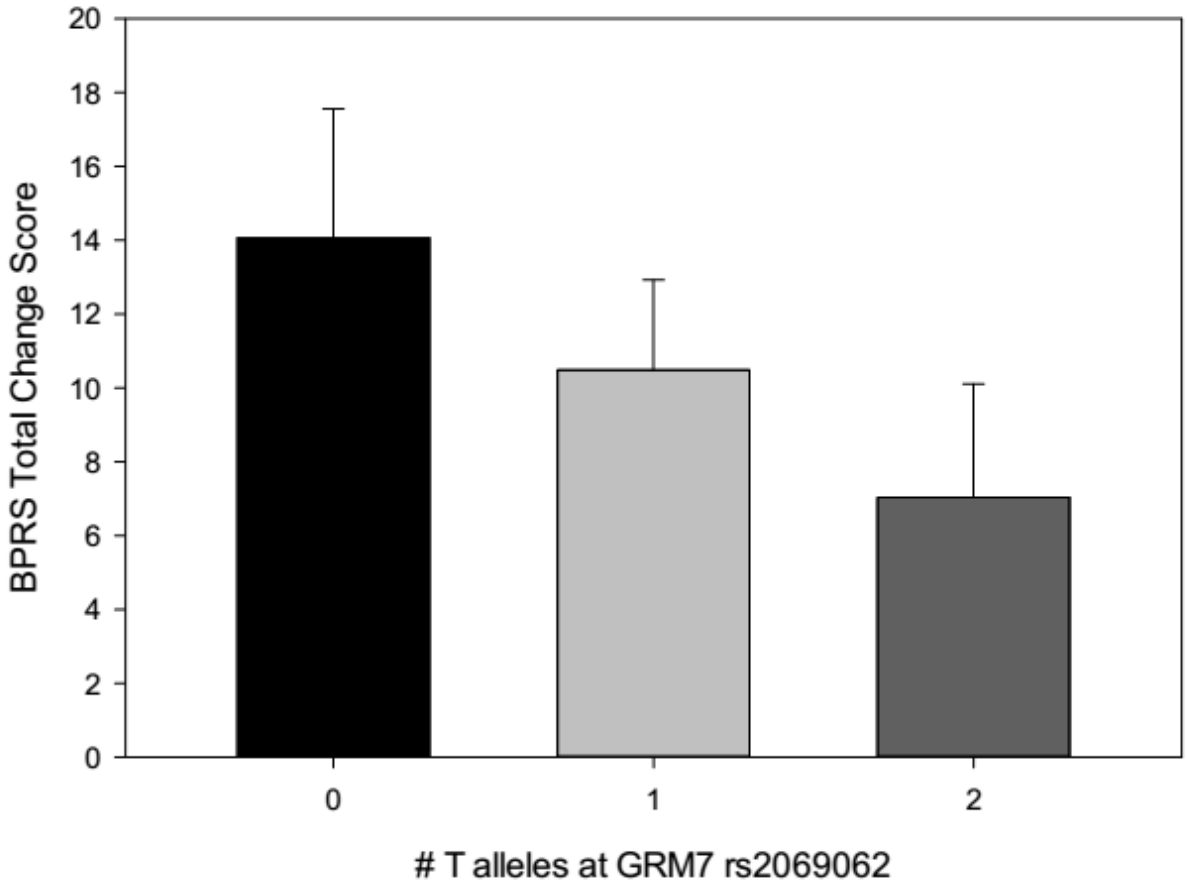

Figure 8. Adjusted BPRS change score by *GRM7* rs2069062 genotype (95% confidence interval)

Candidate gene findings near *SLC38A1* were interesting as well. *SLC38A1* encodes the sodium-coupled neutral amino acid transporter 1, which transports glutamine. Glutamine is a precursor for glutamate. However, this gene has not previously been linked to psychosis or antipsychotic response to our knowledge. The associated markers were downstream of the 3' UTR. They could be tagging polymorphisms in the 3' UTR, which can influence gene expression.

We performed, to our knowledge, the first genome-wide association study of antipsychotic response in first episode psychosis. The most striking finding was an association in *GRID2* that was significant in genome-wide analyses of both the complete sample and the schizophrenia only subpopulation. *GRID2* encodes the ionotropic glutamate receptor delta 2 (GluD2). *GRID2* was not included on the panel of glutamate candidate genes because despite its name, it does not actually bind glutamate [26, 27]. This receptor is expressed almost exclusively in cerebellar Purkinje cells [26] and dysfunction or absence of the protein is known to induce motor, learning, and cognitive deficits in animal models [28-31]. Recently, it was shown that GluD2 acts as an ion channel and the metabotropic glutamate receptor 1 (mGlu1) triggers GluD2 gating [32]. This finding indicates that GluD2 gating can be triggered indirectly by glutamate (through mGlu1). Thus the results of our genome-wide analyses are consistent with the hypothesis that glutamate-related genetic polymorphisms may affect response to antipsychotics.

We identified two SNPs in *GRID2* in full LD that met genome-wide significance. These SNPs, in an intronic region, do not have known functional consequence. We have identified two nearby exonic missense mutations and an in-frame insertion/deletion that may have functional consequences. These polymorphisms are not directly captured by the array data used in this study, and due to close proximity to the significantly associated SNPs, may be in LD. Directly genotyping these nearby and potentially functional polymorphisms is a logical next step in our investigation of *GRID2* and antipsychotic response.

Because allele frequencies differ by self-reported race, we stratified analysis of *GRID2* by race (Table 5). It should be noted that there was no significant effect of self-identified race in our clinical model (Table 3). In In race-stratified genetic analyses, the effect size of rs9307122 was similar across race groups and was highly significant ($p<0.01$) in each. The degree of LD between nearby genetic markers can differ depending on ancestry. Because rs9307122 may not be a functional SNP but may instead be tagging a nearby functional SNP not captured by the array, we needed to investigate the effect of ancestry using AIMs. Ancestry was not significant in any of the race-stratified models (Table 6, all $p>0.15$). If rs9307122 was linked to a causal SNP and LD between these two loci differed by ancestry, we would expect to see a significant ancestry effect in these regressions.

In our genome wide analysis of the schizophrenia-only population, we encountered another SNP that met the genome-wide significance threshold. This SNP, rs687279, is located in a poorly characterized region of chromosome 8. RNA transcripts generated from this region are non-coding and thus are not translated into a protein. Some non-coding RNAs are involved in the regulation of translation and RNA splicing, which represents a potential functional mechanism behind our observed association. However, visual examination of the Manhattan plot for this finding (Figure 6) does not show similar strength of association for nearby SNPs which may be an indicator of Type I error in genome-wide studies.

There are limitations to our analyses. Our sample size was rather modest for these types of analyses, and were only powered to find strong associations for relatively common

SNPs. As a result, we may have been unable to identify SNPs with weaker treatment effects and could not analyze rarer variants. Furthermore, we studied a sample that was heterogeneous in terms of race and ethnicity. We attempted to adjust for this by stratifying results by self-identified race and examining any influence of AIMs. In our sample, we did identify some degree of heterogeneity in terms of initial presentation and treatment response by diagnosis, and although we adjusted analyses for this, there could be residual confounding. Finally, data is presented from an open label, flexible dose design. We adjusted analyses for equivalent antipsychotic dose, which adjusts for both the potency of agent and dose each individual was treated with. However in this open label study it is possible that clinicians' evaluations of patients were influenced by knowing the treatment each patient received.

In conclusion, we identified a novel relationship between *GRID2* and antipsychotic response in first-episode psychosis. Although *GRID2* was not on our list of glutamate candidate genes, recent literature suggests that this finding may be consistent with a glutamate model of psychosis. Our group will work to identify nearby SNPs that alter protein function in an attempt to locate the causal variant. We were unable to detect significant SNPs in our candidate glutamate gene analyses, however we identified potential regions of interest in *GRM7* and *SLC38A1*. The association between *GRM3* promoter region polymorphism rs274622 and negative symptom response to antipsychotics found in schizophrenia patients in Bishop (2005) may also apply to a broader first-episode psychosis population based on our findings. Altogether, our findings suggest that glutamate system polymorphisms may influence antipsychotic response in first episode psychosis.

Our highly significant finding in *GRID2* is plausibly linked to the glutamate hypothesis of psychosis and should be further examined in an independent replication sample.

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PUBLICATIONS:

Original Research

Stevenson JM, Patel JH, Churchwell MD, Vilay AM, Depestel DD, Sorgel F, et al. Ertapenem clearance during modeled continuous renal replacement therapy. International Journal of Artificial Organs. 2008 Dec;31(12):1027-34.

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Book Chapters

Bishop JR, Stevenson JM, Burghardt KJ. Pharmacogenomics in Mental Health. In: Pharmacogenomics: Applications to Patient Care, 2nd Ed. ACCP, Kansas City (2014). (in revision)

ABSTRACTS AND SCIENTIFIC PRESENTATIONS:

Podium Presentations

Stevenson JM, Bishop JR, Fitzgerald JM, Wong M, Pavuluri M. Analysis of the relationship between lithium concentrations, symptom response, and cognitive performance in adolescents with bipolar disorder. ACPE Continuing Education Lecture, Great Lakes Pharmacy Residents Conference. West Lafayette, IN (4/26/2012).

Stevenson JM, Bishop JR, McMahon R, Patel S, Leigh JW, Cook EH, Pavuluri M. Serotonin Transporter 5HTTLPR Polymorphism and Neurocognitive Outcomes in Lithium-Treated Pediatric and Adolescent Bipolar Disorder. College of Psychiatric and Neurologic Pharmacists Annual Meeting. Colorado Springs, CO (4/22/2013).

Stevenson JM, Reilly JL, Patel S, Harris MS, Prasad KM, Badner JA, Nimgaonkar V, Keshavan MS, Sweeney JA, Bishop JR. Glutamate system gene polymorphisms and antipsychotic response in first episode psychosis. College of Psychiatric and Neurologic Pharmacists Annual Meeting. Phoenix, AZ (4/28/2014).

Peer-Reviewed Abstracts

Stevenson JM, Vilay AM, Eyler RF, Mueller BA. Elimination of Glucose During in-vitro Continuous Renal Replacement Therapy. American Society of Health-System Pharmacists Midyear Clinical Meeting and Exposition. Anaheim, CA (12/6/2010). Poster/abstract.

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Drozda K, Nutescu EA, Bress AP, Galanter WL, Stevenson JM, Duarte JD, Cavallari LH. Description and Feasibility of a Comprehensive Warfarin Pharmacogenetics Service. American College of Clinical Pharmacy Annual Meeting. Albuquerque, NM (10/23/2013). Poster/abstract.

Lee YM, Drozda K, Stevenson JM, Galanter WL, Stamos TD, Nutescu EA, Cavallari LH. Clinical factors affecting time to target INR in genotype-guided warfarin dosing of inpatients. American Society of Health-System Pharmacists Midyear Clinical Meeting and Exposition. Orlando, FL (12/9/2013). Poster/abstract.

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Stevenson JM, Reilly JL, Patel S, Harris MS, Prasad KM, Badner JA, Nimgaonkar V, Keshavan MS, Sweeney JA, Bishop JR. First episode psychosis pharmacogenetics: does glutamate affect antipsychotic response? Pharmacogenetics in Psychiatry Annual Meeting. Hollywood, FL (6/15/2014). Poster/abstract.

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Local Abstracts

Stevenson JM and Ellingrod VL. The association between serotonin receptor (HTR2C) -759 C/T polymorphism and metabolic syndrome in schizophrenia patients. Michigan Institute for Clinical and Health Research Annual Clinical Research Symposium. Ann Arbor, MI (10/31/2008). Poster/abstract.

Stevenson JM, Malati CY, Alfaro RM, Penzak SR, Kovacs JA. Echinacea purpurea significantly induces cytochrome P450 3A activity but does not alter lopinavir-ritonavir exposure in healthy subjects. National Institutes of Health Summer Poster Day. Bethesda, MD (8/6/2009). Poster/abstract.

Stevenson JM, Reilly JL, Patel S, Harris MS, Prasad KM, Badner JA, Nimgaonkar V, Keshavan MS, Sweeney JA, Bishop JR. Metabotropic glutamate receptor 7 (GRM7) pharmacogenetics in first episode psychosis. University of Illinois at Chicago College of Pharmacy Research Day. Chicago, IL (3/7/2014). Poster/abstract.

INVITED PRESENTATIONS:

"Dose-Dependent QT Prolongation with Citalopram" ACPE Continuing Education Lecture, University of Illinois at Chicago College of Pharmacy. Chicago, IL (10/13/2011).

Pharmacogenetics of Lithium Treatment for Pediatric Bipolar Disorder: Role of the Serotonin Transporter" Institute of Human Genetics. Chicago, IL (2/8/13).

"Antipsychotic pharmacogenetics in first episode psychosis: a work-in-progress" Institute of Human Genetics. Chicago, IL (12/13/2013).

AWARDS AND HONORS:

Abe Plough Community Pharmacy Fund Scholarship, University of Michigan College of Pharmacy, Ann Arbor, MI, April 2009

Peter Labadie and Suzanne Saxman Scholarship, University of Michigan College of Pharmacy, Ann Arbor, MI, April 2010

Joseph D. Williams Leadership Scholarship, University of Michigan College of Pharmacy, Ann Arbor, MI, April 2010

Winner, Research Trainee Award, College of Psychiatric and Neurologic Pharmacists Annual Meeting, Colorado Springs, CO, April 2013

Winner, New Investigator Award, College of Psychiatric and Neurologic Pharmacists Annual Meeting, Phoenix, AZ, April 2014

Winner, Young Investigator Travel Award, Pharmacogenetics in Psychiatry Annual Meeting, Hollywood, FL, June 2014

Winner, Fellowship Research Award, University of Illinois at Chicago College of Pharmacy, Chicago, IL, June 2014

PROFESSIONAL SERVICE:

Manuscript reviewer: *Current Psychiatry, Pharmacotherapy, Journal of Affective Disorders, Current Drug Safety*

TEACHING:

Past

University of Illinois at Chicago
PMPR 342 Experiential I Intermediate Pharmacy Practice Experience (Required) 2011: Co-preceptor. Provided experiential education on internal medicine to two first-year pharmacy students. Assisted with the preparation and evaluation of case presentations.

PMPR 370 Pharmacy Grand Rounds (Required)
2012: Lecturer. Taught one-hour didactic lecture regarding electroconvulsive therapy and its implications on pharmacotherapy for psychiatric disease. Roster: approximately 180 first-year pharmacy students.

PMPR 388 Advanced Pharmacy Practice Specialty Experience (Required) 2011-2012: Co-Preceptor for cardiology, medicine, and medical intensive care unit rotations. Roster: up to 2 fourth-year pharmacy students per rotation for 4 credit hours.

Current

University of Illinois at Chicago
PMPR 359 Topics & Issues in Clinical Post-Graduate Training Programs (Elective) 2011-2014: Lecturer. One-and-a-half hour lecture to second- and third- year pharmacy students about issues in residency and fellowship training. Allowed students to shadow and learn in experiential environment during overnight on-call shifts. Roster: approximately 60 pharmacy students.

HON 201 A Decade of Pharmacy Experiences (Elective)
2013-present: Lecturer. One hour lecture to Honors program undergraduate students and first-year pharmacy students about non-traditional career paths in pharmacy and the training and preparation required to obtain these positions. Roster: approximately 20 undergraduate Honors students and first-year pharmacy students.

PMPR 388 Advanced Pharmacy Practice Specialty Experience (Elective) 2013-present: Co-preceptor for pharmacogenetics-based clerkship experience. Enrollment – up to 2 fourth-year pharmacy students student per 6 week rotation for 4 credit hours.

PMPR 355 Seminar in Pharmacy Research (Elective)
2013-present: Lecturer. One-hour lecture that briefly describes the process of investigating a research question in the context of a pharmacogenetic study. Roster: 30 first- and second-year pharmacy students.

PMPR 440 Pharmacokinetics (Elective)
2014-present: Lecturer. Two-hour lecture and case-based recitation regarding pharmacokinetic considerations of antipsychotic drugs. Roster: approximately 30 second- and third-year pharmacy students.

SOFTWARE SKILLS SPSS, SAS, Stata, Plink, Golden Helix, Haploview

PRESS A Dose of Genetics – UI Health System uses science to make personalized health a reality for patients taking warfarin.
Published in: *Illinois Health*.
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