Linking Dental Arch Form and Body Mass Index via Genetic Variants within the Hippo Signaling Pathway

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THESIS

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This thesis is dedicated to my husband Andrew, my mom Miran, my stepdad Steven, and my sister Nicole for their unconditional love and support throughout this entire journey.

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LIST OF ABBREVIATIONS

AAOF	American Association of Orthodontists Foundation
BFFQ	Block's Food Frequency Questionnaire
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CNC	Cranial Neural Crest
CVA	Canonical Variate Analysis
ddNTP	Dideoxynucleotide Triphosphate
DHQ	Diet History Questionnaire
DNA	Deoxyribose Nucleic Acid
GPA	Generalized Procrustes Analysis
GH	Growth Hormone
GM	Geometric Morphometrics
IRB	Institutional Review Board
PC	Principal Component
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
SNP	Single Nucleotide Polymorphism
STL	Standard Triangle Language
TAm-Seq	Targeted Amplicon Sequencing
UIC	University of Illinois at Chicago

SUMMARY

Obesity and malocclusions are both problematic health conditions found throughout pediatric populations worldwide.[1] The prevalence of obesity has increased in all racial and ethnic groups, both sexes, as well as all age brackets.[2] This study will investigate the relationship between dental arch form and body mass index (BMI) via genetic variants within the Hippo signaling pathway. Although studies have postulated a relationship between dental arch form and BMI, there are limitations in the number of subjects in these studies and insufficient, existing literature relating dental arch form to specific genetic factors. Therefore, our study was conducted to determine whether a link exists between dental arch form and BMI via the genetic variants in the Hippo signaling pathway.

A cross-sectional, retrospective study was conducted in the Department of Orthodontics at the University of Illinois at Chicago which aimed to analyze how nutritional and genetic components of obesity impact dental arch form. We collected standard pre-treatment orthodontic records on our subjects and specifically included digital dental models, height, and weight from one hundred seventeen patients to be analyzed in this study. In addition to the standard pre-treatment orthodontic records, waist circumference, saliva samples, and nutritional information from the Block Food Frequency Questionnaire were collected and reviewed. Subjects with a medical history of any significant craniofacial anomalies, cleft lip and/or palate, and/or endocrine disorders were excluded from the sample. The subjects ranged from ages 7-17 years old and included both males and females. The height and weight of each subject were measured using a Health O Meter© Digital Physicians Scale, then applied to the calculation of the body mass index of each subject using the following equation: 703 x weight (lbs.) / [height (in)]^2.[3] Previous literature has shown that obese children exhibit wider dental arch forms than normal weight children.[4] The clinical relevance of the results of this study will have an impact on

properly determining the stage for growth-based orthodontic treatment as obese children may require earlier interventions.[4]

Landmark Editor was used to identify and digitally mark eighty coordinate landmarks on the maxillary and mandibular dental casts. Geometric morphometrics software, MorphoJ, was then used to analyze the size and two-dimensional shape variation of the dental casts. A series of Linear Regression Analyses, Principal Components Analyses (PCA), and Canonical Variate Analyses (CVA) were conducted. Normal parametric tests were performed in order to determine whether a particular BMI category correlated to variations of size and shape of the maxillary and mandibular dental arches from the study models.

The results for the genotype-phenotype data showed transversely wide mandibular arch form phenotypes were associated with the following selected SNPs in the Hippo signaling pathway: rs13085791 within the MST1 gene, rs13205080 within the LATS1 gene, rs60842975 and rs6490637 within the LATS2 gene, rs4636447 and rs7522116 within the FOXO6 genes; and rs11758653 within the TEAD3 gene.

The results for the phenotype data illustrated that principal component, PC15, which describe shape variance of the mandibular dental arch form in relation to the obese BMI percentile, was statistically significant. Furthermore, the Linear Regression Analysis suggests that an increase in BMI percentile is correlated with a wider mandibular arch.

While the results suggest that the maxillary arch did not show a significant relationship with BMI and the genetics factors of the Hippo signaling pathway, the mandibular arch exhibited a significant relationship between BMI and the genetic factors of the Hippo signaling pathway.

1. INTRODUCTION

1.1 Background

Orthodontics is a constantly evolving field. With diverse genetic backgrounds, growth patterns, and diet habits among our youth and adolescent population, there are various factors affecting orthodontic treatment.[5] Mandibular growth and malocclusion are predominant features assessed in growing patients.[6,7] An orthodontic assessment involves, but is not limited to the mandibular growth pattern and dental arch development, which are both vital components in establishing a stable occlusion that is also esthetic for the patient.[7] Besides malocclusion, today's youth and adolescent populations are also affected by new conditions that have been less common in the past.[2] For the past three decades, childhood obesity has been a growing epidemic in the United States.[2] Obesity is a medical condition involving excess adiposity, affecting approximately 19% of American children and adolescents in the U.S.[2] In this study, we investigate whether there is a connection between single nucleotide polymorphisms along the Hippo signaling pathway and obesity and how both components influence malocclusion and dental arch development.

1.2 Objectives

- To compare body mass index (BMI) with arch form to see if a correlation exists
- To look for a relationship between BMI, genetic variation in the Hippo signaling pathway, and arch form

1.3 Null Hypotheses

- There is no correlation between genetic variation in the Hippo signaling pathway and dental arch form in children and adolescents.
- There is no correlation between BMI and dental arch form in children and adolescents.

2. REVIEW OF LITERATURE

2.1 Genetics

2.1.1 Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs) are abundant genetic variations among humans and are estimated to occur in 1 out of every 1,000 bases in the human genome.[8] SNPs are normal variations located in the genome that creates genotypic diversity in humans.[8] At the SNP site, there may be a change in a single base pair or all four base pairs and these SNPs can occur in areas of DNA that encode for genomic regulation.[9] SNPs are expected, normal variations and depending on the location of the SNP, it may have various presentations at the phenotypic level.[8] These predicted SNP variations have been mapped in the human genome project.[9] To date, researchers have discovered more than 335 million SNPs across humans from multiple populations.[9] A typical genome differs from the reference human genome at 4 to 5 million sites, most of which is attributed to SNPs.[9] A SNP is considered a candidate SNP when the frequency of two alleles being present among three individuals occurs at greater than 30% in a pooled sample.[8] Specifically pertaining to our research, previous studies have evaluated the genetic makeup of obesity that consists of over eighty identifiable genetic loci in the Hippo signaling pathway.[10]

2.1.2 Polymerase Chain Reaction

Polymerase chain reaction (PCR) is an enzyme-driven reaction that produces an exponential quantity of a single fragment of DNA and is a tool used for multiple purposes including genetic sequencing.[11] It is called a chain reaction because the products of the first reaction are used as substrates for the subsequent reactions.[12] The process of amplifying a small segment of DNA through PCR is beneficial because it is used for multiple purposes which include, but are not limited to the following: diagnosing infections, genetic research, and molecular biology.[13] A thermal cycler machine that houses small test tubes called epindorph

tubes containing Taq polymerase, primers, a DNA template, and nucleotides is used.[13] Taq polymerase is a type of thermostable DNA polymerase which replicates new strands of DNA from a DNA template.[13] Having a heat stable enzyme such as Taq polymerase is critical because high temperatures are necessary to carry out the reaction.[13] Short sequences of nucleotides called primers are necessary to initiate the reaction and select the exact fragment of DNA for amplification.[11] Two specific primers are used in the reaction to isolate the DNA region of interest by binding at the 5'end.[11] One primer binds at the beginning of the area of interest while the other primer binds at the end of the area of interest.[11] The DNA template is the original DNA segment that contains the target region for amplification.[11] Nucleotides are the structural units used to synthesize DNA.[11]

The process of PCR involves three fundamental steps: (1) denaturation, (2) annealing, and (3) extension.[11] In the first step of PCR called denaturation, the temperature of the thermal cycler machine is raised to ninety-six degrees Celsius.[11] This step is used to denature or break up the DNA into two strands.[11] The next step of PCR is known as annealing.[11] The temperature is decreased to fifty-five degrees Celsius.[11] This decrease in temperature provides an ideal environment for the primers to bind to the target sequence on the single-stranded DNA, which will be amplified.[11] The third step called extension requires free nucleotides used to synthesize the new DNA.[11] During this step, the temperature is increased to seventy-two degrees Celsius so that the Taq polymerase binds to the primer regions and synthesizes new DNA, which is complementary to the original DNA strand.[11]

2.1.3 **Sanger Sequencing**

Sanger genetic sequencing uses PCR in order to sequence an area of interest.[14] Sanger genetic sequencing is based on dideoxynucleotides in DNA polymerization reactions.[14] A

nucleotide consists of three components: a nitrogenous base, sugar, and phosphate groups.[14] A nucleotide without a hydroxyl group in its sugar component is called deoxynucleotide (dNTP).[14] Deoxynucleotides are present in DNA and serve as substrates for various DNA polymerases.[14] A nucleotide without the 2' hydroxyl group and the 3' hydroxyl group is called dideoxynucleotide triphosphate (ddNTP).[12,14,15] With the absence of the 3' hydroxyl group, there is no addition of new nucleotides in the polynucleotide chain and the reaction stops.[16] The products of PCR replicating segments of DNA with the area of interest are multiple segments of DNA with varying lengths.[14]

Over the last few years, Sanger sequencing has evolved into a streamlined process called Targeted Amplicon Sequencing (TAm-Seq).[15] TAm-Seq is a simple, efficient method of targeted sequencing that integrates all the conventional steps of Sanger sequencing (thermal cycling, sample purification, and capillary electrophoresis).[15] This method allows researchers to detect genetic variation in specific genomic regions.[15] It is essentially a two-step PCR process that enables researchers to amplify a targeted sequence of DNA called amplicon using the traditional PCR and then an additional PCR that attaches a known 10 bp tag or barcode.[15]

The individual samples used for TAmSeq are initially transformed into libraries by adding adapters.[15] The adapters enable the amplicons to be indexed, or labeled with a unique barcode.[15] The adaptors also allow the amplicons to adhere to the flow cell for sequencing.[15] The purpose of indexing, or adding a barcode to, amplicons is to identify them from different samples.[15] After the addition of indices and a locus specific primer that amplifies the amplicon, the uniquely tagged amplicon library is ready for cluster generation via PCR and then sequencing.[15] A sequencing platform, or next-gen platform, is used to set up and analyze the

run by entering the library prep method and sequencing run parameters.[15] Data is automatically generated through this sequencing platform.[15]

2.2 Hippo Signaling Pathway

2.2.1 Hippo Signaling Pathway and Body Mass Index

The Hippo signaling pathway controls the balanced regulation of adipocyte proliferation and differentiation at both the cellular and organ level.[16] Ardestani et al. (2018) explains, "A key transcription factor orchestrating adipogenesis is peroxisome proliferator-activated receptor gamma (PPARγ), which binds to domains on YAP and TAZ."[16] PPARγ stimulates the expression of genes involved in adipogenesis.[16] When the Hippo pathway is on, TAZ phosphorylation promotes cytoplasmic retention of both TAZ and LATS-induced YAP, a Yes-associated protein.[16,17] YAP and TAZ are transcriptional co-activators for transcription factors of numerous signaling cascades.[16] YAP induces the WNT antagonist, Dkk1, to diminish osteogenic signaling in favor of adipogenesis.[16] LATS kinase, MST1, FOXO6, and TEAD3 are activated while YAP/TAZ are deactivated at high cell density or adipogenesis.[16] It is important to note that YAP levels must be fine-tuned; over- or under-expression of YAP inhibits adipogenesis.[16] On the other hand, cytoplasmic phosphorylated TAZ functions as an inhibitor of WNT signaling by degrading β-catenin, a central WNT signaling element, thus further reducing adipocyte proliferation.[16] When the Hippo pathway is off, KR62980, a ligand for PPARγ, antagonizes adipocyte differentiation by promoting TAZ nuclear localization.[16] Both YAP and TAZ are localized in the nucleus, but there is enhanced interaction between TAZ and PPARγ.[18] Therefore, within the nucleus, YAP and TAZ serve as transcription co-activators involved in self-renewal, apoptosis, and inhibition of adipogenesis.[18] Ardestani et al. (2018) has shown that dysregulation of the Hippo signaling pathway leads to the pathogenesis of several metabolic diseases such as obesity, type II diabetes, fatty liver, and cardiovascular disorders.[16] The Hippo

signaling pathway has also been implicated in various cancers such as breast, colorectal, and liver.[16]

2.2.2 **Hippo Signaling Pathway and Craniofacial Development**

Another function of the Hippo signaling pathway involved was found in craniofacial development and morphology leading to malocclusions.[10] Craniofacial neural crest (CNC) cells originate in the dorsal neural tube and diversify into multiple cell types, including smooth muscle cells, cartilage, bone, neurons, and glia.[10] CNC cells are vital for craniofacial development.[10] The craniofacial skeleton, including the calvaria, mandible, and most midfacial bones, develops through the ossification of CNC-derived progenitor cells.[10] The influence of the Hippo signaling pathway on craniofacial development was investigated by specifically inactivating YAP and TAZ in cranial neural crest cells.[19]

YAP homozygous knockout compound mutants displayed an embryonic lethal phenotype by E10.5, with severe craniofacial defects, such as disrupted frontonasal and mandibular structures, hemorrhage, failed neural tube closure, and neural tube vessel regression.[19] In addition to this pathway, leptin, discovered in 1994 by Zhang et al., is a hormone that has a regulatory function for body fat levels.[19] Cephalometric studies in children with growth hormone (GH) deficiency demonstrated smaller anterior and posterior cranial bases, small posterior facial height, short ramus height, and smaller maxillary and mandibular length.[17] Wang, Yu, and Yu (2017) found that the maxilla seemed to be less affected than the mandible.[17] The mandibular plane angle has been reported to be greater than normal in GH-deficient patients.[17] The mechanisms that regulate craniofacial growth and development are complex and include interplay between genes, hormones, nutrients and epigenetic factors that

give craniofacial bones their final form.[20] Mechanisms that interfere with the dynamic between genes, hormones, nutrients, and epigenetic factors may result in an aberrant growth pattern.[20]

2.2.3 Hippo Signaling Pathway and Tooth Development

The active participants in the Hippo signaling pathway are also involved in tooth development.[20] Wang et al. (2017) looked at the teeth of mice and found that the overexpression of YAP had greatly widened dental lamina.[20] On the other hand, the loss of function of YAP showed small tooth germs as a result of reduced epithelial cell proliferation.[20]

2.3 BMI and Childhood Obesity

Body mass index (BMI) is calculated as a person's weight in kilograms divided by the square of height in meters.[21] A BMI of <18.5 is considered underweight, a BMI between 18.5-24.99 is considered normal weight, a BMI between 25-29.99 is considered overweight, and a BMI > 30 is considered obese.[21] A high BMI can be an indicator of high body fat content and can be used to screen for weight categories.[21] Although BMI is not considered a diagnostic tool, it identifies children who have excess adiposity and may explain their risk for certain health conditions.[21] Freedman et al. (2009) states, "Among relatively fat children, BMI is a good indicator of excess body fat, but differences in the BMIs of relatively thin children can be largely due to fat-free mass."[21] Freedman et al. (2008) have found that a high BMI has a moderately high (70% to 80%) sensitivity and positive predictive value, along with a high specificity (95%), which signifies that children with a high BMI are much more likely to have adverse risk factor levels and to become obese adults than are thinner children.[21] Waist circumference and skinfold thickness may also be useful in delineating children with moderately elevated levels of BMI (85th to 94th percentiles) who truly have excess body fatness or adverse risk factor levels.[21]

The CDC recommends using BMI percentiles calculated using age and sex along with height and weight, as adult BMI calculations are misleading in growing children.[3]

2.4 **Block Food Frequency Questionnaire**

The Block Food Frequency Questionnaire (BFFQ) has been shown to be a good indicator of caloric consumption throughout the year.[22] Furthermore, according to Hunsberger, et al. (2012), the BFFQ has good relative validity, can be self-administered to young people of an appropriate age, and is a relatively inexpensive method for assessing dietary intake.[22] Servings from 24-hour recalls were used to calculate the average daily intake of fruits, vegetables, potatoes, whole grains, legumes, meat/fish/poultry and dairy.[22] Protein (g), total kilocalories, glycemic index (glucose reference), glycemic load (glucose reference), total saturated fat (g), whole grain content of food (g), and added sugar (g) were also calculated.[22]

Even though the Diet History Questionnaire (DHQ) performed best overall, results from this study show that the DHQ and BFFQ tended to track similarly in the correlations before energy adjustment by sex.[23] The DHQ and the BFFQ are better at estimating absolute intakes than is the Willett FFQ.[23] A plausible explanation for the differences in absolute intakes may be attributed to how information about portion size is handled in the three questionnaires.[23] Unlike the other two instruments, the Willett FFQ does not ask portion size, and the standard data processing program provided by Harvard does not assign different portion sizes to males and females.[23] However, after adjusting for energy intake and nutrient density based on sex, all three questionnaires were found to be more comparable for purposes of assessing diet-disease risk.[23] Furthermore, Subar et al. provides information that the BFFQ produces mean estimates statistically equivalent to the six-day records for most of the nutrients.[23]

The BFFQ has been used in several other studies. A cross-sectional study on youth aged 10 to 17 years evaluated the reliability and validity of the BFFQ to assess their diet during the past seven days.[24] The participants were 83 children and adolescents (57% Hispanic, 21% African American, and 23% white; 53% were females, mean age of 13 years).[24] Cullen et al. found that the BFFQ mean daily consumption values were higher for percent energy from carbohydrate, servings of fruit, 100% fruit juice, and vegetables while it was lower for all other categories compared to the 24-hour dietary recall.[24] There were significant differences in the means between the two dietary assessment methods for most nutrients and food groups.[31] These results suggested that the BFFQ is valid for some nutrients and particularly useful for adolescents.[24] According to Marshal et al., the BFFQ showed reasonable estimates of milk, calcium, and vitamin D consumption in comparison to three-day diaries.[25]

Fatiha et al. referred to a study by Wilson and Lewis, which found that the BFFQ shows disagreement of energy and macronutrient intakes when compared to the three-day diet record of their subjects.[26,27] The BFFQ overestimates intakes for energy (2,180 vs 1,749 kcal), protein (68.3 vs 57.9), carbohydrate (298.7 vs 244.7), and fat (83.6 vs 62.3 g/day).[26] In addition, Fatiha et al. (2015) noted that the nutrients assessed using the BFFQ and the three-day diet records were only moderately correlated (r=0.50 to 0.55).[26] In a study conducted on Hmong American children, the authors found that the BFFQ did not appear to be a good measure of protein, grain, meat, and bean intake.[28] It was determined that the BFFQ was not a culturally competent assessment to address the ethnic diet of the Hmong population.[28] The authors recommended that the modifications should be made to the current BFFQ to reflect the food and beverages of the ethnic population in interest. [28]

2.5 Childhood Malocclusion

The etiology of malocclusions has been associated with genetic and environmental factors affecting each individual.[5,29] Orofacial structures such as mandibular size and tooth size appear to be hereditary.[5] Environmental factors such as diet, changes in soft tissue, early loss of primary teeth, the presence of oral habits, and the use of or lack of use of masticatory muscles affect mandibular size and tooth size.[30] Based on Profitt et al., the interactions between genetic and environmental factors are attributed to the balance of the jaw and tooth alignment, which in turn determine the equilibrium and occlusion for each individual.[5] An imbalance may, but does not always, lead to malocclusion.[5] Previous literature illustrates that the etiology of malocclusions is multifactorial.[5]

2.6 Effects of BMI on Skeletal Growth Rate, and Dental Development

BMI has been shown to have an impact on skeletal maturation,[31,32] dental development,[33–35] and the resulting soft tissue profiles.[36] Several studies have shown that obese children, when compared with age- and sex-matched controls, exhibit larger maxillary and mandibular measurements in all dimensions leading to bimaxillary prognathism and the opposite holds true for underweight children.[31,36] In addition, tooth development and time of eruption are processes influenced by factors that are not yet well-determined.[33] However, multiple studies have demonstrated that children with a high BMI are frequently found to have a precocious skeletal maturation and dental development.[33] Being able to accurately predict skeletal maturation and dental development in orthodontic patients is of high clinical relevance because it can determine when growth-modification based interventions are necessary and most effective.[23] Wang and Martin (2017) explained, “Even though the role of genetics and obesity has been evolving throughout the years, its implications in craniofacial and dental development are still poorly understood.”[19] It has been shown in the literature that there is a

difference in craniofacial measurements between children in the normal BMI range and children considered obese.[37] In general, research on this subject has indicated that obese subjects had a more prognathic maxilla and mandible, less convex profile and broader facial measurements.[37]

Despite low levels of GH, obese children showed more insulin-like growth factor which could link craniofacial growth to obesity rather than normal growth hormone.[37] Not only was the effect of BMI on mandibular growth studied, but researchers also investigated the effects of dental development on BMI. Numerous studies have indicated that children who were overweight or obese have accelerated dental development.[38] Obese patients also showed a greater differential between their chronological age and their skeletal age.[36] Studies show that higher BMI can lead to earlier pubertal growth but not necessarily more growth overall.[36]

2.7 **Effects of BMI on Malocclusion and Arch Form**

While there is currently limited research on this topic, a few recent studies have postulated that there is a relationship between BMI and dental arch forms characteristic of various classifications of malocclusions.[4,39] Guevara et al. evaluated dental arch casts of subjects with BMIs within normal range and subjects with BMI considered to be overweight.[4] Twenty-six three-dimensional landmarks were analyzed using Principal Components Analysis (PCA) to determine significant aspects of dental arch variation within the subjects.[4] PC1 (65.6% of the total variance) and PC3 (6.8% of the total variance) demonstrated significant relationships with BMI.[4] Along PC1, individuals with scores indicative of anterior-posterior dental arch discrepancy where the mandibular arch was protrusive beyond the maxillary arch, were significantly ($p<0.01$) related to an increase in BMI.[4] PC3, which highlights variation in mandibular arch protrusion and dental arch widths, was significantly ($p<0.01$) correlated with

BMI.[4] Even though the causes of malocclusion and obesity are multifactorial, Guevara et al. (2016) found that a significant relationship exists between patterns of dental arch forms indicative of a Class III malocclusion and increased BMI.[4] According to the results of a study conducted by Jasim et al. (2016), there was no association between BMI and anterior and posterior crossbite.[40]

Another recent study has shown that there is a correlation between BMI and arch form. The widths of dental arches of normal weight and overweight subjects from 8 to 13 years of age were measured using a digital, calibrated caliper from dental casts.[34] The upper and lower intercanine width was measured between the cusps of the contralateral canines.[39] The upper and lower intermolar width was measured from the central fossa of the first molar to the contralateral first molar.[39] The authors of this study found that there were statistically significant differences in the intercanine and intermolar widths between normal weight and overweight subjects, with dental arches being wider in overweight subjects compared to normal weight children.[39]

2.8 **Effects of BMI on Dental Crowding**

The World Health Organization (WHO) defines dental crowding as a misalignment in the position of teeth measured in millimeters.[40] The authors, Jasim et al. (2016), evaluated the dental arches of 600 subjects from 9 to 11 years old.[40] Jasim et al. (2016) considered the arches crowded when there was a shortage of 2 mm or more of space preventing the correct alignment of all the teeth.[40] Crowding was classified as present (in one or both arches) or absent (in neither arches).[40] The results showed significant association between BMI and dental crowding with high prevalence of crowding in overweight boys and girls, 76.56% and 74.55% respectively.[40] This was a surprising finding because overweight subjects tend to have

increased width and length of skeletal and dental arches, which would provide more space for dental alignment.[40] However, Jasim et al. (2016) attributed the association between BMI and dental crowding due to another association between BMI and carious lesions.[40] There is loss of space due to carious lesions, which further changes the development of the subjects' occlusion.[40] There has been an increase in dental caries concomitantly with increasing urbanization and westernization in most countries around the world, which is further associated with diets high in fat, high in sugar, and a sedentary lifestyle.[40]

2.9 Effects on BMI on the Rate of Dental Eruption

According to a study conducted in children from the Brazilian Amazon region, Evangelista et al. (2018) found the mean number of permanent teeth was higher in the overweight/obesity group ($p<0.001$) than the normal weight group for age-matched groups.[34] Another study by Mohamedhussein et al. (2019) found that there is a positive correlation between obesity and the rate of dental eruption, specifically in the early eruption of first and second permanent molars in obese children.[35] Nicholas et al. (2018) also confirmed that a pattern of precocious tooth eruption has been seen in overweight and obese children.[33]

2.10 Geometric Morphometrics

Hallgrimsson et al. (2015) defines morphometrics as the "quantification and statistical analysis of form, which is the combination of size and shape of a geometric object in an arbitrary orientation and location."[41] The shape of a geometric object is the remaining geometry once you standardize for size.[41] A significant feature of this quantitative shape analysis is that morphology can be plotted in a methodical way with morphospace.[41] Morphospaces are maps that illustrate how shapes are defined by quantitative traits which "are essential in quantitatively comparing and situating morphologies relative to each other."[41] When interpreting morphospaces, it is vital

to interpret morphospaces within the context in which they are constructed.[41] Hallgrimsson et al. (2015) emphasizes the importance of morphospaces having a few key properties: (1) relative locations and distances in such spaces must have biological meaning, namely, that similar forms should cluster together while those that are dissimilar should be far apart; (2) directions within the morphospace should have biological meaning in order to predict morphologies based on a continuous relationship or determine whether a group of related mutations or treatments produce effects in the same direction; (3) parallel trajectories in morphospace should represent comparable axes of phenotypic change, which signifies the ability to compare the effect of a continuous variable such as age, size, or treatment in two samples and expect that these effects would produce a displacement in the same direction for both shapes even though they are at different locations in morphospace; and (4) the axes of morphospace should be independent and have proportional units of measurement.[41] However, it is difficult for all four criteria to be met; therefore, there are several approaches to doing morphometrics with all approaches having advantages and disadvantages.[41]

According to Zelditch (2012), geometric morphometrics (GM) is the most established method of handling landmark-based data.[42] GM is defined as the multivariate statistical analysis of form as represented by the Cartesian coordinate data, which relies on superimposition of landmark coordinate data in order to place individuals into a common morphospace.[41] Currently, the most widely used form of superimposition is the Generalized Procrustes Analysis (GPA).[41] GPA aligns multiple individual objects into the same shape space by scaling, translating, and rotating the landmark coordinates.[41] There are several advantages of geometric morphometrics over other methods.[41] GM preserves geometry throughout an analysis, which means that "variation within and between groups can be visualized as displacements of individual landmarks."[41] These displacements can be used to generate two- or three-dimensional

deformations of an anatomical object, which displays how the object changes across the morphospace."[41] Another related advantage of GM is that the Procrustes superimposition-based method generates morphospaces in which multiple groups can be compared in a meaningful way.[41] Shape variation can be further analyzed into components that are related to biological factors corresponding to the deformations of landmark configurations, which is a significant advantage when determining biological relevance.[41] However, the GM approach also has its disadvantages. The most critical disadvantage is that superimpositions distribute some of the variation across landmarks, also known as the Pinocchio effect.[41] Although researchers have proposed different methods to minimize the distorting effects of variation at certain landmarks, this is still an area of further investigation.[41]

Several studies have used GM to evaluate malocclusion. For example, Banabilh et al. (2006) quantified and localized differences in Class I and Class II relationships in Malay children using geometric morphometrics of digitized dental models.[43] Another study observed the dental arch morphology in southeast Asian adults with obstructive sleep apnea in comparison to the control group through the use of geometric morphometrics.[43] Standardized digital photographs of the subjects' upper and lower study models were taken and the mean OSA and control dental arch configurations were computed using twenty-five homologous landmarks.[43] Another study compared the measurements of digital models versus plaster casts with the use of geometric morphometrics.[44] When the geometric measurements acquired from the landmarks from the digital models as well as the plaster casts were analyzed, the authors found a decrease in the variances of the distances between the canines related to the distance between the second premolars after the treatment.[45] The authors also found that the distance measurements obtained from the digital models and the plaster casts had similar precisions.[44] With GM, many

studies have been able to delineate size and shape differences in dental arch morphology between their test groups.

3. MATERIALS AND METHODS

3.1 Patient Selection

This study was funded by the American Association of Orthodontists Foundation (AAOF). Informed consent, parental authorization for personal health information, and assent for participation in the Hippo BMI Study were obtained. Records of 117 patients who presented for treatment to the Orthodontic Clinic at the University of Illinois at Chicago (UIC) were reviewed (IRB: 2017-1276). Standard pre-treatment orthodontic digital intraoral scans were obtained with the iTero Element 2 (Align Technology, San Jose, CA). Scans were obtained between October 2018 and August 2019. In addition to the standard digital intraoral scan, saliva samples and nutritional data from the Block Food Frequency Questionnaire were obtained. Other demographic information, including the age at the time of initial records, height, weight, sex, and race were also collected.

After the completion of the study, each of the 117 subjects were compensated a total of $20.00. Out of the 117 subjects in observation, 81 subjects ranging from 7 to 17 years of age were included in this study. 33 subjects were eliminated from the study due to incomplete and/or distorted scans and 3 subjects were eliminated due to failed amplicon sequencing. The intraoral scans, saliva samples, and nutritional data from the Block Food Frequency Questionnaire were all de-identified and randomly assigned a unique identifying number.

The criteria for inclusion and exclusion in this study are listed below.

3.1.1. Inclusion Criteria

- Male and female subjects ages 7-17 years old at the time of initial records

- Subjects without craniofacial anomalies
- Subjects without diagnosis of diseases and/or taking medications that affect growth and development
- Initial digital intraoral scans must be available
- Height and weight data must have been recorded at the time of initial records

3.1.2. **Exclusion Criteria**

- Non-growing
- Subjects who have previously received orthodontic treatment
- Subjects with craniofacial anomalies
- Subjects diagnosed with disease and/or taking medications that affect growth and development
- Subjects diagnosed with any significant endocrine disorders
- Distorted or missing records

3.2 Body Mass Index Calculation

The height and weight of each subject was measured using a Health O Meter© Digital Physicians Scale. Height and weight measurements were used in the calculation of the body mass index of each subject. BMI is calculated using the following equation: 703 x weight (lbs.) / [Height (in)]^2 .[45] The BMI percentile was then determined using the Center for Disease Control and Prevention (CDC) age- and sex-specific growth charts (Figure 1). The BMI percentiles were then used to identify the weight status of each subject as either underweight (less than 5th percentile), normal weight (5th to 84th percentile), overweight (85th to 94th percentile), or obese (greater than 95th percentile).[45]

3.3 Block Food Frequency Questionnaire

The Block Food Frequency Questionnaire (BFFQ) was used to review the energy intake of all subjects based on the quantity of food as well as the specific type of food in each food group they consumed on average per day in the past year. The first page of the questionnaire collected information about the age at the time of initial records, height, and weight of the subjects. The remaining pages had the subjects fill in whether or not they consumed a specific type of food and if they did, how much they consumed the type of food based on the quantities listed. The food groups included the following: whole grains and starchy vegetables; fruits and non-starchy vegetables, dairy; fish, poultry, meat, and eggs; fats and oils; vitamins and minerals; and elective calories such as sugar. The last part of the questionnaire inquires subjects about the type of physical activity they participate in, duration of physical activity, as well as frequency of the physical activity per week.

3.4 Digital Landmark Identification

The intraoral scans were converted into to STL files and landmarked using a dental cast landmarking software, Landmark Editor 3.6 (Institute for Data Analysis and Visualization and University of California, Davis). There were 80 landmarks on the maxillary cast and 80 landmarks on the mandibular cast that identified on the digital intraoral scans of each subject (Appendix G, H). Inter-observer reliability and intrareliability testing were completed prior to landmarking to minimize observer error as best as possible. Landmarks below 80% reliability were re-calibrated until a minimum of 80% reliability (less than 20% measurement error) was achieved. 10 casts were eliminated due to missing or primary teeth being present. After the 80 landmarks were located on 117 maxillary dental casts and 80 landmarks were located on 117 mandibular dental casts, 33 casts were eliminated from the study due to incomplete and/or distorted scans and 3 subjects were eliminated due to failed amplicon sequencing.

3.5 **Geometric Morphometrics**

Using MorphoJ 1.0d (Christian Peter Klingenberg, The University of Manchester), a software for geometric morphometrics, differences in shape and size of the maxillary and mandibular dental arch forms were quantified and analyzed.[46] Geometric morphometrics is a branch of mathematics that analyzes shape, provides comparisons in shape, and localizes where changes in shape occur. Phenotypic analysis of our dataset was completed to derive maxillary and mandibular arch shape data as a function of obesity. Generalized Procrustes Analysis (GPA) was a mathematical superimposition method used to calculate an average shape with three operations: translating, scaling, and rotation. The average shape was then used as a reference to calculate differences in shape for the dental arch forms. Principal Components Analysis (PCA) was used to simplify the descriptions of variance within the dataset by producing a set of complex variables (PC1, PC2, PC3, etc.) that account for the largest to the smallest proportion of shape variation. ANOVA tests were then run in SPSS version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0 Armonk, NY: IBM Corp) in order determine which SNPs in the Hippo signaling pathway were correlated with the phenotypic findings for each BMI category. In addition to PCA, we employed linear regression to determine if dental arch shape varies as a function of BMI percentile. Finally, Canonical Variate Analysis (CVA) was used to determine specific aspects of dental arch shape that differentiate our BMI categories (normal, overweight, obese).

3.5 **SNP Analysis**

The saliva samples were sent to the DNA Services Center at the UIC College of Medicine where the DNA was extracted and analyzed via amplicon sequencing. 37 SNPs in the Hippo signaling pathway were selected to be analyzed (Table I).

TABLE I

SNPs with associated genes along the Hippo signaling pathway

SNP	Gene	SNP	Gene	SNP	Gene
rs4870529	LATS1	**rs13085791**	MST1	**rs11758653**	TEAD3
rs13205080	LATS1	**rs62262683**	MST1	**rs72894781**	TEAD3
rs13210297	LATS1	**rs113893148**	MST1	**rs72894784**	TEAD3
rs12174349	LATS1	**rs147997200**	MST1	**rs71002565**	TEAD3
rs593390	LATS2	**rs4636447**	FOXO6	**rs10848754**	TEAD4
rs73169516	LATS2	**rs7522116**	FOXO6	**rs60833991**	TEAD4
rs613375	LATS2	**rs12029493**	FOXO6	**rs11062461**	TEAD4
rs9509499	LATS2	**rs56233836**	FOXO6	**rs113515288**	TEAD4
rs58568294	LATS2	**rs1317183**	FOXO6	**rs11062462**	TEAD4
rs60842975	LATS2	**rs55784313**	FOXO6	**rs12214749**	RUNX2
rs142801103	LATS2	**rs7740758**	TEAD3	**rs62617809**	TAZ
rs6490637	LATS2	**rs10638006**	TEAD3		
rs112991009	LATS2	**rs61501470**	TEAD3		

4. RESULTS

4.1 Descriptive Statistics

The BMI percentile calculation for individuals in the sample was conducted using the CDC BMI calculator for children and adolescents, which accounts for age and sex.[47] 50.6% of the total sample size was classified as normal weight (BMI between the 5th and 85th percentile).[48] There were 23 normal weight females and 18 normal weight males. 19.8% of the total sample size was overweight (86th percentile to 94th percentile) and 29.6% of the total sample size was obese (greater than 95% percentile) (Table II).[48] There were no test subjects who were underweight (below the 5th percentile). The different ethnic groups identified and included in the study were the following: 54 Hispanic, 12 African American, 12 Caucasian, 1 Hispanic/African American, and 2 Asian/Indian (Table III).

TABLE II

Description of sample based on BMI and sex

	Male	Female	**Total**
Normal	18	23	41
Overweight	7	9	16
Obese	15	9	24
Total	40	41	81

TABLE III

Description of sample based on BMI and ethnicity

	Normal	Overweight	Obese	Total
Hispanic	27	10	17	54
African American	4	3	5	12
Caucasian	7	3	2	12
Hispanic/African American	1	0	0	1
Asian/Indian	2	0	0	2
Total	41	16	24	81

4.2 Statistical Analysis of Maxillary Dental Arch Morphology

Preliminary analyses indicated that there is no association between BMI and the maxillary arch form. Based on the Linear Regression Analysis, only 1.588% of the variation in the entire maxillary arch phenotype data set is due solely to BMI status (p-value = 0.3032).

4.3 Statistical Analysis of Mandibular Dental Arch Morphology

After accounting for variation due to ethnicity, the GM analysis illustrated that there is a greater association between obese BMI percentiles and a wider dental arch form posteriorly (Figures 1-2). A Linear Regression Analysis was performed which found that 3.654% of the variation in the entire mandibular arch phenotype data set is due solely to BMI status (p-value = 0.0077; Figure 3).

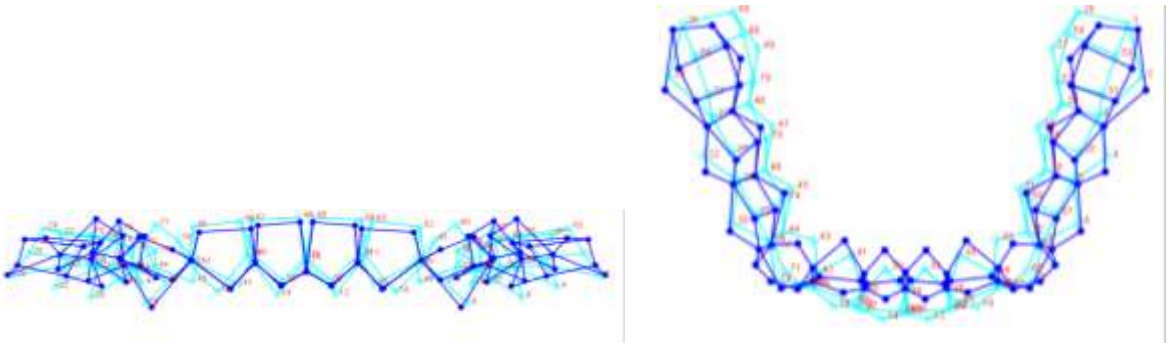

Figure 1. BMI percentile regression mandibular frontal and occlusal view
light blue wire frame: the average dental arch shape
dark blue wire frame: shape of the dental arch based on the scale factor

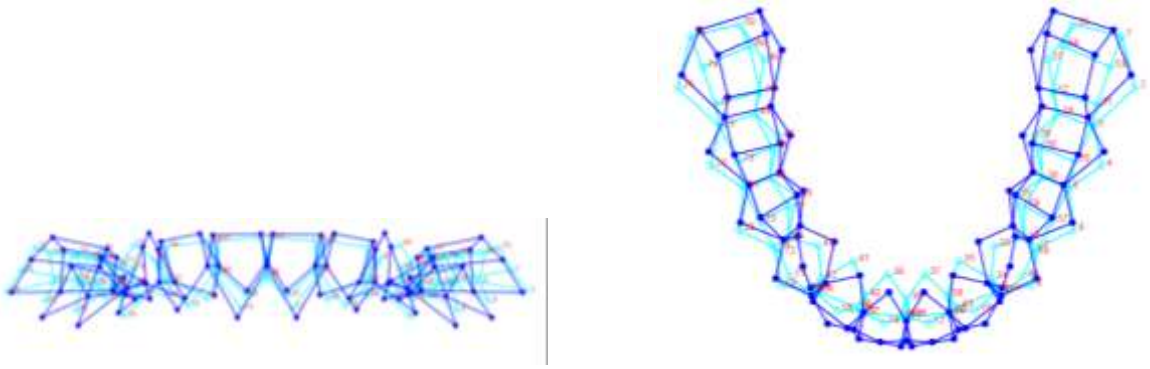

Figure 2. BMI percentile regression mandibular frontal and occlusal view

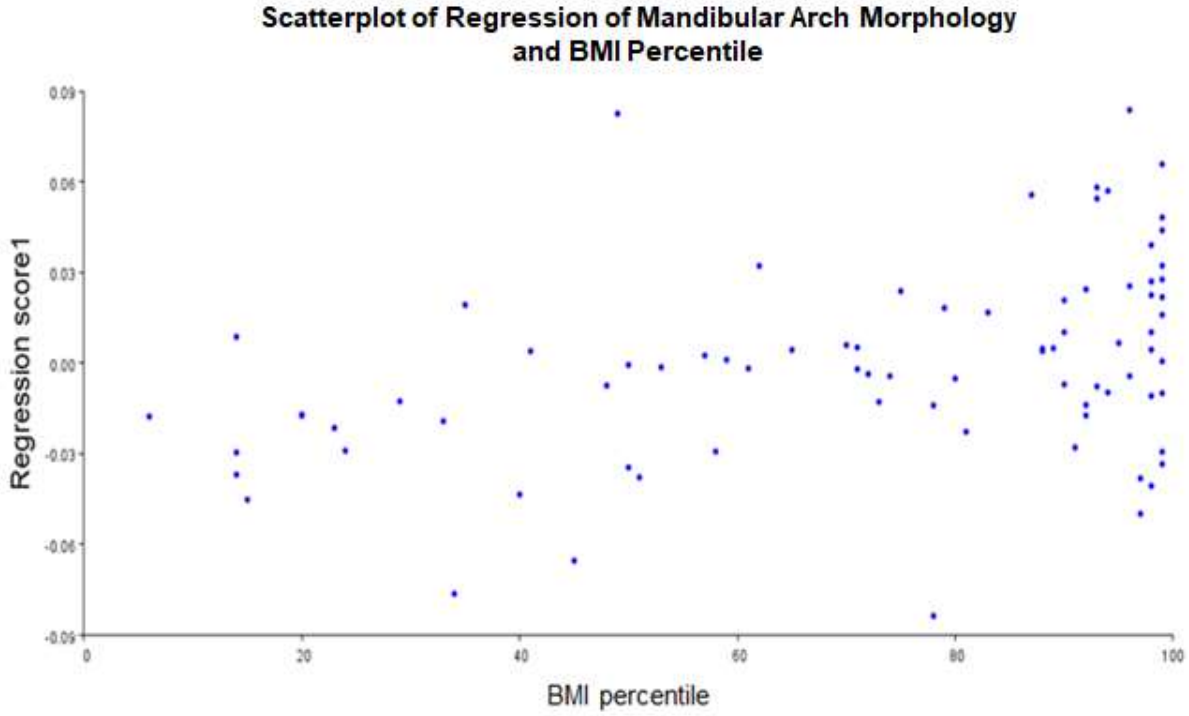

Figure 3. Scatterplot of regression of mandibular arch morphology and BMI percentile

A Canonical Variate Analysis (CVA) further identified aspects of dental arch shape that distinguish between normal, overweight, and obese subjects. The light blue wire frame represents the average dental arch shape. The dark blue wire frame represents the shape of the dental arch based on the scale factor of ±20 (Figures 4-7). CV1 with a scale factor of +20

shows that wider mandibular arch form in the posterior area as well as shorter incisor, canine, and premolar clinical crowns are associated with obese BMI percentiles. CV1 shows that more constricted mandibular arch form in the posterior area as well as shorter incisor, canine, and premolar clinical crowns are associated with overweight BMI percentiles. CV2 illustrates that more constricted mandibular arch form in the posterior area as well as longer incisor and molar clinical crowns are associated with normal BMI percentiles. CV2 depicts wider mandibular arch form in the posterior area as well as shorter incisor clinical crowns. Figure 8 is a CV plot of the phenotypes CV1 and CV2. The individuals are color coded by BMI status (normal in red, overweight in blue, and obese in green) and this plot illustrates that all three BMI categories have different shapes that separate out on CV1 and CV2. Based on the Mahalanobis distance, the CV phenotype shape variations between the three categories are significant ($p<0.001$); however, using the Procrustes distance, the CV phenotype shape variations are not significantly different.

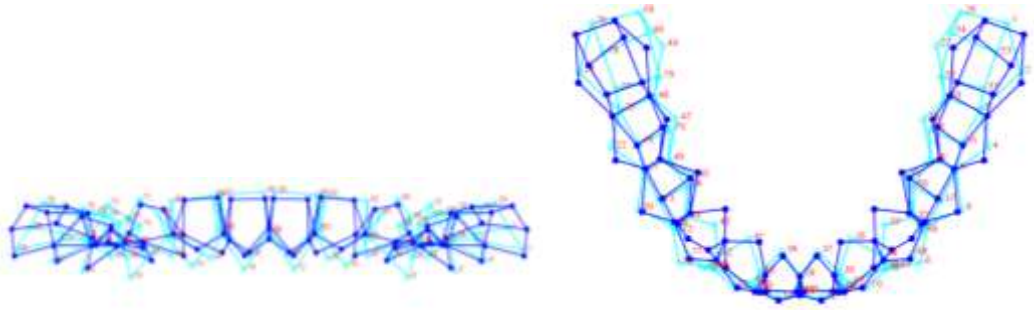

Figure 4. CV1 mandibular frontal and occlusal view

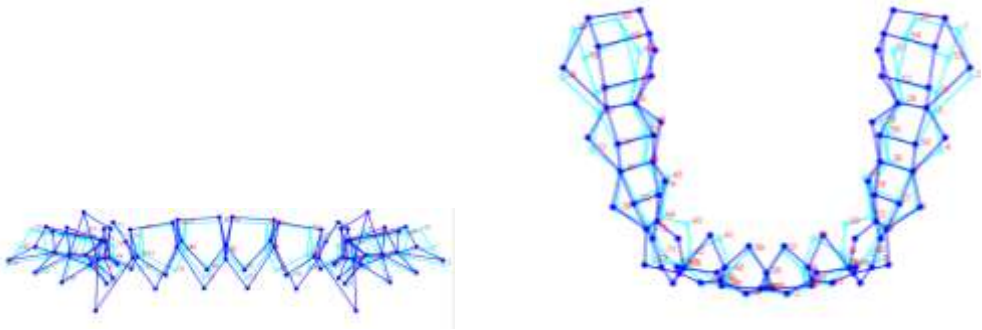

Figure 5. CV1 mandibular frontal and occlusal view

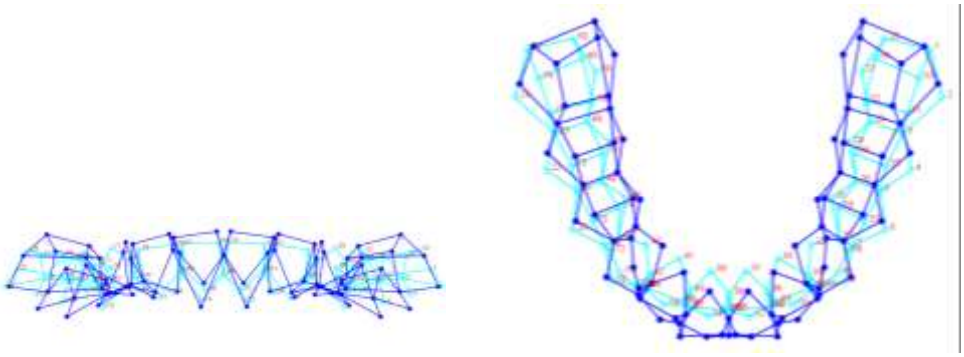

Figure 6. CV2 mandibular frontal and occlusal view

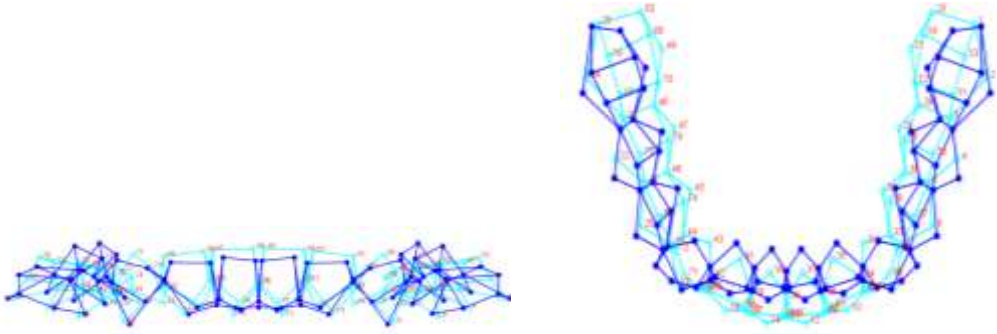

Figure 7. CV2 mandibular frontal and occlusal view

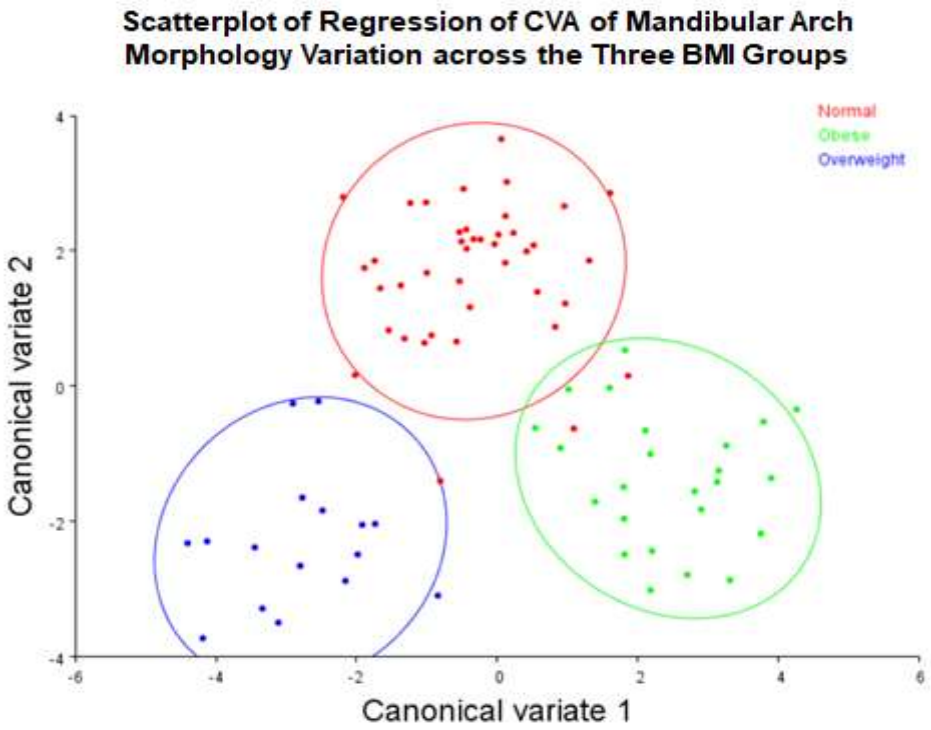

Figure 8. Scatterplot of regression of CVA of mandibular arch morphology variation across the three BMI groups (red: normal BMI; green: obese BMI; blue: overweight BMI)

A PCA yielded 75 principal components (PCs). PC15 and PC23 represent greater than 1.276% and 0.605% of the overall mandibular arch shape variation respectively. The light blue wire frame represents the average dental arch shape. The dark blue wire frame represents the shape of the dental arch based on the scale factor of ±0.1 (Figures 9-12). PCA 15 and 23 illustrate a wider arch form in the posterior dentition and less projecting arch form in the anterior dentition (Figures 9-12). PCA 15 further depicts the canine position, namely a wider intercanine width (Figures 9-10).

In Figure 13, the PC plot of PC15 vs. PC 23 does not depict as much separation as the CV Plot in Figure 8; however, the two components that are significantly different are between

the normal and obese BMI groups. While there is overlap between the three BMI groups, there is a distinct separation between the three groups on both PC axes.

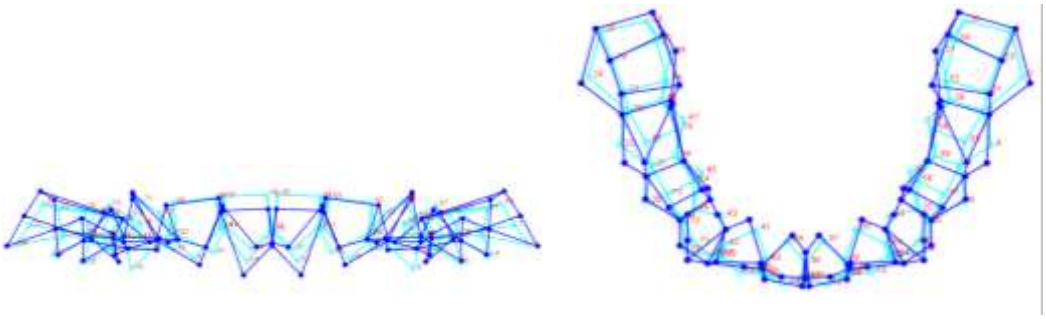

Figure 9. PC15 mandibular frontal and occlusal view

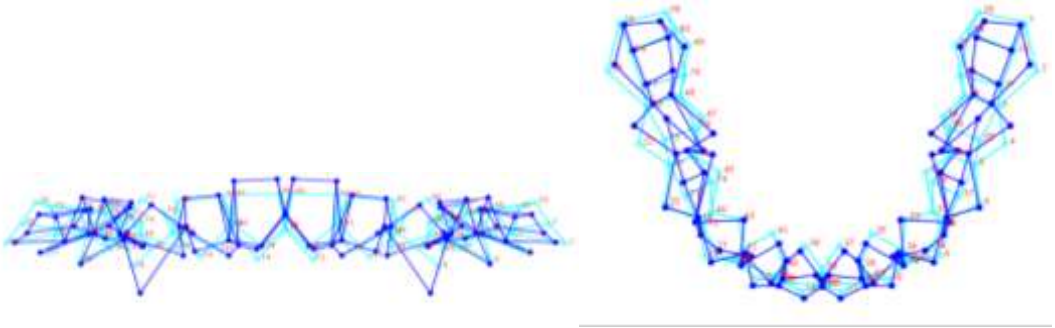

Figure 10. PC15 mandibular frontal and occlusal view

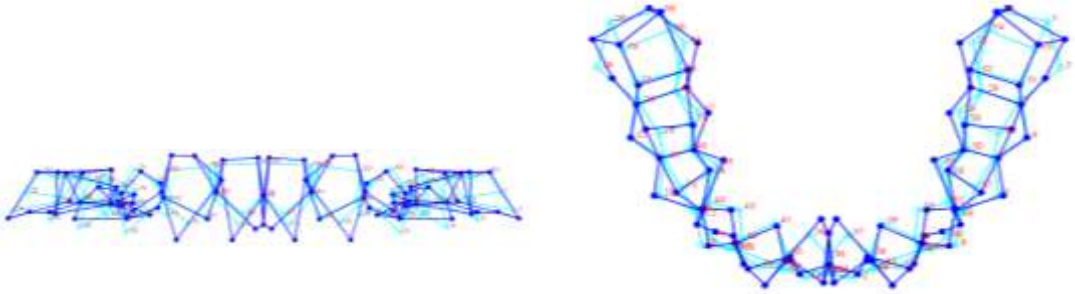

Figure 11. PC23 mandibular frontal and occlusal view

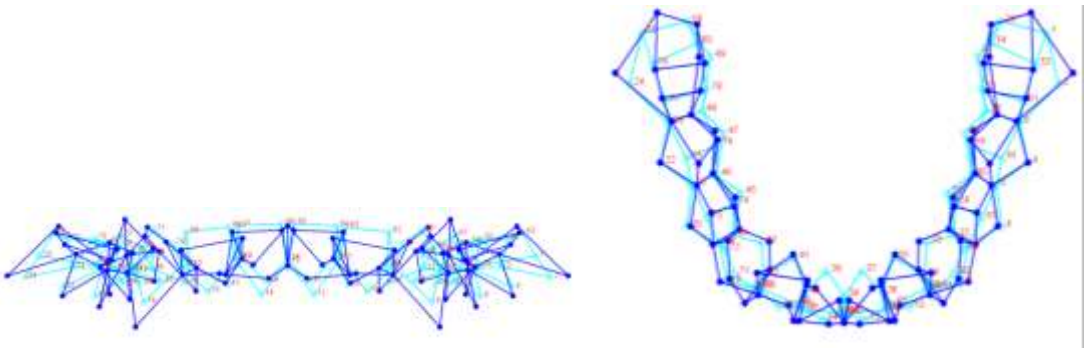

Figure 12. PC23 mandibular frontal and occlusal view

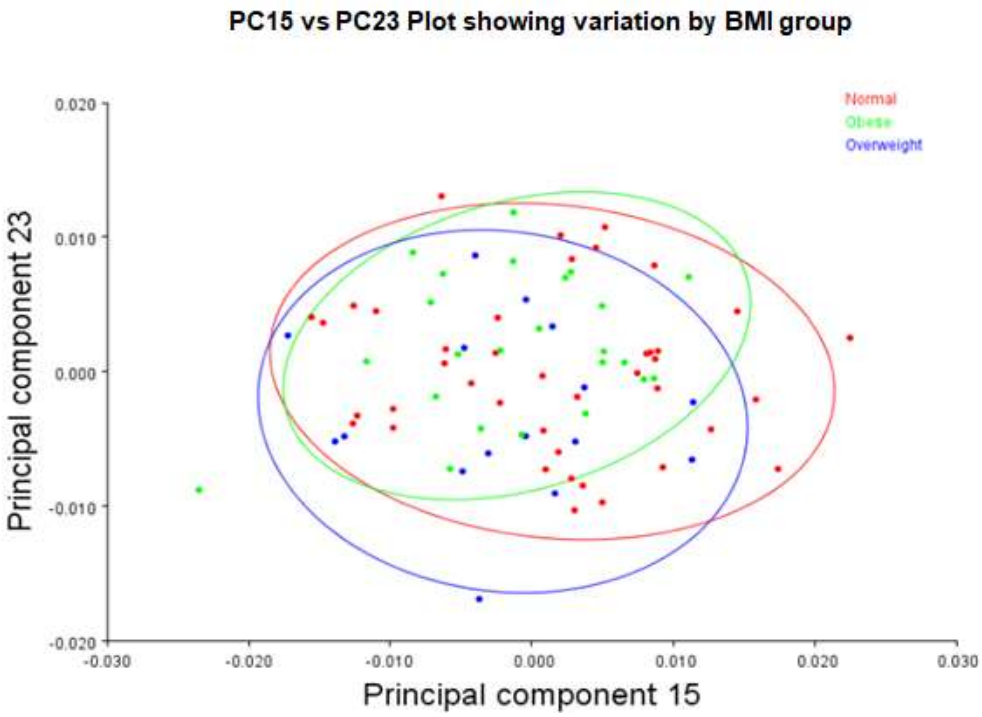

Figure 13. PC15 vs PC23 Plot showing variation by BMI group
(red: normal BMI; green: obese BMI; blue: overweight BMI)

4.4 **Statistical Analysis of SNPs in relation to BMI**

ANOVA tests were run for data that was found to be normally distributed. The ANOVA tests determined which of the 37 selected specific SNPs in the genes in the Hippo signaling pathway were associated with the wider mandibular arch phenotype as depicted with the linear

regression analysis, CVA, and PCA. However, for the selected SNPs that failed the tests for homogeneity of variance, we conducted non-parametric Welsh tests (Table III).

The following were significant findings from our ANOVA analyses: the selected SNPs in MST1 (p = 0.036), LATS1 (0.013), and LATS2 (p = 0.045 and p = 0.031) were correlated with wide mandibular arch phenotypes (Table III).

TABLE IV

Regression of BMI category and SNP

SNP	p-value
rs4636447 (FOXO6)	0.677[2]
rs7522116 (FOXO6)	0.745[2]
rs12029493	0.331[2]
rs56233836	0.208[2]
rs1317183	0.996[2]
rs55784313	0.207[2]
rs13085791 (MST1)	0.036[1]
rs62262683	0.969[2]
rs113893148	0.319[2]
rs147997200	0.270[2]
rs7740758	0.666[2]
rs10638006	0.466[2]
rs61501470	0.611[1]
rs11758653 (TEAD3)	0.483[1]
rs72894781	0.673[2]
rs72894784	0.673[2]
rs71002565	0.561[2]
rs12214749	0.961[2]
rs4870529	0.681[2]
rs13205080 (LATS1)	0.013[1]
rs12174349	0.765[2]
rs10848754	0.588[2]
rs60833991	0.055[2]
rs11062461	0.434[2]
rs113515288	0.791[1]

rs11062462	0.737[2]
rs593390	0.483[1]
rs73169516	0.428[2]
rs613375	0.395[2]
rs58568294	0.235[2]
rs9509499	0.948[2]
rs60842975 (LATS2)	0.045[1]
rs142801103	0.086[2]
rs6490637 (LATS2)	0.031[1]
rs112991009	0.425[2]
rs62617809	0.398[2]

p^1 = p-value derived from ANOVA
p^2 = p-value derived from Welsh test

Figures 14 to 20 are boxplots of the various average phenotype scores (regression score, PC score, CV score) organized by SNP genotype. These plots help visualize whether we can also observe differences in the phenotype scores as a function of the SNP genotype at a given SNP along the Hippo signaling pathway. Along the x-axis are two or three variables, which are homozygous common (C,C), heterozygous (C,G), and homozygous rare (G,G). In some cases, there were no subjects with the homozygous rare genotype, only homozygous common or heterozygous genotypes. Figure 14 shows that we observe differences in phenotype score as a function of the genotype of MST1 ($p = 0.036$). Figure 15 shows that we observe differences in the BMI regression phenotype score as a function of the genotype of LATS1 ($p = 0.013$). Figure 17 depicts the difference in the BMI regression phenotype score as function of the SNP genotype of LATS2 ($p = 0.045$ and $p = 0.031$).

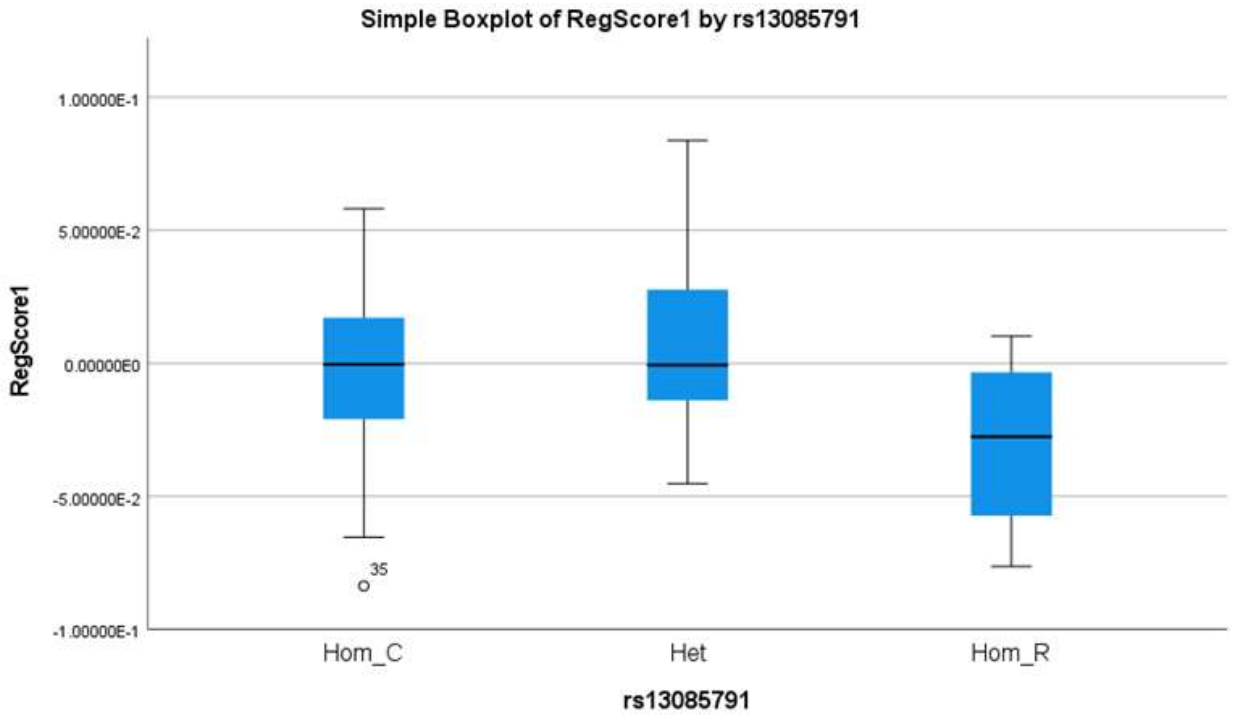

Figure 14. Boxplot of dental arch phenotype based on regression score by genotype MST1 (SNP rs13085791)

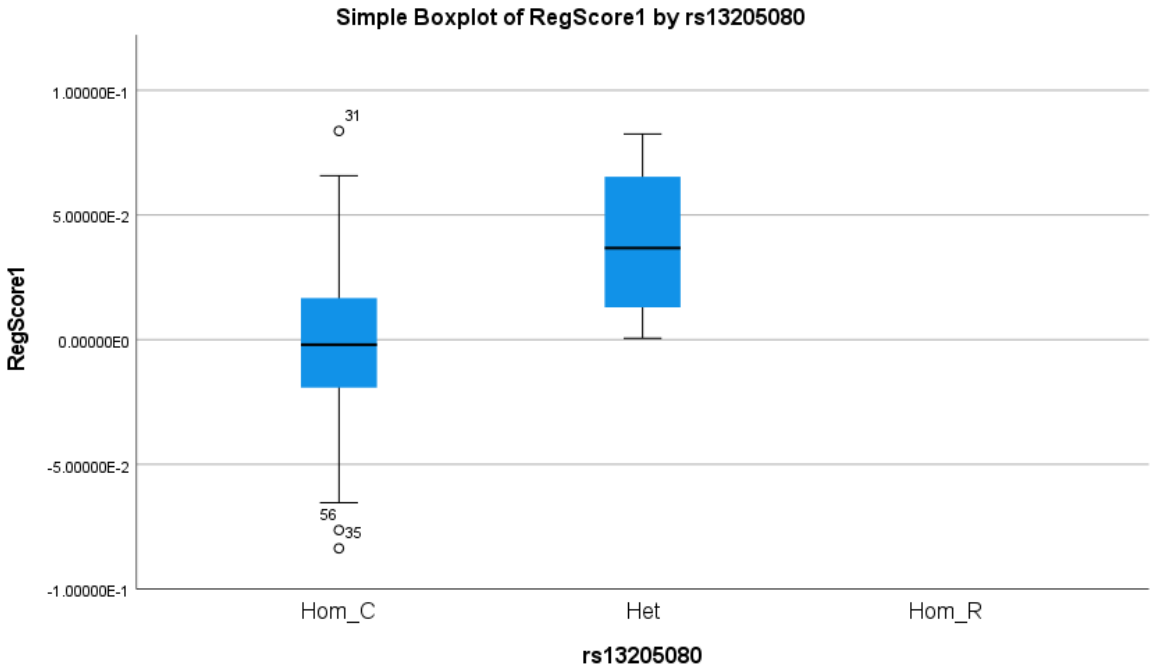

Figure 15. Boxplot of dental arch phenotype based on regression score by genotype LATS1 (SNP rs13205080)

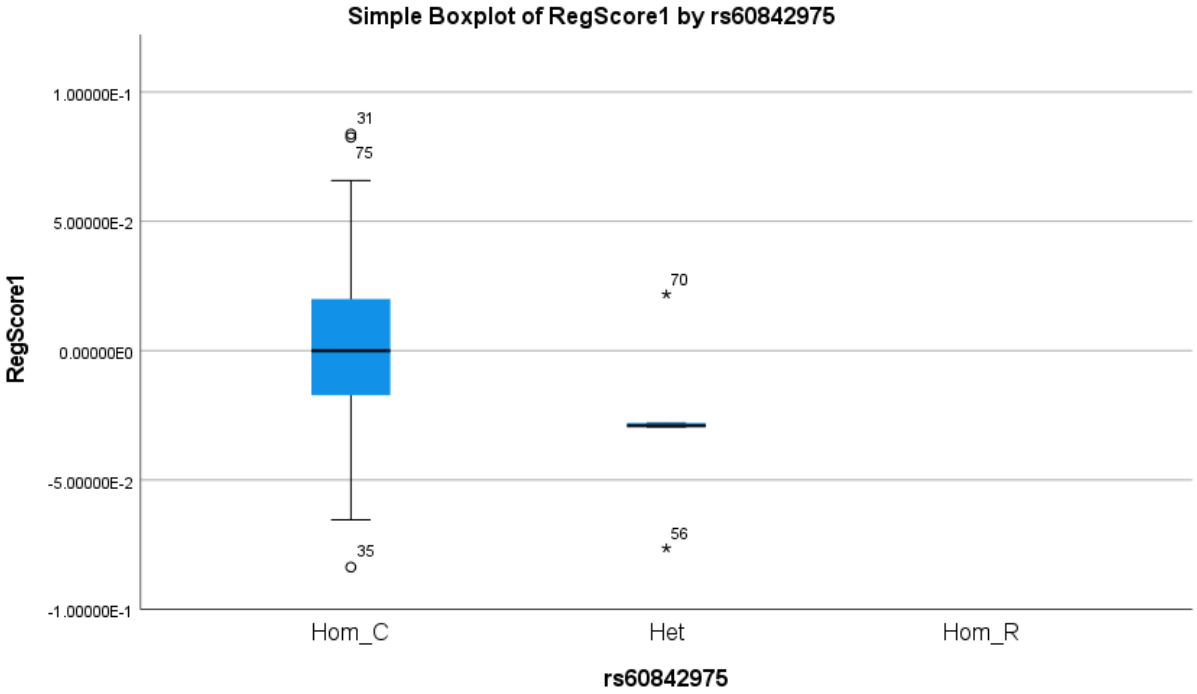

Figure 16. Boxplot of dental arch phenotype based on regression score by genotype LATS2 (SNP rs60842975)

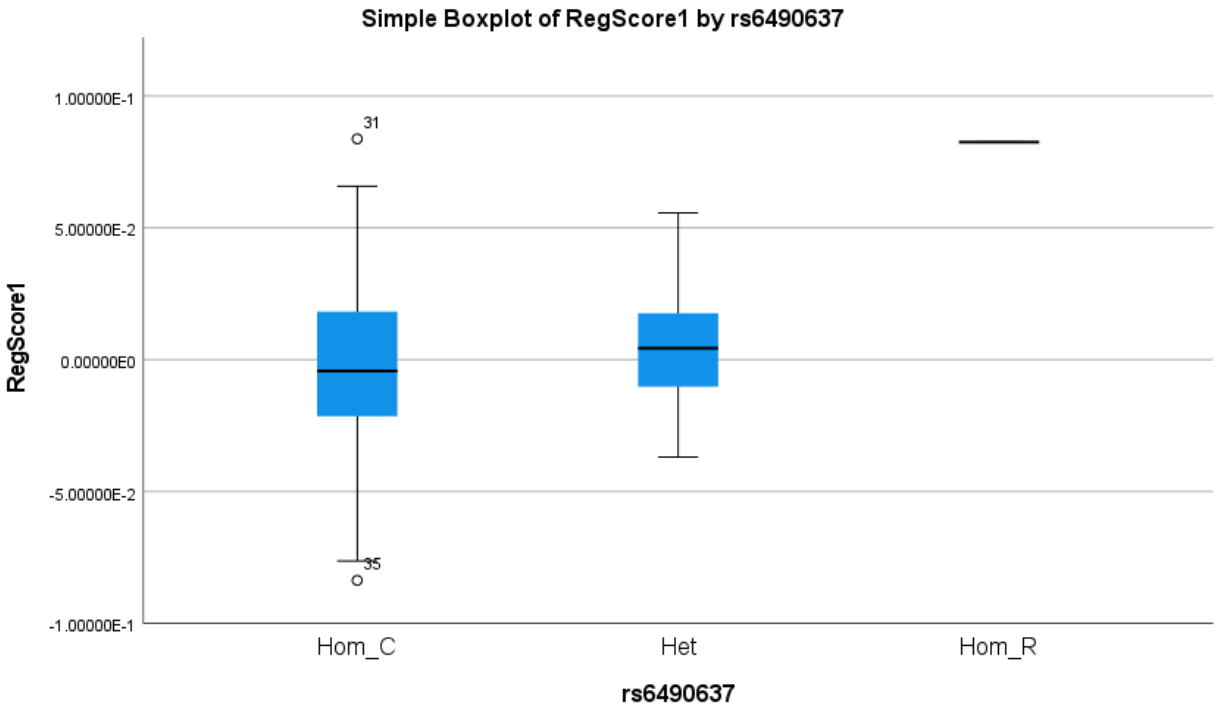

Figure 17. Boxplot of dental arch phenotype based on regression score by genotype LATS2 (SNP rs6490637)

For the 37 selected SNPs on genes found in the Hippo signaling pathways that have equal variance and wide mandibular dental arch phenotypes found in obese subjects based on the CVA and PCA, a series of ANOVA tests were completed. For those with unequal variance, Welsh tests were completed. The ANOVA results illustrate that there is a statistically significant association between the selected SNPs in FOXO6 ($p = 0.025$ and $p = 0.042$) and in TEAD3 ($p = 0.029$) and the CV1 phenotype (Table IV). Additionally, there is a relationship between the selected SNP in TEAD3 ($p = 0.035$) and the CV2 phenotype (Table V).

TABLE V

CV1 output of BMI category and SNP

SNP	p-value
rs4636447 (FOXO6)	0.025[1]
rs7522116 (FOXO6)	0.042[1]
rs12029493	0.490[2]
rs56233836	0.355[2]
rs1317183	0.328[2]
rs55784313	0.301[1]
rs13085791 (MST1)	0.799[1]
rs62262683	0.803[2]
rs113893148	0.899[2]
rs147997200	0.558[2]
rs7740758	0.382[2]
rs10638006	0.937[1]
rs61501470	0.232[1]
rs11758653 (TEAD3)	0.029[1]
rs72894781	0.618[2]
rs72894784	0.618[2]
rs71002565	0.982[2]
rs12214749	0.867[2]
rs4870529	0.098[2]
rs13205080 (LATS1)	0.161[1]
rs12174349	0.093[2]
rs10848754	0.074[2]
rs60833991	0.592[2]
rs11062461	0.765[2]
rs113515288	0.808[2]
rs11062462	0.179[2]
rs593390	0.118[2]
rs73169516	0.371[1]
rs613375	0.231[2]
rs58568294	0.215[2]
rs9509499	0.782[2]
rs60842975 (LATS2)	0.640[1]
rs142801103	0.657[2]
rs6490637 (LATS2)	0.855[1]
rs112991009	0.436[2]
rs62617809	0.963[2]

p^1 = p-value derived from ANOVA
p^2 = p-value derived from Welsh test

TABLE VI

CV2 Output of BMI Category and SNP

SNP	p-value
rs4636447 (FOXO6)	0.096[2]
rs7522116 (FOXO6)	0.420[1]
rs12029493	0.490[2]
rs56233836	0.664[2]
rs1317183	0.772[2]
rs55784313	0.991[1]
rs13085791 (MST1)	0.614[2]
rs62262683	0.886[2]
rs113893148	0.633[2]
rs147997200	0.364[2]
rs7740758	0.621[2]
rs10638006	0.505[1]
rs61501470	0.412[1]
rs11758653 (TEAD3)	0.035[1]
rs72894781	0.991[2]
rs72894784	0.991[2]
rs71002565	0.721[2]
rs12214749	0.658[2]
rs4870529	0.527[2]
rs13205080 (LATS1)	0.515[1]
rs12174349	0.441[2]
rs10848754	0.425[2]
rs60833991	0.362[1]
rs11062461	0.744[1]
rs113515288	0.289[1]
rs11062462	0.600[1]
rs593390	0.659[2]
rs73169516	0.662[1]
rs613375	0.379[2]
rs58568294	0.735[2]
rs9509499	0.430[1]
rs60842975 (LATS2)	0.682[2]
rs142801103	0.875[2]
rs6490637 (LATS2)	0.773[1]
rs112991009	0.516[2]
rs62617809	0.965[2]

p^1 = p-value derived from ANOVA
p^2 = p-value derived from Welsh test

Figure 18 depicts the difference in the CV1 phenotype score as function of the genotype of FOXO6 ($p = 0.025$ and $p = 0.042$). Figure 19 depicts the difference in the CV2 phenotype score as function of the genotype of TEAD3 ($p = 0.035$).

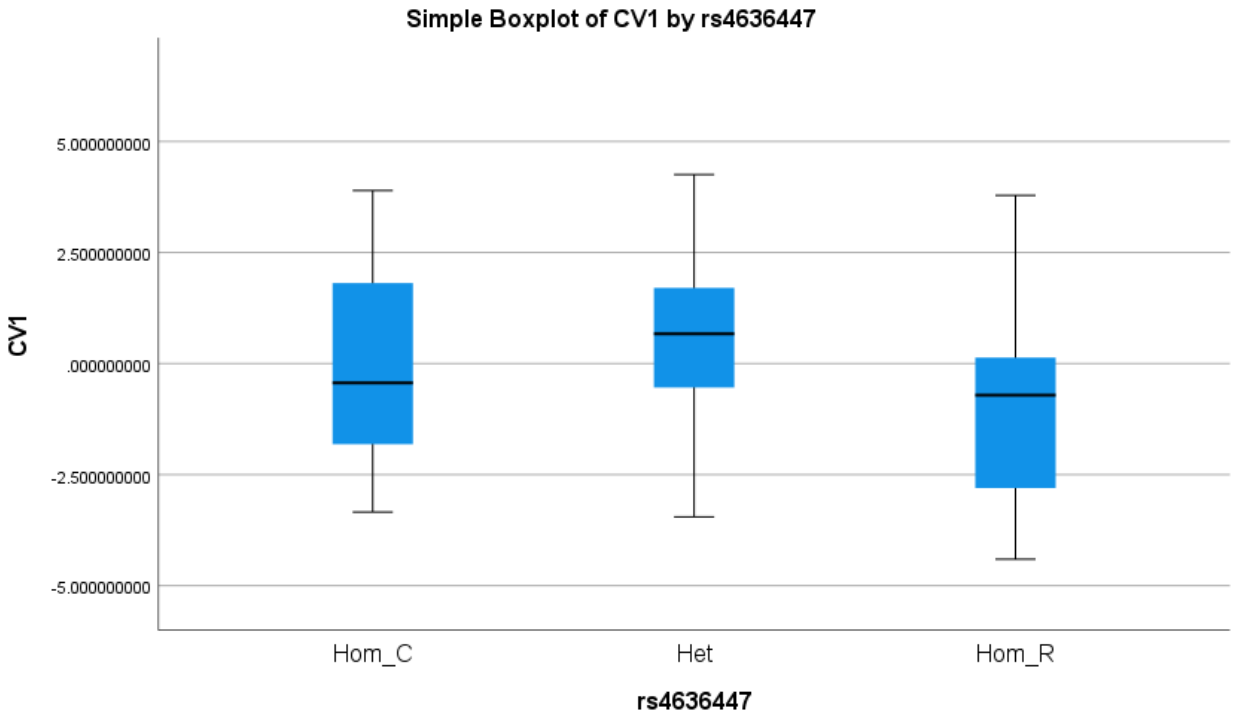

Figure 18. Boxplot of dental arch phenotype based on CV1 by genotype FOXO6 (SNP rs4636447)

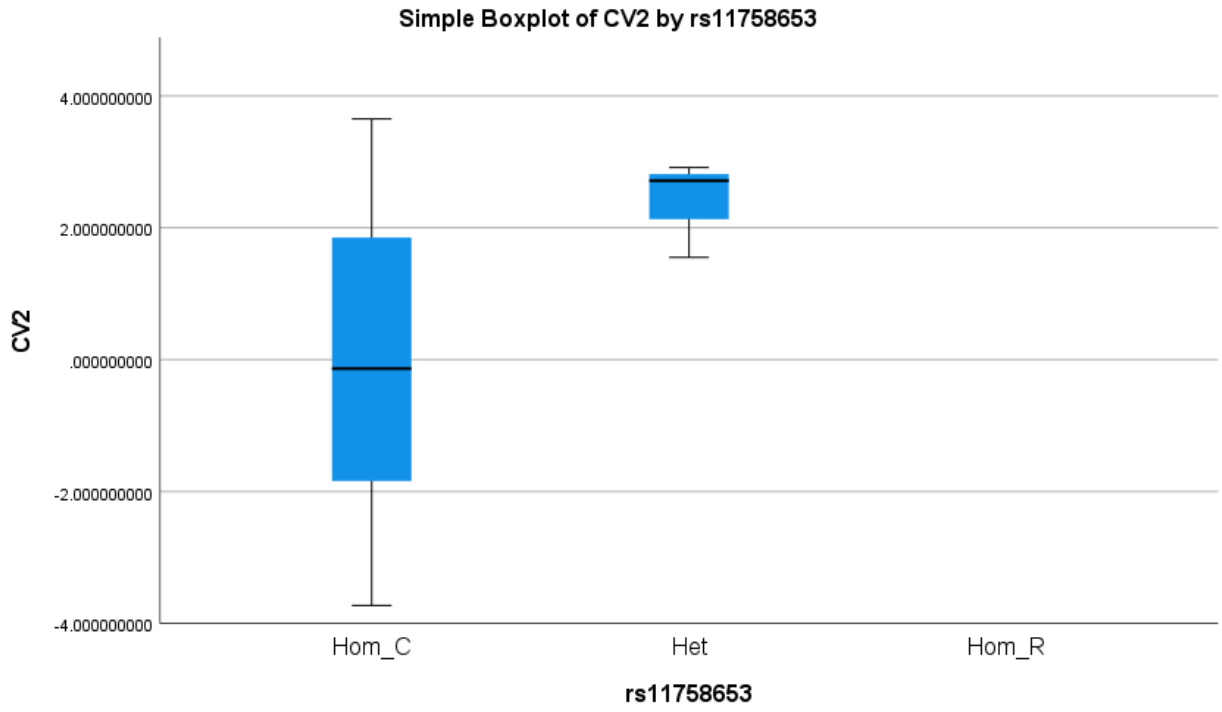

Figure 19. Boxplot of dental arch phenotype based on CV2 by genotype TEAD3 (SNP rs11758653)

There is a statistically significant relationship between the selected SNP on MST1 (rs13085791) and the PC15 phenotype (p=0.035; Table VI). There was no significant relationship between the 37 selected SNPs found in the Hippo signaling pathway and the PC23 phenotype (p=0.851).

In summary, wide mandibular arch form phenotypes were associated with seven of the selected SNPs in the Hippo signaling pathway: rs13085791 in the MST1 gene, rs13205080 in the LATS1 gene, rs60842975 and rs6490637 in the LATS2 gene, rs4636447 and rs7522116 in the FOXO6 gene; and rs11758653 in the TEAD3 gene.

TABLE VII

PC15 output of BMI category and SNP

SNP	p-value
rs4636447 (FOXO6)	0.369[2]
rs7522116 (FOXO6)	0.676[2]
rs12029493	0.693[2]
rs56233836	0.920[1]
rs1317183	0.824[2]
rs55784313	0.873[1]
rs13085791 (MST1)	0.035[1]
rs62262683	0.935[2]
rs113893148	0.383[2]
rs147997200	0.751[2]
rs7740758	0.589[2]
rs10638006	0.178[1]
rs61501470	0.388[1]
rs11758653 (TEAD3)	0.687[2]
rs72894781	0.226[2]
rs72894784	0.226[2]
rs71002565	0.663[2]
rs12214749	0.388[2]
rs4870529	0.135[2]
rs13205080 (LATS1)	0.689[1]
rs12174349	0.200[2]
rs10848754	0.617[2]
rs60833991	0.419[1]
rs11062461	0.262[2]
rs113515288	0.857[1]
rs11062462	0.251[2]
rs593390	0.330[2]
rs73169516	0.698[2]
rs613375	0.616[2]
rs58568294	0.122[2]
rs9509499	0.324[2]
rs60842975 (LATS2)	0.057[1]
rs142801103	0.701[2]
rs6490637 (LATS2)	0.257[1]
rs112991009	0.294[2]
rs62617809	0.623[2]

p^1 = p-value derived from ANOVA
p^2 = p-value derived from Welsh Test

MST1 (SNP rs13085792) is significantly associated with a wide mandibular arch phenotype based on the ANOVA test (Figure 20; Table VII).

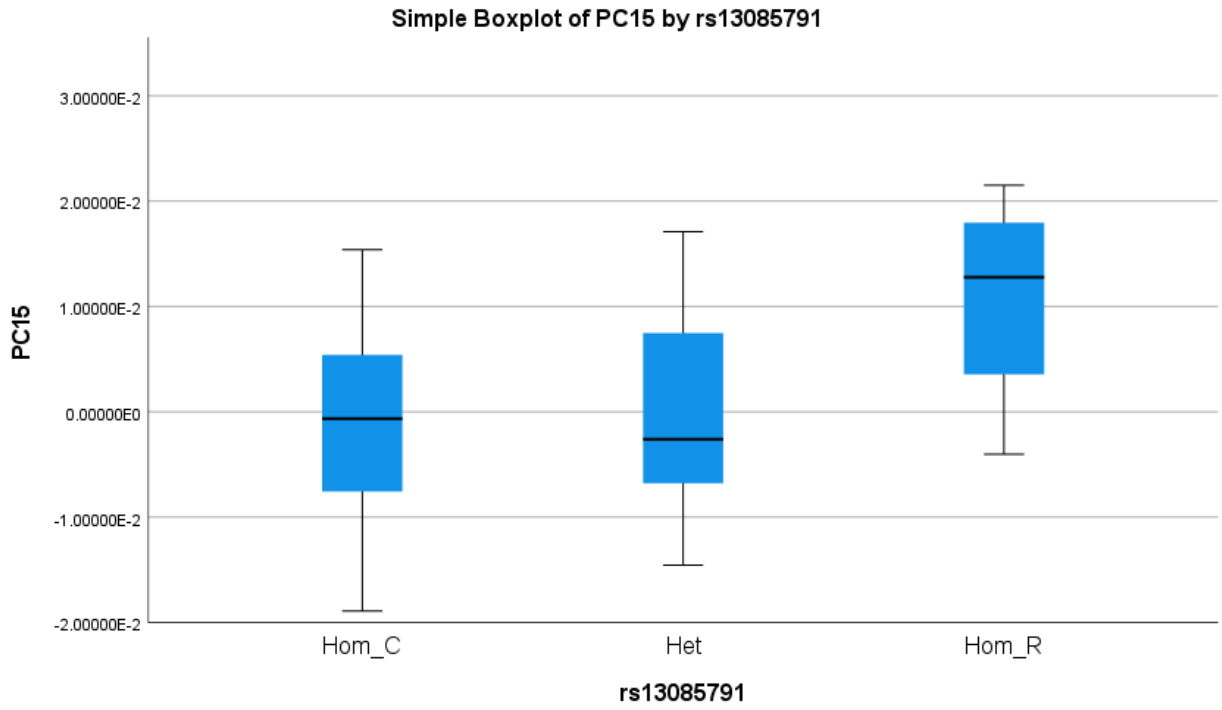

Figure 20. Boxplot of dental arch phenotype based on PC15 by genotype MST1 (SNP rs13085791)

5. DISCUSSION

5.1 Subjects

Childhood obesity is becoming more prevalent throughout the world, affecting approximately 19% of children and adolescents in the U.S. and 43 million overweight and obese children under five years of age worldwide in 2017.[48] According to the Chicago Department of Public Health, in 2013, 18.4% of the children in Chicago between the ages of 6 to 15 years of age were overweight and 24.9% were considered obese.[48] The BMI profile of the population of this study was comparable to the BMI profile of the Chicagoland area with 19.8% of our subjects being overweight and 29.6% being obese.

5.2 Ethnic and Racial Diversity of Subjects

There is insufficient existing literature on the relationship between obesity and dental arch form, let alone obesity and dental arch form in the context of the Hippo Signaling Pathway. This study is novel in that it further investigates the relationship in an ethnically and racially diverse sample. Our study included Hispanic, African American, Caucasian, Hispanic/African American, and Asian/Indian subjects. After accounting for variation due to ethnicity, it was found that there is a still an association between obese BMI percentiles and a wider mandibular arch form posteriorly. The prevalence of obesity has increased in all racial and ethnic groups, both sexes, as well as all age brackets.[2] More studies on how the prevalence of obesity is correlated with dental arch form will need to be conducted.

5.3 BMI and Genetics

The SNPs, rs13085791 and rs13085791 in MST1, rs13205080 in LATS1, rs60842975 and rs6490637 in LATS2, rs4636447 and rs7522116 in FOXO6, and rs11758653 in TEAD3 were all present as a homozygous rare genotype in obese test subjects and associated with a

wide mandibular arch phenotype. Given that we see an association between LATS2, MST1, FOXO6, and TEAD3 with obese subjects, it is interesting to note that a study conducted by Ardestani et al. that showed LATS kinase, MST1, FOXO6, and TEAD3 are activated while YAP/TAZ are deactivated at high cell density or adipogenesis.[12] Our results therefore suggest an association with the genotype of these SNPs in the Hippo signaling pathway and the dental arch phenotype associated with obese individuals.

There is insufficient literature to currently postulate the mechanism by which the Hippo signaling pathway may be involved in dental arch form. Olszewska as well as Wang and Martin found a correlation between obesity and craniofacial morphology.[7,19] Prior work has shown that inactivation of YAP and TAZ of the Hippo signaling pathway, which occurs in adipogenesis, led to severe craniofacial defects such as disrupted frontonasal and mandibular structures, disrupted frontonasal and mandibular structures, hemorrhage, failed neural tube closure, and neural tube vessel regression.[19] Although these studies included how there are craniofacial morphology phenotypes associated with genes in the Hippo signaling pathway, they did not further elaborate on which particular mandibular structures were disrupted nor did they mention about any shape variations in mandibular dental arch form. Consequently, more investigation is necessary to support our finding that wide mandibular dental arch phenotypes are associated with specific SNPs in the Hippo signaling pathway and our current results may be considered exploratory.

5.4 **BMI and Variation in Dental Shape, Size, and Malocclusion**

Our study showed that there is no significant relationship between maxillary arch form, BMI, and SNPs in the Hippo signaling pathway. Cephalometric studies in children with GH deficiency demonstrated smaller anterior and posterior cranial bases, small posterior facial height, short ramus height, and smaller maxillary and mandibular length.[20] Wang, Yu, and Yu

found that the maxilla seemed to be less affected than the mandible.[20] This finding from the cephalometric studies by Wang, Yu, and Yu may be a plausible reason that we did not see a significant association between the maxilla, BMI, and SNPs in the Hippo signaling pathway. There is insufficient, existing literature regarding the maxillary dental arch form in relation to BMI and genetic factors in the Hippo signaling pathway.

A wider arch form posteriorly on the mandibular arch form may signify that more posterior crossbites could be seen in individuals with high BMI. As seen in the Principal Component Analysis, a wider intercanine width in obese individuals illustrates a square arch form with the anterior segment being straight and posterior segments moving mesially. The putative increase in mesially displaced mandibular molars, indicating likely Class III dental malocclusion, in obese subjects may be a result of this dental arch conformation; however, more studies need to be conducted to confirm this observation. A study by Yzquierdo-Correa et al. supports our results in that they found there were statistically significant differences in the intercanine and intermolar widths between normal weight and overweight subjects, with dental arches being wider in overweight subjects compared to normal weight children.[39] Another vital study further illustrates our finding that there is more Class III malocclusion correlated with obese individuals. Guevara et al. determined that along PC1, individuals with scores indicative of anterior-posterior dental arch discrepancy where the mandibular arch was protrusive beyond the maxillary arch, were significantly ($p<0.01$) related to an increase in BMI, which is consistent with our results of mesially displaced mandibular molars, indicating likely Class III dental malocclusion, being more prevalent in our obese subjects than our normal weight subjects.[4] Furthermore, although Gordon et al. found no significant variation in facial shape across all three BMI categories (normal weight, overweight, and obese), they noted that obese children appeared to have accelerated facial growth in their obese sample and larger mandibles

(condylion – pogonion) in obese females.[32] Taking these results together, we posit that larger mandibles, a trait also found by Ohrn and colleagues,[6] may reflect mandibular overgrowth, ultimately leading to a Class III molar relationship.

Identifying a wider mandibular arch phenotype associated with genes in the Hippo signaling pathway in our study may provider greater insight on how to develop an orthodontic treatment plan specifically for children with obesity. Treatment plans for such patients may involve skeletal arch expansion as well as maxillary arch development to yield better arch coordination with the mandibular arch and to resolve posterior crossbites if present. Additionally, orthodontists may expect to find more Class III malocclusion in pediatric patients with obesity. Prior knowledge of this characteristic may allow providers to develop the proper treatment to correct the dental relationship and even prevent Class III malocclusion for pre-pubescent patients with obesity.

5.5 **Limitations of the Study**

The limitations of the study include a small sample size and the potential for distorted casts due to inaccurate scanning and/or processing into the Landmark Editor software. Additionally, we collected data about diet; however, we were unable to aggregate and analyze this data at this time.

5.6 **Future Considerations**

Future studies will benefit from a larger sample size, more diverse population, as well as investigating other adipogenic and inflammatory pathways that are related to obesity and dental arch form. Another consideration is to study the effects of soft tissue, namely tongue size in

subjects with normal BMI versus obese BMI, which may contribute to a wider dental arch form. This is an exploratory study to see if an association exists between BMI, dental arch form, and the Hippo signaling pathway. Other areas to explore the relationship between dental arch form and BMI further would be the effects of dietary factors and nutritional status. We cannot definitively say that obesity and the Hippo signaling pathway are causing the wide mandibular arch phenotypes; however, based on our results, we do see a correlation. Further research must be conducted to see if this association is causative.

6. CONCLUSION

In conclusion, the objectives of our study were to determine if dental arch is correlated with BMI and if there are any associations between dental arch phenotypes and genes in the Hippo Signaling Pathway. The evidence from this study delineated a correlation between high BMI percentile and wide mandibular arch forms when controlling for age and sex. Furthermore, wide mandibular arch form phenotypes were associated with 7 out of the selected 37 SNPs in the Hippo signaling pathway: rs13085791 in the MST1 gene, rs13205080 in the LATS1 gene, rs60842975 and rs6490637 in the LATS2 gene, rs4636447 and rs7522116 in the FOXO6 gene; and rs11758653 in the TEAD3 gene. We did not see any significant associations between the maxillary arch form, BMI, and genetic factors found in the Hippo signaling pathway.

Our results are not sufficient enough to provide any specific clinical recommendations; however, we hope to eventually reach a point where wider mandibular arch forms found in obese children as well as those possessing the SNPs within the genes in Hippo signaling pathway that lead to obesity can be integrated as clinical considerations during diagnosis and treatment planning.

We reject the following null hypotheses for the mandibular arch form only:

- There is no correlation between genetic variation in the Hippo signaling pathway and dental arch form in children and adolescents.
- There is no correlation between BMI and dental arch form in children and adolescents.

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APPENDICES

APPENDIX A

IRB Initial Approval Notice

Approval Notice
Initial Review (Response To Modifications)

February 1, 2018

Jennifer Caplin, BS, DMD, MS
Orthodontics
801 S. Paulina St Room 131
M/C 841
Chicago, IL 60612
Phone: (312) 996-0230 / Fax: (312) 996-0893

RE: Protocol # 2017-1276
"Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors"

Dear Dr. Caplin:

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on January 30, 2018. You may now begin your research

Please note the following information about your approved research protocol:

The cover letter response indicated approval from Midwestern University's IRB would be provided, but the document referenced as an approval did not appear to be and IRB approval document (it did not reference the IRB, the FWA, nor the federal regulations governing human subjects research). The Appendices L-2 for the personnel from Midwestern University were not approved, since these documents do not apply if the Midwestern University IRB will review this research. Therefore, Midwestern University was not cited as an approved non-UIC performance site. Once their IRB approval is obtained, and before and research is conducted in conjunction with this site, an amendment will need to be submitted to the UIC IRB to formally add this site.

Protocol Approval Period:	January 30, 2018 - January 30, 2019
Approved Subject Enrollment #:	250
Additional Determinations for Research Involving Minors:	The Board determined that this research satisfies 45CFR46.404, research not involving greater than minimal risk. Therefore, in accordance with 45CFR46.408, the IRB determined that only one parent's/legal guardian's permission/signature is needed. Wards of the State may not be enrolled unless the IRB grants specific approval and assures inclusion of additional protections in the research required under 45CFR46.409. If you wish to enroll Wards of the State contact OPRS and refer to the tip sheet.
Performance Sites:	UIC
Sponsor:	American Association of Orthodontics Foundation
PAF#:	N/A
Grant/Contract No:	N/A
Grant/Contract Title:	N/A
Research Protocol(s):	

APPENDIX A (continued)

a) Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors, PI: Jennifer Caplin DMD MS; Version: 1.1, Date: 1/22/18

Assent(s):

a) Written assent, no version #/date, submitted with IR under file name Assent v1.1 Clean 01-22-18_30

Parental Permission(s):

a) Parental Permission, Version #1.1, 1/22/18

HIPAA Authorization(s):

a) HIPAA authorization, Version #1.1, 1/22/18

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

(3) Prospective collection of biological specimens for research purposes by noninvasive means.
(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
11/27/2017	Initial Review	Expedited	12/05/2017	Modifications Required
01/22/2018	Response To Modifications	Expedited	01/30/2018	Approved

Please remember to:

→ Use your **research protocol number** (2017-1276) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the guidance,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
201 AOB (MC 672)
1737 West Polk Street
Chicago, Illinois 60612
Phone (312) 996-1711

APPENDIX A (continued)

amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Rachel Olech, B.A., CIP
Assistant Director, IRB # 3
Office for the Protection of Research Subjects

Enclosure(s): **Approved and stamped documents are available for download via the protocol record in OPRS Live.**

1. **Assent Document(s):**
   a) Written assent, no version #/date, submitted with IR under file name Assent v1.1 Clean 01-22-18_30
2. **Parental Permission(s):**
   a) Parental Permission, Version #1.1, 1/22/18
3. **HIPAA Authorization(s):**
   a) HIPAA authorization, Version #1.1, 1/22/18

cc: Budi Kusnoto, Orthodontics, M/C 841
OVCR Administration, M/C 672

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
203 AOB (MC 672)
1737 West Polk Street
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APPENDIX B

Amendment to IRB

Approval Notice
Amendment to Research Protocol and/or Consent Document – Expedited Review
UIC Amendment # 1

March 7, 2018

Jennifer Caplin, BS, DMD, MS
Orthodontics
801 S. Paulina St Room 131
M/C 841
Chicago, IL 60612
Phone: (312) 996-0230 / Fax: (312) 996-0893

RE: Protocol # 2017-1276
"Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors"

Dear Dr. Caplin:

Members of Institutional Review Board (IRB) #3 have reviewed this amendment to your research and/or consent form under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2) and/or 21 CFR 56.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: March 7, 2018
Amendment:
Summary: UIC Amendment #1 received on March 5, 2018 involves the addition of Midwestern University as a research site. Appendix K and IRB approval from Midwestern University were provided.
Approved Subject Enrollment #: 250
Performance Sites: Midwestern University, UIC
Sponsor: American Association of Orthodontics Foundation

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
03/05/2018	Amendment	Expedited	03/07/2018	Approved

Please be sure to:

→ Use your research protocol number (2017-1276) on any documents or correspondence with the IRB concerning your research protocol.

APPENDIX B (continued)

→ Review and comply with all requirements on the guidance,
"UIC Investigator Responsibilities, Protection of Human Research Subjects"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB #3 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Rachel Olech, B.A., CIP
Assistant Director, IRB # 3
Office for the Protection of Research Subjects

Enclosure(s): None

cc: Budi Kusnoto, Orthodontics, M/C 841

UNIVERSITY OF ILLINOIS AT CHICAGO
Office for the Protection of Research Subjects
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APPENDIX C

AAOF Grant Approval

American Association of Orthodontists

AAOF
Advancing the Specialty

401 North Lindbergh Blvd.
St. Louis, Missouri 63141-7816

314-292-6546 or 800-424-2841, ext. 546
Fax: 800-708-1364

www.aaofoundation.net

March 8, 2018

Dr. Jennifer Caplin
University of Illinois Chicago
801 S Paulina St., Room 131
Chicago, IL 60612

Dear Dr. Caplin:

Thank you for your 2018 Orthodontic Faculty Development Fellowship Award proposal, entitled ***"Project 1: (Barriers/Access to Care) The Effect of the Implementation of the HLD Index for Medicaid Patients on Access to Orthodontic Care in Illinois / Project 2: Linking Malocclusion and Body Mass Via Genetic Variants within the Hippo Signaling Pathway,"*** requesting $20,000.

Your proposal was reviewed by the Foundation's Planning and Awards Review Committee (PARC) and then considered by the AAO Foundation Board at our meeting in late February.

Congratulations! Your application was among those approved for funding. Your proposal was named the ***2018 Robert E. Gaylord Teaching Fellowship Award.***

- This funding, however, is contingent upon your satisfying the reviewers' concerns for IRB approval for Project #2

This year once again we are providing reviews of all proposals received regardless of the funding status. Attached is your review, along with some important information about the review process which we encourage you to look at carefully and study so that your next proposal will be even stronger.

The entire funding amount of $20,000 will be sent upon receipt of the following:

- completed and signed Letter of Agreement and Promissory Note (copy attached)
- a brief video of the PI and the project sent separately to cyoung@aaortho.org
- a black and white photograph of the P/I, and
- a synopsis (500 words) of the project/research/use of funds, submitted electronically to cyoung@aaortho.org. This synopsis is to include:
  - a short biography
  - a brief description of their project

APPENDIX C (continued)

- how orthodontic education will benefit from their award
- why the Foundation is important to the project
- how Foundation funding might help advance your career, and how it has helped advance your career, assuming you have received AAOF funding in the past.

No Progress Report is required for an OFDFA, but a Final Report, in an electronic format, is due no later than July 1, 2019, unless you have received a No Cost Extension. (Final Report form attached.)

Your Final Report will be posted on the AAOF website. Also, it may be summarized and/or distributed to the **AJO/DO** and **Bulletin** as well. See examples of other Final Reports on the AAO Foundation website at: http://www.aaofoundation.net/AwardsProgram/SummaryofAwardResults.aspx.

It is understood that the recipient will make a good faith effort to publish or otherwise disseminate the findings of the project. Publications or presentations made by Recipient relating to the project must contain appropriate reference to support provided by the Foundation.

Should you have any questions, please contact Mr. Robert Hazel, AAOF Executive Vice President, at 800/424-2841, #546.

Kind regards,

David J. Angus, DMD
President

cc: Dr. Budi Kusnoto
Mr. Robert Hazel

Enclosures: Explanation of Review Process (PARC)
Individualized Review
Letter of Agreement/Promissory Note – Fellowship
Final Report Form

APPENDIX D

University of Illinois at Chicago
Consent/Parental Permission and Authorization for Personal Health Information

University of Illinois at Chicago
Research Information and Parental Permission for Participation in Biomedical Research

Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors

Your child is being asked to participate in a research study. Researchers are required to provide a consent form such as this one to tell you about the research, to explain that taking part is voluntary, to describe the risks and benefits of participation, and to help you to make an informed decision. You should feel free to ask the researchers any questions you may have.

Principal Investigator Name and Title: Dr. Jennifer Caplin, Clinical Assistant Professor
Department and Institution: University of Illinois at Chicago, College of Dentistry, Department of Orthodontics
Address and Contact Information:
University of Illinois at Chicago, College of Dentistry
Department of Orthodontics
801 S. Paulina St., Room 131
Chicago IL, 60612
312-996-0320
Emergency Contact Name and Information: Dr. Jennifer Caplin
Sponsor: American Association of Orthodontics Foundation

Conflict of Interest

Your child's health care provider may be an investigator on this research protocol, and as an investigator, is interested in both your child's clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your child's care from a clinician who is not associated with this project. Your child is not obligated to participate in any research project offered by your child's clinician. Your child's participation in this research study is voluntary and your child does not have to participate. The decision to not participate will not affect your child's clinical care now or in the future.

Why am I being asked?

Your child is being asked to be a subject in a research study about the relationship between body mass and malocclusion (crooked teeth and jaw discrepancies) via the Hippo signaling pathway (a collection of genes) and dietary factors. The purpose of this study is to explore the potential links between body mass, the size and shape of the bones of the face, the position of the teeth, diet, and genetics.

APPENDIX D (continued)

Your child has been asked to participate in the research because you are seeking orthodontic treatment for your child.

Your child's participation in this research is voluntary. Your decision whether or not to permit your child to participate will not affect your or your child's current or future dealings with the University of Illinois at Chicago. **If you decide to permit your child to participate, you are free to withdraw your child at any time without affecting that relationship.**

Approximately 250 subjects may be involved in this research at UIC.

What is the purpose of this research?

This research is being done to better understand the potential links between body mass, the size and shape of the bones of the face, the position of the teeth, diet, and genetics.

What procedures are involved?

This research will be performed at University of Illinois at Chicago, College of Dentistry Department of Orthodontics, Room 131

Your child will need to come to the study site 1 time.

That visit will take about 1-2 hours

The study procedures are:

- Collection of orthodontic records-digital dental models, x-ray of skull, height, weight, waist circumference, and age by the orthodontic resident.
  - All of these records are collected on all orthodontic patients and therefore will be collected regardless of your child's participation in this study
- Your child will be asked to spit into a test tube to collect saliva.
- Your child, or a representative on behalf of your child, will be asked to fill out a questionnaire (the Block Food Frequency Questionnaire) about your child's diet.

Genetic Testing

The genetic testing will involve analyzing several candidate genes to see how they are unique to your child. We will not test the entire gene, only the segment that differs among people.

Before your child's DNA is analyzed, all identifiers and personal information will be removed, and there will be no way to link the DNA back to your. Your child's DNA will be assigned a random code, which cannot be traced back to your child.

The results of the analysis will be shared with members of the approved research team. All identifiers and personal information will be removed prior to sharing.

APPENDIX D (continued)

The results of the analysis will not be shared with you or your child, because we will have no way of identifying your child.

Your child's DNA will be stored for future use. Future research may be conducted to further study the link between genetics and malocclusion (position of the jaws and teeth). The DNA will be stored with no identifiers that can be linked to your child. It will be linked to your child's x-rays, dental models, height, weight, and age. It will be stored indefinitely in an investigator's laboratory.

Unfortunately, once in the bank, we cannot withdraw your child's DNA, as we will not be able to identify which DNA sample belongs to your child.

☐ I agree to allow genetic testing to be performed on my child's saliva sample for the current present research study.
Initials _____.

☐ I agree to allow my child's genetic data to be kept by the University of Illinois at Chicago DNA Services Facility for use by other researchers for future genetic research to learn more about how to prevent, detect, or treat malocclusion.
Initials _____.

☐ I do not agree to allow my child's genetic data to be kept by the University of Illinois at Chicago DNA Services Facility for use by other researchers for future genetic research to learn more about how to prevent, detect, or treat malocclusion.
Initials _____.

☐ I agree to allow my child's genetic data to be kept by University of Illinois at Chicago DNA Services Facility for use by other researchers for future genetic research to learn more about how to prevent, detect, or treat other health problems.
Initials _____.

☐ I do not agree to allow my child's genetic data to be kept by University of Illinois at Chicago DNA Services Facility for use by other researchers for future genetic research to learn more about how to prevent, detect, or treat other health problems.
Initials _____.

What are the potential risks and discomforts?

The less likely risks and discomforts expected in this study are:

The risk of inadvertent or inappropriate use or disclosure of individually identified genetic information, including denial of employment or insurance of a research participant (or a relative or ethnic group or population) and psychosocial harms, such as stress, anxiety, or embarrassment resulting from inadvertent disclosure of information on family relationships, ethnic heritage, or potentially stigmatizing conditions. The researchers will do their best to minimize this risk by removing all personal identifiers from the genetic information prior to analysis. The genetic information will in no way be linked to your child.

APPENDIX D (continued)

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

There is a risk that someone could get access to the genetic information we have stored about your child. Genetic testing can create information about a subjects' and their families' personal health risks and can cause or increase anxiety, and/or interfere with your child's ability to get insurance or a job, and can even lead to discrimination. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. There are laws against this kind of misuse, but they may not give full protection. There may be other unforeseen privacy risks. We believe the chance these things will happen is very small, but we cannot make guarantees. Your child's privacy and the confidentiality of your child's data are very important to us and we will make every effort to protect them. These efforts are described in the section below called "What about privacy and confidentiality?"

Will I be told about new information that may affect my decision to participate?

During the course of the study, you will be informed of any significant new research findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about permitting your child to continuing in the study. If new information is provided to you, your consent to permit your child to continue participating in this study may be re-obtained.

Are there benefits to taking part in the research?

Your child will not directly benefit from participation in the research.

It is hoped that knowledge gained from this research may benefit others with malocclusion (crooked teeth and jaw discrepancies) in the future.

Your child's orthodontic treatment will in no way be affected if you decline to participate in this study.

What other options are there?

You have the option to not participate in this study.

What about privacy and confidentiality?

The people who will know that your child is a research subject are members of the research team, and if appropriate, your child's physicians and nurses. No information about your child, or provided by you or your child, during the research, will be disclosed to others without your written permission, except if necessary to protect your rights or welfare (for example, if you are

APPENDIX D (continued)

injured and need emergency care or when the UIC Office for the Protection of Research Subjects monitors the research or consent process) or if required by law.

Study information which identifies your child and the consent form signed by you will be looked at and/or copied for examining the research by:

- The research team
- The University of Illinois at Chicago Institutional Review Board
- State of Illinois Auditors

A possible risk of the research is that your child's participation in the research or information about your child and your child's health might become known to individuals outside the research.

All of your child's personal information will be removed from the data by the research team immediately upon collection of the complete set of records. This information will be destroyed and the records will not link to your child in any way. Your child's records will be assigned a random code that will not link to your child in any way. All records will be stored on a password protected server at the University of Illinois at Chicago College of Dentistry, Department of Orthodontics. Genetics data will be stored at in a secure freezer and secure password protected computer at the University of Illinois at Chicago DNA Services Facility. All personal information will be removed from all records, including genetic information, prior to analysis, and will in no way be linked to you.

When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity.

What are the costs for participating in this research?

There are no costs to you or your child for participating in this research.

Will I be reimbursed for any of my expenses or paid for my participation in this research?

You will receive compensation for participation in the study. If your child completes the study, you will receive a total of $20.00. You will receive your payment immediately after your child's visit in person.

Can I withdraw or be removed from the study?

If you decide to permit your child to participate, you are free to withdraw your consent and discontinue participation at any time without affecting your future care at UIC.

You have the right to leave a study at any time without penalty.

The researchers and sponsor also have the right to stop your child's participation in this study without your consent if:

- They believe it is in your child's best interests;

APPENDIX D (continued)

In the event you withdraw your child or are asked to leave the study, you will still be compensated as described above.

Who should I contact if I have questions?

Contact the researcher Dr. Jennifer Caplin at 312-996-0230 or email address, jcapli3@uic.edu:

- If you have any questions about this study or your part in it,
- If you feel you have had a research-related injury (or a bad reaction to the study treatment), and/or
- If you have questions, concerns or complaints about the research.

What are my rights as a research subject?

If you have questions about your child's rights as a research subject or concerns, complaints, or to offer input you may call the Office for the Protection of Research Subjects (OPRS) at 312-996-1711 or 1-866-789-6215 (toll-free) or e-mail OPRS at uicirb@uic.edu.

Signature of Subject or Legally Authorized Representative

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to permit my child to participate in this research. I will be given a copy of this signed and dated form.

_____ _____

Signature of Parent Date

_____

Printed Name of Parent

_____ _____

Printed Name of Child Age of Child

_____ _____

Signature of Person Obtaining Parental Permission Date (must be same as subject's)

_____

Printed Name of Person Obtaining Parental Permission

APPENDIX E

University of Illinois at Chicago
Consent/Parental Permission and Authorization for Participation in Biomedical Research

HIPAA Authorization Template V2.9, 03/13/07

University of Illinois at Chicago
Authorization To Use And Disclose (Release) Health Information For a Research Study

Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors

State and Federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect your health information. This form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information in this research study. **Please read this form carefully.**

You have been asked to take part in a research study. The study has already been described to you in a separate consent form. By signing this form you are permitting Dr. Jennifer Caplin, Department of Orthodontics and her research team to create, get, use, store, and share protected health information that identifies you for the purposes of this research study.

Description of protected health information that may be used and released (disclosed or shared)

The health information includes all information created and/or collected during the research as described in the 'Consent for Participation in Research' entitled 'Examining the Relationship between Body Weight and Malocclusion via the Hippo Signaling Pathway and Dietary Factors'. Protected health information may include results of tests, procedures or surveys that are part of the research. Health information in your medical record may be used and released if it is needed for the research; for example, past medical conditions or medications or information related to illness or hospitalizations that occur during your participation in the research

The health information includes: Age, x-ray, digital dental models, height, weight, and genetic data.

Research use of your protected health information:

During the conduct of the research, the researchers may use or share your health information:

- With each other and with other researchers involved with the study;
- With law enforcement or other agencies, when required by law;
- With non-UIC collaborators of the research study: Midwestern University, Chicago College of Osteopathic Medicine, Department of Anthropology;
- With review boards including the University of Illinois at Chicago Institutional Review Board, and other persons who watch over the conduct of research

Protection of your health information

APPENDIX E (continued)

The researchers and the American Association of Orthodontics Foundation agree to protect your health information and will only share this information as described in this Authorization and the research consent form.

When your health information is given to people outside of the research study, those agencies that receive your health information may not be required by federal privacy laws (such as the Privacy Rule) to protect it. They may also share your information with others without your permission, if permitted by laws that they have to follow.

Removal of your identifying information (De-Identification)

If all information that identifies you is removed from your health information, the remaining information is no longer subject to the limits of this Authorization or to the HIPAA privacy laws. Therefore, the de-identified information may be used and released by the researchers (as permitted by law) for other purposes, such as other research projects.

Expiration of Authorization

This Authorization does not have an expiration date, but can be canceled sooner if you decide to withdraw your permission.

Withdrawal or removal from the study

You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to:

Jennifer Caplin
University of Illinois at Chicago, College of Dentistry
Department of Orthodontics
801 S. Paulina St., Room 131
Chicago IL, 60612

If you cancel this Authorization, you may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information they have already obtained to maintain the integrity and reliability of the research and to report any adverse (bad) effects that may have happened to you.

Contact information for questions about my rights under HIPAA

If you have questions or concerns regarding your privacy rights under HIPAA, you should contact the University of Illinois at Chicago Privacy Officer at Ph: (312) 996-2271.

If you have not already received a copy of the Notice of Privacy Practices, you should ask for one. You will be given a copy of this Authorization after it has been signed to keep for your records.

Right to Refuse to Sign this Authorization

You do not have to sign this Authorization. If you decide not to sign this Authorization form, it will only mean you cannot take part in this portion of the research that involves the use and release of your health information. Not signing this form will not affect your non-research related treatment, payment or enrollment in any health plans or your eligibility for other medical benefits.

APPENDIX E (continued)

Signature of Subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions, and my questions have been answered to my satisfaction. I authorize the use and disclosure of my protected health information for this research.

_____ _____

Signature of Subject Date

_____

Printed Name of Subject

[*OPTIONAL --If all subjects will be adults with the capacity to provide consent/authorization for the research, delete the parent/guardian/legally authorized representative signature lines. If not, replace the previous signatures with the following section*].

_____

Printed name of Subject

_____ _____

Signature of Parent /Guardian or Legally Authorized Representative of Subject

Date (must be same as Subject's)

_____

Printed name of Parent / Guardian or Legally Authorized Representative of Subject

Describe relationship to subject including the legal authority this individual has to act on behalf of the subject. (Check one below)

- ☐ Parent
- ☐ Medical Power of attorney/representative
- ☐ Legal guardian
- ☐ Health care surrogate
- ☐ Other; specify _____

_____

_____

_____ _____

Signature of Witness Date (must be same as Subject's)

_____

Printed name of Witness

APPENDIX F

University of Illinois at Chicago
Assent for Participation in Hippo BMI Study

Linking Malocclusion and Body Mass Via Genetic Variants Within the Hippo Signaling Pathway and Dietary Factors

1. My name is Dr._____.

2. We are asking you to take part in a research study because we are trying to learn more about how body mass and genetics affect the position of your jaws and teeth.

3. If you agree to be in this study, you will be asked to spit into a test tube. You or your parent/guardian will be asked to fill out a survey about what you eat. We will also take an impression of your teeth, take an x-ray of your skull, weigh you on a scale, and measure your height. We will take the impression, the x-ray, your weight, and your height regardless of whether or not you agree to participate in the research, as we need these for your orthodontic treatment. If you have already had your impressions, x-ray, weight, and height taken, we will not re-take them.

4. The biggest risk to you is that other people may discover that you were a part of this study. We will try to prevent that by removing your name, address, birthday, and all other personal information from everything that we use (saliva, survey results, models of your teeth, and x-ray of your skull) as soon as possible.

5. While there is no direct benefit to you for participation in this research, we hope that it will help other children like you in the future who are seeking orthodontic treatment.

6. Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

7. If you don't want to be in this study, you don't have to participate. Remember, being in this study is up to you and no one will be upset if you don't want to participate or even if you change your mind later and want to stop.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me at 312-996-0230 or ask me next time.

9. Signing your name at the bottom means that you agree to be in this study. Your doctors will continue to treat you whether or not you participate in this study. You and your parents will be given a copy of this form after you have signed it.

APPENDIX F (continued)

Name of Subject		Date
Signature	Age	Grade in School

APPENDIX G

Selected Maxillary Landmarks and Descriptions

OCCLUSION		EXTERIOR
Name	**No.**	**Description**
s0	1	Rt 1st Molar embrasure point - Maxilla
s1	2	Most cervical point of tooth on edge of gingiva - Rt 1st molar - Maxilla
s2	3	Rt 2nd Premolar embrasure point - Maxilla
s3	4	Most cervical point of tooth on edge of gingiva - Rt 2nd premolar - Maxilla
s4	5	Rt 1st Premolar embrasure point - Maxilla
s5	6	Most cervical point of tooth on edge of gingiva - Rt 1st premolar - Maxilla
s6	7	Rt Canine embrasure point - Maxilla
s7	8	Most cervical point of tooth on edge of gingiva - Rt canine - Maxilla
s8	9	Rt Lateral Incisor embrasure point - Maxilla
s9	10	Most cervical point of tooth on edge of gingiva - Rt lateral incisor - Maxilla
s10	11	Rt Central Incisor embrasure point - Maxilla
s11	12	Most cervical point of tooth on edge of gingiva - Rt central incisor - Maxilla
s12	13	Central incisor embrasure point - Maxilla
s13	14	Most cervical point of tooth on edge of gingiva - Lt central incisor - Maxilla
s14	15	Lt Central Incisor embrasure point - Maxilla
s15	16	Most cervical point of tooth on edge of gingiva - Lt lateral incisor - Maxilla
s16	17	Lt Lateral Incisor embrasure point - Maxilla
s17	18	Most cervical point of tooth on edge of gingiva - Lt canine - Maxilla
s18	19	Lt Canine embrasure point - Maxilla
s19	20	Most cervical point of tooth on edge of gingiva - Lt 1st premolar - Maxilla
s20	21	Lt 1st Premolar embrasure point - Maxilla
s21	22	Most cervical point of tooth on edge of gingiva - Lt 2nd premolar - Maxilla
s22	23	Lt 2nd Premolar embrasure point - Maxilla
s23	24	Most cervical point of tooth on edge of gingiva - Lt 1st molar - Maxilla
s24	25	Lt 1st Molar embrasure point - Maxilla
s25	26	Lingual Rt 1st Molar embrasure point - Maxilla
s26	27	Lingual Most cervical point of tooth on edge of gingiva - Rt 1st molar - Maxilla
s27	28	Lingual Rt 2nd Premolar embrasure point - Maxilla
s28	29	Lingual Most cervical point of tooth on edge of gingiva - Rt 2nd premolar - Maxilla
s29	30	Lingual Rt 1st Premolar embrasure point - Maxilla
s30	31	Lingual Most cervical point of tooth on edge of gingiva - Rt 1st premolar - Maxilla
s31	32	Lingual Rt Canine embrasure point - Maxilla
s32	33	Lingual Most cervical point of tooth on edge of gingiva - Rt canine - Maxilla
s33	34	Lingual Rt Lateral Incisor embrasure point - Maxilla
s34	35	Lingual Most cervical point of tooth on edge of gingiva - Rt lateral incisor - Maxilla
s35	36	Lingual Rt Central Incisor embrasure point - Maxilla

Appendix G (continued)

s36	37	Lingual Most cervical point of tooth on edge of gingiva - Rt central incisor - Maxilla
s37	38	Lingual Central incisor embrasure point - Maxilla
s38	39	Lingual Most cervical point of tooth on edge of gingiva - Lt central incisor - Maxilla
s39	40	Lingual Lt Central Incisor embrasure point - Maxilla
s40	41	Lingual Most cervical point of tooth on edge of gingiva - Lt lateral incisor - Maxilla
s41	42	Lingual Lt Lateral Incisor embrasure point - Maxilla
s42	43	Lingual Most cervical point of tooth on edge of gingiva - Lt canine - Maxilla
s43	44	Lingual Lt Canine embrasure point - Maxilla
s44	45	Lingual Most cervical point of tooth on edge of gingiva - Lt 1st premolar - Maxilla
s45	46	Lingual Lt 1st Premolar embrasure point - Maxilla
s46	47	Lingual Most cervical point of tooth on edge of gingiva - Lt 2nd premolar - Maxilla
s47	48	Lingual Lt 2nd Premolar embrasure point - Maxilla
s48	49	Lingual Most cervical point of tooth on edge of gingiva - Lt 1st molar - Maxilla
s49	50	Lingual Lt 1st Molar embrasure point - Maxilla
s50	51	Rt 1st Molar Buccal-Mesial Cusp tip
s51	52	Rt 1st Molar Lingual-Mesial Cusp tip
s52	53	Rt 1st Molar Buccal-Distal Cusp tip
s53	54	Rt 1st Molar Lingual-Distal Cusp tip
s54	55	Rt 2nd Premolar Buccal Cusp
s55	56	Rt 2nd Premolar Lingual Cusp
s56	57	Rt 1st Premolar Buccal Cusp
s57	58	Rt 1st Premolar Lingual Cusp
s58	59	lateral edge of Rt canine
s59	60	Cusp tip - Rt canine
s60	61	medial edge of Rt canine
s61	62	lateral incisal edge of Rt lateral incisor
s62	63	medial incisal edge of Rt lateral incisor
s63	64	lateral incisal edge of Rt central incisor
s64	65	medial incisal edge of Rt central incisor
s65	66	medial incisal edge of Lt central incisor
s66	67	lateral incisal edge of Lt central incisor
s67	68	medial incisal edge of Lt lateral incisor
s68	69	lateral incisal edge of Lt lateral incisor
s69	70	medial edge of Lt canine
s70	71	Cusp tip - Lt canine
s71	72	lateral edge of Lt canine
s72	73	Lt 1st Premolar Buccal Cusp
s73	74	Lt 1st Premolar Lingual Cusp
s74	75	Lt 2nd Premolar Buccal Cusp
s75	76	Lt 2nd Premolar Lingual Cusp

Appendix G (continued)

s76	77	Lt 1st Molar Buccal-Mesial Cusp tip
s77	78	Lt 1st Molar Lingual-Mesial Cusp tip
s78	79	Lt 1st Molar Buccal-Distal Cusp tip
s79	80	Lt 1st Molar Lingual-Distal Cusp tip

Appendix H

Selected Mandibular Landmarks and Descriptions

OCCLUSION		EXTERIOR
Name	**No.**	**Description**
s0	1	Lt 1st Molar embrasure point - Mandible
s1	2	Most cervical point of tooth on edge of gingiva - Lt 1st molar - Mandible
s2	3	Lt 2nd Premolar embrasure point - Mandible
s3	4	Most cervical point of tooth on edge of gingiva - Lt 2nd premolar - Mandible
s4	5	Lt 1st Premolar embrasure point - Mandible
s5	6	Most cervical point of tooth on edge of gingiva - Lt 1st premolar - Mandible
s6	7	Lt Canine embrasure point - Mandible
s7	8	Most cervical point of tooth on edge of gingiva - Lt canine - Mandible
s8	9	Lt Lateral Incisor embrasure point - Mandible
s9	10	Most cervical point of tooth on edge of gingiva - Lt lateral incisor - Mandible
s10	11	Lt Central Incisor embrasure point - Mandible
s11	12	Most cervical point of tooth on edge of gingiva - Lt central incisor - Mandible
s12	13	Central incisor embrasure point - Mandible
s13	14	Most cervical point of tooth on edge of gingiva - Rt central incisor - Mandible
s14	15	Rt Central Incisor embrasure point - Mandible
s15	16	Most cervical point of tooth on edge of gingiva - Rt lateral incisor - Mandible
s16	17	Rt Lateral Incisor embrasure point - Mandible
s17	18	Most cervical point of tooth on edge of gingiva - Rt canine - Mandible
s18	19	Rt Canine embrasure point - Mandible
s19	20	Most cervical point of tooth on edge of gingiva - Rt 1st premolar - Mandible
s20	21	Rt 1st Premolar embrasure point - Mandible
s21	22	Most cervical point of tooth on edge of gingiva - Rt 2nd premolar - Mandible
s22	23	Rt 2nd Premolar embrasure point - Mandible
s23	24	Most cervical point of tooth on edge of gingiva - Rt 1st molar - Mandible
s24	25	Rt 1st Molar embrasure point - Mandible
s25	26	Lingual Lt 1st Molar embrasure point - Mandible
s26	27	Lingual Most cervical point of tooth on edge of gingiva - Lt 1st molar - Mandible
s27	28	Lingual Lt 2nd Premolar embrasure point - Mandible
s28	29	Lingual Most cervical point of tooth on edge of gingiva - Lt 2nd premolar - Mandible
s29	30	Lingual Lt 1st Premolar embrasure point - Mandible
s30	31	Lingual Most cervical point of tooth on edge of gingiva - Lt 1st premolar - Mandible
s31	32	Lingual Lt Canine embrasure point - Mandible
s32	33	Lingual Most cervical point of tooth on edge of gingiva - Lt canine - Mandible
s33	34	Lingual Lt Lateral Incisor embrasure point - Mandible
s34	35	Lingual Most cervical point of tooth on edge of gingiva - Lt lateral incisor - Mandible

Appendix H (continued)

s35	36	Lingual Lt Central Incisor embrasure point - Mandible
s36	37	Lingual Most cervical point of tooth on edge of gingiva - Lt central incisor - Mandible
s37	38	Lingual Central incisor embrasure point - Mandible
s38	39	Lingual Most cervical point of tooth on edge of gingiva - Rt central incisor - Mandible
s39	40	Lingual Rt Central Incisor embrasure point - Mandible
s40	41	Lingual Most cervical point of tooth on edge of gingiva - Rt lateral incisor - Mandible
s41	42	Lingual Rt Lateral Incisor embrasure point - Mandible
s42	43	Lingual Most cervical point of tooth on edge of gingiva - Rt canine - Mandible
s43	44	Lingual Rt Canine embrasure point - Mandible
s44	45	Lingual Most cervical point of tooth on edge of gingiva - Rt 1st premolar - Mandible
s45	46	Lingual Rt 1st Premolar embrasure point - Mandible
s46	47	Lingual Most cervical point of tooth on edge of gingiva - Rt 2nd premolar - Mandible
s47	48	Lingual Rt 2nd Premolar embrasure point - Mandible
s48	49	Lingual Most cervical point of tooth on edge of gingiva - Rt 1st molar - Mandible
s49	50	Lingual Rt 1st Molar embrasure point - Mandible
s50	51	Lt 1st Molar Buccal-Mesial Cusp tip
s51	52	Lt 1st Molar Lingual-Mesial Cusp tip
s52	53	Lt 1st Molar Buccal-Distal Cusp tip
s53	54	Lt 1st Molar Lingual-Distal Cusp tip
s54	55	Lt 2nd Premolar Buccal Cusp
s55	56	Lt 2nd Premolar Lingual Cusp
s56	57	Lt 1st Premolar Buccal Cusp
s57	58	Lt 1st Premolar Lingual Cusp
s58	59	lateral edge of Lt canine
s59	60	Cusp tip - Lt canine
s60	61	medial edge of Lt canine
s61	62	lateral incisal edge of Lt lateral incisor
s62	63	medial incisal edge of Lt lateral incisor
s63	64	lateral incisal edge of Lt central incisor
s64	65	medial incisal edge of Lt central incisor
s65	66	medial incisal edge of Rt central incisor
s66	67	lateral incisal edge of Rt central incisor
s67	68	medial incisal edge of Rt lateral incisor
s68	69	lateral incisal edge of Rt lateral incisor
s69	70	medial edge of Rt canine
s70	71	Cusp tip - Rt canine
s71	72	lateral edge of Rt canine
s72	73	Rt 1st Premolar Buccal Cusp
s73	74	Rt 1st Premolar Lingual Cusp
s74	75	Rt 2nd Premolar Buccal Cusp
s75	76	Rt 2nd Premolar Lingual Cusp
s76	77	Rt 1st Molar Buccal-Mesial Cusp tip
s77	78	Rt 1st Molar Lingual-Mesial Cusp tip

Appendix H (continued)

s78	79	Rt 1st Molar Buccal-Distal Cusp tip
s79	80	Rt 1st Molar Lingual-Distal Cusp tip

APPENDIX I

Raw SNP Variant Data

#CH	POS	REF	ALT	avsnp147	TYPE
chr1	41369961	A	G	rs4636447	snp
chr1	41369981	G	A	rs191294221	snp
chr1	41370013	C	T	rs7522116	snp
chr1	41370069	C	T		snp
chr1	41370133	T	C	rs12029493	snp
chr1	41370166	CGGGA	TGGGA	rs4660529	snp
chr1	41370173	T	G		snp
chr1	41370176	A	G		snp
chr1	41370199	A	G	rs4660191	snp
chr1	41370202	A	C		snp
chr1	41370206	C	A		snp
chr1	41370209	T	C		snp
chr1	41370216	T	G		snp
chr1	41370220	C	G		snp
chr1	41370226	A	G		snp
chr1	41370234	T	C		snp
chr1	41370241	CAAAAAAAAAAAAAAAAA	CAAAAAAAAAAAAAAAAG	rs35454700	del
chr1	41371501	C	T	rs56233836	snp
chr1	41376652	C	T	rs1317183	snp
chr1	41376676	TAC	TAT,CAT		snp,complex
chr1	41379717	G	A	rs142582620	snp
chr1	41379869	G	A	rs55784313	snp
chr1	41379920	C	T	rs150540821	snp
chr3	49684329	A	G		snp
chr3	49684333	GC	AA		mnp
chr3	49684365	C	A	rs13085791	snp
chr3	49685708	A	G	rs144982232	snp
chr3	49685714	T	C	rs62262683	snp
chr3	49687893	C	T		snp

K:T121:Genotype	K:T071:Genotype	K:T115:Genotype	K:T048:Genotype	K:T091:Genotype	K:T051:Genotype	K:T003:Genotype	K:T126:Genotype	K:T058:Genotype	K:T090:Genotype	K:T004:Genotype	K:T122:Genotype	K:T001:Genotype	K:T030:Genotype	K:T113
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
1/1	0/0	0/1	0/0	1/1	0/0	0/0	0/1	0/1	0/0	0/1	1/1	.	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	.	1/1	1/1
0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1
0/1	0/0	0/0	0/1	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/1	.	0/0	0/1
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	.	1/1	1/1
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1
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0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	.	0/0	0/1
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	1/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	.	0/1	0/0
.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
.	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0

APPENDIX I (continued)

T035:Genotype	T002_02:Genotype	T061:Genotype	T083:Genotype	T101:Genotype	T008:Genotype	T010:Genotype	T078:Genotype	T047:Genotype	T114:Genotype	T042:Genotype	T096:Genotype	T093:Genotype	T008:Genotype	T05
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/0	0/1	0/1	0/1	0/0	0/0	0/1
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

T072:Genotype	T024:Genotype	T025:Genotype	T065:Genotype	T079:Genotype	T073:Genotype	T095:Genotype	T043:Genotype	T021:Genotype	T002:Genotype	T106:Genotype	T117:Genotype	T012:Genotype	T007:Genotype	T011
0/1	0/0	0/0	1/1	1/1	0/0	0/1	0/0	0/0	0/0	0/0	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1	.	1/1	1/1	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1	.
0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/1	0/1	0/1	0/1	.	0/1	0/1	.
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	.	1/1	1/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/1	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/1	.	0/0	0/0	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/1	0/0	.
0/1	1/1	0/1	0/0	0/0	1/1	0/1	1/1	1/1	1/1	1/1	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
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0/0	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.

APPENDIX I (continued)

K-T062:Genotype	K-T092:Genotype	K-T034:Genotype	K-T057:Genotype	K-T056:Genotype	K-T023:Genotype	K-T080:Genotype	K-T053:Genotype	K-T001_02:Genotyp	K-T015:Genotype	K-T046:Genotype	K-T040:Genotype	K-T070:Genotype	K-T118:Genotype	K-T04
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/1	0/1	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	1/1	0/1	1/1	1/1	1/1	0/0	0/0	0/1	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/1	0/1	0/0	0/1	0/0
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

K-T107:Genotype	K-T076:Genotype	K-T111:Genotype	K-T108:Genotype	K-T089:Genotype	K-T098:Genotype	K-T019:Genotype	K-T026:Genotype	K-T069:Genotype	K-T005:Genotype	K-T018:Genotype	K-T017:Genotype	K-T110:Genotype	K-T020:Genotype	K-T06
0/1	0/0	0/1	0/0	0/1	0/0	0/0	0/1	0/1	0/0	1/1	0/0	0/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	0/1	1/1	0/1	1/1	1/1	0/1	0/1	0/1	0/0	1/1	0/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/1	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/1
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
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0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	0/1	1/1	0/1	1/1	1/1	0/1	0/1	0/1	0/0	1/1	0/1	0/0	0/1
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0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

APPENDIX I (continued)

K-T112:Genotype	K-T029:Genotype	K-T066:Genotype	K-T081:Genotype	K-T074:Genotype	K-T084:Genotype	K-T075:Genotype	K-T032:Genotype	K-T039:Genotype	K-T104:Genotype	K-T103:Genotype	K-T060:Genotype	K-T077:Genotype	K-T013:Genotype	K-T08
1/1	0/1	0/1	0/0	0/1	0/1	0/0	0/1	0/0	0/0	0/1	0/0	0/0	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	1/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	1/1	1/1	0/0	0/1
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0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1
0/0	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/0	0/1	0/0	0/1
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/1	0/0	0/0	0/0
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0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	1/1	1/1	0/1	0/0	0/1	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

K-T099:Genotype	K-T055:Genotype	K-T054:Genotype	K-T028:Genotype	K-T119:Genotype	K-T068:Genotype	K-T120:Genotype	K-T050:Genotype	K-T016:Genotype	K-T009:Genotype	K-T041:Genotype	K-T109:Genotype	K-T067:Genotype	K-T052:Genotype	K-T03
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0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1	0/1	1/1	0/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/1	0/1	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/1	0/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1	1/1	0/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

APPENDIX I (continued)

r.Genotype	K-T005:Genotype	K-T027:Genotype	K-T022:Genotype
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0/0	0/0	0/0	
1/1	1/1	1/1	
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0/1	0/1	0/1	
1/1	1/1	1/1	
0/0	0/0	0/0	
0/0	0/0	0/0	
0/0	0/0	0/0	
0/0	0/0	0/0	
0/0	0/0	0/0	
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0/0	0/0	0/0	
0/0	0/0	0/0	
0/0	0/0	0/1	
0/0	0/0	0/0	
0/0	0/0	0/0	
0/0	0/0	0/0	

chr3	49687907	A	G	rs113893148	snp
chr3	49687940	A	C		snp
chr3	49687999	AGG	AG		del
chr3	49688745	G	A	rs147997200	snp
chr6	35489619	G	T	rs7740758	snp
chr6	35489696	GAG	AAG,CAG,CAT		snp,snp,complex
chr6	35493327	CG	CATG	rs10638006	ins
chr6	35493351	A	T,C	rs6925503	snp,snp
chr6	35493420	A	G	rs61501470	snp
chr6	35494021	G	A	rs142812873	snp
chr6	35494023	G	A	rs11758653	snp
chr6	35494090	C	A	rs72894781	snp
chr6	35494091	A	T	rs146976128	snp
chr6	35494103	C	A	rs138027205	snp
chr6	35494123	C	T		snp
chr6	35494528	T	C	rs72894784	snp
chr6	35496821	CC	CTC	rs71002565	ins
chr6	35496866	C	A		snp
chr6	45340169	A	G	rs12214749	snp
chr6	45366244	G	T	rs76595706	snp
chr6	45366370	TAA	TA		del
chr6	149716436	A	G	rs4870529	snp
chr6	149716438	C	T	rs13205080	snp
chr6	149717955	G	A	rs13210297	snp
chr6	149718012	G	A	rs12174349	snp
chr6	149718029	C	T	rs190555603	snp
chr12	2964459	CTTTTTTTTTTTTTTTG	CTTTTTTTTTTTTTTG		del
chr12	2964482	A	G		snp
chr12	2964493	T	C		snp
chr12	2964515	T	C	rs10848754	snp
chr12	2964553	A	T		snp
chr12	2964562	A	T		snp
chr12	2964594	A	T		snp
chr12	2964615	A	C		snp

APPENDIX I (continued)

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	.	0/0	0/0
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0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	.	0/0	0/1
0/0	1/1	0/1	0/1	0/0	1/2	0/0	0/0	0/2	1/2	0/1	0/0	.	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	.	1/1	1/1
0/0	2/2	0/2	0/0	0/1	0/2	1/1	0/2	1/1	0/0	0/1	0/1	.	1/1	0/1
0/0	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/1	0/0	1/1	0/0	1/1	0/0	0/1	0/1	.	1/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	0/0	1/1	1/1	0/0	1/1	0/1	.	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
1/1	1/1	1/1	1/1	1/1	1/1	0/0	1/1	1/1	0/0	1/1	0/1	.	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/0	.	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0
0/0	0/1	0/1	0/1	0/0	1/1	0/1	0/0	0/0	1/1	0/0	0/0	.	0/1	0/0
0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	.	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1
0/0	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	1/1	0/1	0/1	0/1	0/1	1/1	0/1	0/1	0/0	0/0	0/0	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0
0/0	0/0	0/0	0/1	0/1	0/0	0/1	0/0	0/1	0/0	0/0	0/1	0/1	0/0	0/0
0/0	0/0	0/0	0/1	1/2	0/1	0/1	0/0	0/1	0/0	0/0	0/1	2/2	0/0	0/0
1/1	0/1	1/1	0/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1
0/1	0/0	1/1	0/0	0/0	0/2	0/1	0/2	0/0	1/2	1/1	0/2	0/0	1/2	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0
0/1	0/0	1/1	0/0	0/0	0/0	0/1	0/0	0/0	0/1	1/1	0/0	0/0	0/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1
0/1	1/1	0/1	0/1	0/0	0/1	0/1	0/1	1/1	1/1	0/0	1/1	0/1	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	0/1	0/1	0/0	0/1	0/1	0/1	1/1	1/1	0/0	1/1	0/1	1/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/0	0/0	1/1	0/1	0/0	0/1	0/1	1/1	0/1	1/1	1/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1
0/1	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0

APPENDIX I (continued)

0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
1/1	0/1	1/1	0/1	0/0	1/1	1/1	0/1	1/1	1/1	0/1	.	1/1	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/1	.
0/0	0/1	0/0	0/0	0/1	0/0	0/1	0/1	0/1	0/0	0/1	.	0/0	0/1	.
0/0	1/1	0/0	0/2	1/2	1/1	0/1	0/1	0/1	0/0	1/1	.	0/0	0/1	.
1/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	1/1	.	1/1	1/1	.
0/2	0/0	2/2	1/2	0/2	0/0	0/0	0/2	0/2	0/0	0/0	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/1	.
0/1	0/0	1/1	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/1	0/0	1/1	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	1/1	0/0	0/0	.
0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	.	0/0	0/0	.
0/1	1/1	0/1	1/1	0/1	0/1	1/1	0/0	1/1	1/1	0/1	.	0/1	1/1	.
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0	0/0	.	0/0	0/0	.
0/1	1/1	0/1	1/1	0/1	0/1	1/1	0/0	1/1	1/1	0/1	.	0/1	1/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	.	0/0	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	.	0/0	0/0	.
0/0	0/1	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/1	1/1	.	0/1	0/1	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	.	0/1	0/1	.
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	.	0/0	0/1	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1	.
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	.	0/1	0/1	.

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	0/1	1/1	0/0	0/1	1/1	0/1	1/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/1	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/1	1/2	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/2	0/0	0/1	0/1	0/2
1/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
0/2	0/1	1/2	0/1	0/2	0/1	0/1	0/1	1/1	1/2	1/2	0/1	1/1	0/0	1/2
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/1
0/0	0/1	0/1	0/1	0/0	0/1	0/1	0/1	1/1	0/1	0/1	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	0/1	0/0	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	0/1	0/0	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	1/1	1/1	1/1	0/1	0/1	0/1	0/1	1/1	0/0	1/1	0/1	1/1	0/0	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/1	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1

APPENDIX I (continued)

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/0	0/1	1/1	0/0	1/1	0/1	0/1	0/1	1/1	1/1	0/1	1/1
0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	1/1	0/0
0/2	1/1	0/2	0/1	1/2	0/1	0/0	0/0	0/0	0/0	1/2	0/0	0/1	0/1	0/0
0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1
0/2	0/0	1/2	0/1	0/2	0/1	2/2	0/2	0/2	0/1	0/0	0/1	1/1	0/0	1/2
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/0	0/1	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/0	0/1	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/1	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/1	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/0	0/1	0/1	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/1	1/1	0/0	0/1	1/1	1/1	1/1	1/1	1/1	0/0	0/1	1/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	1/1	0/0	1/1	0/0	0/0	0/1	0/1	0/1	1/1	1/1	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/1	0/2	0/0	1/1	0/0	0/0	0/0	0/0	0/2	0/0	0/1	0/0	0/1	0/0
1/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1
0/1	0/1	1/2	1/1	0/0	0/1	1/1	0/1	1/1	0/2	0/0	0/0	1/2	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	1/1	0/0	0/1	1/1	0/1	1/1	0/0	0/0	0/0	0/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	1/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/0	0/1	1/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1

APPENDIX I (continued)

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	1/1	0/0	1/1	0/0	0/0	0/1	0/1	0/1	1/1	1/1	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/1	0/2	0/0	1/1	0/0	0/0	0/0	0/0	0/2	0/0	0/1	0/0	0/1	0/0
1/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1
0/1	0/1	1/2	1/1	0/0	0/1	1/1	0/1	1/1	0/2	0/0	0/0	1/2	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	1/1	0/0	0/1	1/1	0/1	1/1	0/0	0/0	0/0	0/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	1/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1

0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
1/1	1/1	0/0	1/1	0/0	0/0	0/1	0/1	0/1	1/1	1/1	0/1	1/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/1	0/0	0/0	0/0	0/1	0/0	0/1	0/0
0/0	0/1	0/2	0/0	1/1	0/0	0/0	0/0	0/0	0/2	0/0	0/1	0/0	0/1	0/0
1/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1	0/1	1/1	1/1	1/1	1/1
0/1	0/1	1/2	1/1	0/0	0/1	1/1	0/1	1/1	0/2	0/0	0/0	1/2	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/1	1/1	0/0	0/1	1/1	0/1	1/1	0/0	0/0	0/0	0/1	0/0	0/1
0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1
0/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	1/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	0/1	0/0	0/1	1/1	1/1	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	0/1	0/0	0/0	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/0	0/0	0/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/0	0/1	0/1	0/1	0/1

APPENDIX I (continued)

0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/1	1/1	1/1	1/1	0/0	1/1	0/1	0/1	0/1	1/1	0/0	1/1	1/1	1/1	0/1
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/1	0/0	0/0	0/0	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/1	0/0	1/1
0/1	0/0	0/0	0/1	0/2	0/1	0/1	0/2	0/1	0/2	0/0	0/0	0/1	0/2	1/1
1/1	0/1	1/1	1/1	0/1	1/1	1/1	0/1	1/1	1/1	0/0	0/1	1/1	0/1	1/1
0/0	0/1	1/1	0/2	0/0	0/1	0/1	0/1	0/0	1/1	0/0	0/1	0/0	0/2	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/0
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0/1	1/1	0/0
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