



SCHOOL of
GRADUATE STUDIES
EAST TENNESSEE STATE UNIVERSITY

East Tennessee State University
**Digital Commons @ East
Tennessee State University**

Electronic Theses and Dissertations

Student Works

8-2010

Spousal Concordance in Academic Achievements and Intelligence and Family-Based Association Studies Identified Novel Loci Associated with Intelligence.

Yue Pan

East Tennessee State University

Follow this and additional works at: <https://dc.etsu.edu/etd>



Part of the [Biostatistics Commons](#)

Recommended Citation

Pan, Yue, "Spousal Concordance in Academic Achievements and Intelligence and Family-Based Association Studies Identified Novel Loci Associated with Intelligence." (2010). *Electronic Theses and Dissertations*. Paper 1734. <https://dc.etsu.edu/etd/1734>

This Thesis - Open Access is brought to you for free and open access by the Student Works at Digital Commons @ East Tennessee State University. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of Digital Commons @ East Tennessee State University. For more information, please contact digilib@etsu.edu.

Spousal Concordance in Academic Achievements and Intelligence and Family-Based

Association Studies Identified Novel Loci Associated with Intelligence

A thesis

presented to

the faculty of the Department of Mathematics

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Master of Science in Mathematical Sciences

by

Yue Pan

August 2010

Anant Godbole, Ph.D., Chair

Ke-sheng Wang, Ph.D.

Robert B Gardner, Ph.D.

Keywords: Achievements, IQ, Spousal Concordance, Assortative Mating, Intelligence, Cognitive Ability, Family-Based Association Test, Genome-Wide Association Study, Haplotype, NTM, NR3C2.

ABSTRACT

Spousal Concordance in Academic Achievements and Intelligence and Family-Based Association Studies Identified Novel Loci Associated with Intelligence

by

Yue Pan

Assortative Mating, the tendency for mate selection to occur on the basis of similar traits, plays an essential role in understanding the genetic variation on academic achievements and intelligence (IQ). It is an important mechanism explaining spousal concordance. We used principal component analysis (PCA) for spousal correlation. There is a significant positive correlation between spouses by the new variable PC1 (correlation coefficient=0.515, $p<0.0001$). We further research the genetic factor that affects IQ by using the same data. We performed a low density genome-wide association (GWA) analysis with a family-based association test to identify genetic variants that associated with intelligence as measured by WAIS full-score IQ (FSIQ). NTM at 11q25 (rs411280, $p=0.000764$) and NR3C2 at 4q31.23 (rs3846329, $p=0.000675$) were 2 novel genes that haven't been associated with IQ from other studies. This study may serve as a resource for replication in other populations and a foundation for future investigations.

Copyright by Yue Pan 2010

ACKNOWLEDGMENTS

The following is the acknowledgement of my graduate thesis: At the very first, I am honored to express my deepest gratitude to my dedicated supervisor, Dr. Ke-sheng Wang from Department of Biostatistics and Epidemiology and Dr. Anant Godbole from Department of Mathematics and Statistics, for their valuable instructions and suggestions with their profound knowledge and rich research experience as well as their careful reading of the manuscript. Besides, they always put high priority on our thesis writing and are willing to discuss with me when time is available. I have learnt a lot from them not only about thesis writing but also the professional ethics. I am also extremely grateful to Dr. Bob Gardner and Dr. Jeff Knisley whose patient and meticulous guidance and invaluable suggestions are indispensable to the completion of this thesis. I could not make it without their support and encouragement. In addition, I wish to extend my thanks to the faculty of Department of Mathematics and Statistics and Department of Biostatistics and Epidemiology for their support of this study. I owe special thanks to Dr. Xuefeng Liu, Dr. Edith Seier, Dr. Robert Price, and Dr. Yali Liu for their priceless assist during my graduate study and graduate works. I would also like to thank Dr. Debra Knisley and Dr. Haynes Teresa for their help and valuable suggestions. It was a pleasant experience and memory working as a graduate assistant student with them. Thanks are also due to my graduate friends who never failed to give me great encouragement and suggestions. Special thanks should go to Miss. McMahan, Stephanie, Mr. Yu Daoping, Mr. Mehraban, Arash, Mr. Numfor, Eric Shu, and Mr. Balkew, Teshome M.

At last but not least, I would like to thank my family for their support all the way from the very beginning of my graduate study. I am thankful to all my family members for their thoughtfulness and encouragement.

CONTENTS

	Page
ABSTRACT.....	2
ACKNOWLEDGMENTS	4
Chapter	
1. INTRODUCTION	10
2. MATERIALS AND METHODS	15
Datasets	15
Collaborative Study on the Genetics of Alcoholism (COGA) Data for Spousal Concordance Analysis.	15
Data for Genetic Association Study.....	16
International Multi-Center ADHD Genetics Project (IMAGE) Dataset.....	17
Statistical Analysis	17
Principal Component Analysis For Spousal Concordance.	17
Assessment of Hardy-Weinberg Equilibrium (HWE)	18
Family-Based Association Test.....	18
Multiple Testing	19
Haplotype Block and Haplotype Analysis	19
3. RESULTS.....	21
Spousal Concordance Analysis	21
Normality Test and Gender Difference	21
Spousal Concordance Based on Simple Correlation Analysis.....	21

Spousal Concordance Based on Correlation Analysis Using	
PC Scores	22
Genetic Association Study for IQ	25
Genome-Wide Association Analysis in COGA Sample	25
Replication Study in IMAGE Sample.....	27
Haplotype Block and Haplotype Analysis	29
4. DISCUSSION	32
5. CONCLUSION.....	43
REFERENCES	45
APPENDICES	57
APPENDIX A: Data Source	57
APPENDIX B: Glossary.....	60
APPENDIX C: Affymetrix Panel FBAT- $p < 0.01$ Results and Related Test	
Results.....	67
APPENDIX D: IMAGE FBAT- $p < 0.05$ Results and Related Test Results.....	75
VITA	82

LISTS OF TABLES

Table	Page
1 Characteristics of Husbands and Wives, Correlation Analysis and t-test.....	22
2 Principal Components Loadings for Husbands and Wives.....	23
3 Affymetrix Panel FBAT- $p < 10^{-3}$ Results and Related Test Results	26
4 IMAGE FBAT- $p < 10^{-3}$ Results and Related Test Result.....	28
5 Haplotype Analyses for NR3C2 and NTM ($p < 10^{-3}$).....	30

LISTS OF FIGURES

Figure	Page
1 Relationship Between Husband and Wife PC1 Scores.....	24
2 LD Structures for NR3C2.....	31
3 LD Structures for NTM	31

CHAPTER 1

INTRODUCTION

Mate selection is a major biological event whose outcome is a substantial determinant of an individual's return on his or her whole reproductive investment (Lott, 1979). Assortative mating, the tendency for mated pairs to be more similar to each other phenotypically than would be expected if they were married or mated at random, occurs for a variety of phenotypic traits including both genetically determined traits (e.g., height) and environmentally determined traits (e.g., religion) (Merikangas, 1982). Assortative mating plays an essential role on society and the individual. It will increase the population variance of a given trait and the proportion of individuals who are homozygous for the trait. Assortative mating can influence the course and outcome of marriage in addition to determining the genetic and biological makeup and parenting of offspring (Low, Cui, & Merikangas, 2007).

Assortative mating has been shown for height (Ginsburg, Livshits, Yakovenko, & Kobylansky, 1998; Pawlowski, 2003; Wolanski, 1974), attitude domain of personality (Dubuis-Stadelmann, Fenton, Ferrero, & Preisig, 2001; Farley & Davis, 1977; Farley & Mueller, 1978; Feng & Baker, 1994; Heun & Maier, 1993; Luo & Klohnen, 2005), religion (al-Kandari, Crews, & Poirier, 2002; Hur, 2003), politics (Watson et al., 2004), smoking habits (Bloch, Klein, de Souza e Silva, Nogueira Ada, & Salis, 2003; Sutton, 1980; S. E. Wilson, 2002), and antisocial behavior and psychiatric disorder (Grant et al., 2007; Maes et al., 1998; K. R. Merikangas, 1982;

Merikangas & Brunetto., 1996; Smith & Farrington, 2004). Assortative mating plays an essential role in understanding the genetic variation on academic achievements and intelligence (IQ). IQ is also an important mechanism explaining spousal concordance. At present assortative mating with respect to academic achievement and IQ has been of long standing interest to researchers (al-Kandari et al., 2002; Halpin, 2003; Hur, 2003; Mascie-Taylor, 1989; Mascie-Taylor & Boldsen, 1984; Mascie-Taylor & Vandenberg, 1988; Nolan et al., 2003; Wainwright, Wright, Luciano, Geffen, & Martin, 2005; Watson et al., 2004; Wolff & Melngailis, 1994). However, few studies focus on multivariate analysis.

Intelligence Quotient (IQ) is a score measured by several different standardized psychological tests such as Wechsler Adult Intelligence Scale Test to assess intelligence. Family, twin, and adoption studies have indicated that IQ has significant genetic components (Bouchard & McGue, 1981). From 40% in young childhood to 80% in late adulthood while meta-analyses suggest an overall heritability around 50%, with evidence for increasing importance of genetic effects from childhood to adulthood (Devlin, Daniels, & Roeder, 1997; McGue, Jr., Iacono, & Lykken, 1993).

Most of the heritable variance in IQ is conceptualized as general intelligence and cognitive ability represent the covariance that exists across different dimensions of cognitive ability such as verbal ability, spatial ability, memory, and processing speed. Plomin et al. (2004) reported that the average correlation among those diverse

neuropsychological abilities is approximately 0.3 while around 40% for the total phenotypic variance among the tests is accounted for by a general cognitive factor, considered to represent general intelligence. Genetics contributes not only to learning abilities and disabilities but also to mathematics and other academic areas as well. The shared genes largely contribute to the construct of general intelligence because multivariate genetic research studies showed that although the phenotypic correlation between diverse tests of intelligence is only 0.3, the genetic correlations between tests are generally greater than 0.8 (Petrill, 2002).

Low IQ that is caused by disturbance in cognitive functioning or mutations of gene is also a predictor that related to several diseases such as schizophrenia (Shirts et al., 2007), mental retardation (Cardoso et al., 2009; Petit et al., 1996), and autism (Yu et al., 2007). A recent study also found heart disease and cardiovascular disease are related to low intelligence and cognition (Batty, Deary, Benzeval, & Der, 2010). Identification of the actual genetic factors that influence cognitive ability will help elucidate the etiological basis of individual differences in both normal and abnormal cognitive functioning.

Although substantial research in genetic influences on IQ has been conducted, the identification of specific genes that contribute to the variation in IQ across the full distribution of scores has been difficult (Flint, 1999). Several candidate genes have been reported to be associated with IQ including cholinergic receptor, muscarinic 2

(CHRM2) on 7q (Comings et al., 2003; Dick et al., 2007); cathepsin D (CTSD) on 11p (Payton et al., 2003) and catechol-O-methyltransferase (COMT) on 22q (Egan et al., 2001; Malhotra et al., 2002); Brain-derived neurotrophic factor (BDNF) on 11p (Fountoulakis, 2010; Gao et al., 2010). Candidate gene studies that select genes for study based on known or suspected disease mechanisms or linkage analysis design that is required to use relatively large pedigree data has the disadvantages of low mapping resolution, low allele richness, and low or intermediate statistical power (Ruano et al., 2010).

In the present study, first, we hypothesize that there is a spousal concordance with respect to eight variables that represent people's academic achievements and intelligence. We tested this hypothesis by using simple correlation analysis and multivariate analysis. Second, we conducted a genetic association study for IQ. The conventional genome-wide association (GWA) study approach is a hypothesis-free, systematic search of tagging SNPs across the genome to identify novel associations with common diseases and traits such as IQ. It has emerged as a powerful tool to identify disease-related genes for many common human disorders and other phenotypes (Browning & Browning, 2008; Guessous, Gwinn, & Khoury, 2009). Therefore, after identifying the spousal concordance for IQ, we conducted a family-based low density GWA study to search for novel genetic factors affecting IQ by combining the phenotypes from the Collaborative Study on the Genetics of Alcoholism (COGA) with genotypes provided by Genetic Analysis Workshop (GAW)

14 (Edenberg et al., 2005; Reich, 1996). We also used a dataset from The International Multi-Center ADHD Genetics Project (IMAGE) for replication.

CHAPTER 2

MATERIALS AND METHODS

Datasets

Collaborative Study on the Genetics of Alcoholism (COGA) Data for Spousal

Concordance Analysis

The COGA is a multisite collaboration with the goal of identifying genes contributing to alcoholism and related phenotypes (Reich, 1996). A total of 2,282 individuals from 262 multiplex alcoholic families (pedigrees) are available for genetic analyses. Of the 262 families, 219 were Caucasian families, 35 were African-American families, and 7 were of another race. Phenotypes include alcohol dependence, personal traits, academic achievement, and IQ.

In order to conduct the analysis for achievement and intelligence variables, we chose 8 variables in the COGA data sets that represent the spouses' standard achievement and intelligence level as measured by the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The WAIS (Wechsler, 1981, 1997) is a traditional intelligence test with high test-retest reliability, stability across different age spans, concurrent and predictive validity, and substantial heritability (Bouchard & McGue, 1981). The eight variables are reading (standard), spelling (standard), arithmetic (standard), vocabulary (scaled), comprehension (scaled), verbal IQ (VIQ),

performance IQ (PIQ), and full scale IQ (FSIQ) (Dick et al., 2006; Dick et al., 2007). From the 262 multiplex pedigrees, we found 84 independent Caucasian spouse pairs with these eight achievements and intelligence variables (Table 1).

Data for Genetic Association Study

The GAW 14 data set from the COGA included 1,350 family members, genotyping data for 143 pedigrees at 11,555 SNPs from the Affymetrix Genechips 10K mapping array (Edenberg et al., 2005). Each SNP has two alleles 1 and 2. Genotypes for each SNP were coded as combinations of 11, 12, and 22. In order to reduce genetic heterogeneity, we selected 122 Caucasian pedigrees (292 nuclear families with 1,335 individuals) that have a majority of individuals who self-reported to be 'white' (both Hispanic and non-Hispanic). Among the 1,335 individuals, 670 are males and 665 are females with the age range from 7 to 93.

We combined IQ phenotype from the original CODA data with genotype data from GWA14. The number of individuals with an IQ score is 632. The mean IQ in participants in the sample was 100 for all scales, comparable to national general population norms. The means in the full sample were 98.796, 100.06, and 98.00 for full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ), respectively. The correlation between FSIQ and PIQ was 0.798, between FSIQ and VIQ 0.911, and between the VIQ and PIQ subscales 0.583. This pattern of correlations roughly

approximates the respective correlations reported in the WAIS-R standardization sample (WAIS-III Manual 2002, p.78), 0.92, 0.95, and 0.75 (Dick et al., 2007).

International Multi-Center ADHD Genetics Project (IMAGE) Dataset

IMAGE is a project with the goal to identify genes that are responsible for the genetic transmission of ADHD in children. The IMAGE dataset includes 674 families from eight countries (Belgium, England, Germany, Holland, Ireland, Israel, Spain, and Switzerland) ascertained from clinics for combined-type attention deficit hyperactivity disorder (ADHD) in an offspring with 958 parent-child trios with 2,835 participants at 600,000 SNPs. Both parents and one or more sibling were available for study, while no autism, epilepsy, IQ<70, brain disorder, or genetic disorder were known to mimic ADHD. We used part of this data to replicate our results for IQ. The number of individuals with an IQ score is 614. The mean IQ of participants in the sample was 100.36.

Statistical Analysis

Principal Component Analysis for Spousal Concordance

PROC UNIVARIATE was used to detect the normality of these continuous traits and outlier. Paired t-test was conducted to compare means of eight variables between husbands and wives. Then, spouse resemblance was assessed by using Pearson correlation for each variable. Finally, we used principal component analysis (PCA) to

generate PC scores as new variables to represent the achievement and intelligence level for husbands and wives and test if there is a relationship between them. All the statistical analyses were performed using SAS version 9.2.

Assessment of Hardy-Weinberg Equilibrium (HWE)

Departure from Hardy-Weinberg equilibrium (HWE) was tested for unaffected founders using PLINK software (Purcell et al., 2007).

Family-Based Association Test

Comparing to the case-control study designs, family-based association designs are particularly attractive because they test not only for linkage but also for association. Family-based association designs can avoid the potential confounding effects of population stratification by using the parents as controls for the case, who are their affected offspring thereby providing convenience in refining linkage findings in family samples (N.M. Laird & Lange, 2009). IQ is a quantitative trait that shows continuous variation and has a normal distribution in COGA and IMAGE data. FBAT can be adapted to the complex situation such as multivariate or longitudinal data sources with quantitative traits (Laird & Lange, 2006) and applied to nuclear families as well as extended pedigrees (Hoffmann & Lange, 2006).

FBAT v2.0.3 was used for testing the association between SNPs and FSIQ. The FBAT option “-o” uses an offset μ for the trait in the test construction, while the value of μ is chosen to minimize the variance of the test statistic (Lunetta, Faraone, Biederman, & Laird, 2000). For both COGA and IMAGE datasets we used both additive model and dominant model. Additive model is the default model in the FBAT software because it performs well (Horvath, Xu, & Laird, 2001) while dominant model and the recessive model will give the same p-value so we just chose dominant model to conduct our study.

Multiple Testing

For genome-wide statistical significance we used conservative per-test significance level of $\alpha = 5 \times 10^{-7}$ ("Wellcome Trust Case Control Consortium," 2007). In order to find more related specific loci we also used a moderate criterion of “suggestive association” with the cut-off $\alpha = 10^{-3}$. For COGA and IMAGE sample, we also used permutation procedure in PLINK to calculate the empirical p-values derived from 100,000 permutations (Purcell et al., 2007).

Haplotype Block and Haplotype Analysis

Pairwise linkage disequilibrium (LD) statistics (D' and r^2) were assessed for controls in IMAGE data using HAPLOVIEW (Barrett, Fry, Maller, & Daly, 2005). We

identified haplotype blocks within which SNPs have strong LD ($r^2 > 0.5$) each other for interesting candidate genes or regions. Then we chose several SNPs within blocks including the associated SNPs for further analyses. Haplotype analysis was performed using FBAT version 2.0.3.

CHAPTER 3

RESULTS

Spousal Concordance Analysis

Normality Test and Gender Difference

Based on the results of PROC UNIVARIATE all 16 tests (eight variables for husbands and eight variables for wives) showed that they were normally distributed ($p>0.05$) and no outlier was found. Because the traits were all normally distributed, we used paired t-test to test the gender difference. The paired t-test showed that husbands had lower scores for spelling than wives and higher scores for verbal IQ (Table1). The other variables did not differ between the male and female spouses.

Spousal Concordance Based on Simple Correlation Analysis

Pearson correlation (Table 1) showed that husbands and wives had significant positive correlation for reading ($r=0.60115$, $p<0.001$), spelling ($r= 0.58040$, $p<0.001$), arithmetic ($r=0.33865$, $p=0.0016$), vocabulary ($r=0.43152$, $p<0.001$), verbal IQ ($r=0.27463$, $p=0.0115$), and full scale IQ ($r=0.28090$, $p=0.0096$), while no significant correlations for comprehension ($r=0.16864$, $p=0.1252$) and performance IQ ($r=0.14197$, $p=0.1977$) were found.

Table 1.

Characteristics of Husbands and Wives, Correlation Analysis and Paired-t-test

Variable	N	husband-mean	wife-mean	corr-coef	Pc	T	Pt
<i>reading(standard)</i>	84	99.66667	99.2619	0.60115	<.0001	0.28	0.7784
<i>spelling(standard)</i>	84	93.79762	100.3571	0.5804	<.0001	-4.03	0.0001
<i>arithmetic(standard)</i>	84	101.4048	99.72619	0.33865	0.0016	0.95	0.3429
<i>vocabulary(scaled)</i>	84	10.14286	10.25	0.43152	<.0001	-0.33	0.7441
<i>comprehension(scaled)</i>	84	10.67857	9.92857	0.16864	0.1252	1.8	0.0749
<i>verbal IQ(scaled)</i>	84	105.1905	101.4524	0.27463	0.0115	2.05	0.044
<i>performance IQ(scaled)</i>	84	102.9286	102.2619	0.14197	0.1977	0.38	0.7015
<i>full scale IQ(scaled)</i>	84	104.381	101.8691	0.2809	0.0096	1.49	0.1404

N, number of individuals. Corr-coef, Correlation coefficient between spouses.

Pc = probability-value of correlation coefficient between spouses

T, t-statistics of paired-t test. Pt = probability-value of paired-t test between spouses.

Spousal Concordance Based on Correlation Analysis Using PC Scores

Because most of the variables were significantly correlated with each other, we used principal component analysis (PCA) to generate first and second principal components (PC1 and PC2), which are independent each other. Table 2 shows the principal component loadings for PC1 and PC2 in husband and wife groups. We found that there is a 86.37% of accumulative contribution ratio for male spouse by PC1 and PC2, while there is a 87.99% of accumulative contribution ratio for female spouse by PC1 and PC2, which means that PC1 and PC2 can explain 86.37% (PC1=73.61%, PC2=12.76%) of the achievement and intelligence in male spouses and 87.99% (PC1=72.86%, PC2=15.13%) of the achievement and intelligence in female spouses.

Table 2.

Principal Components Loadings for Husbands and Wives

Husband variables	PC1	PC2
<i>reading(standard)</i>	0.432491	-0.196181
<i>spelling(standard)</i>	0.488106	-0.442378
<i>arithmetic(standard)</i>	0.394913	-0.458365
<i>vocabulary(scaled)</i>	0.081872	0.068215
<i>comprehension(scaled)</i>	0.071645	0.108926
<i>verbal IQ(scaled)</i>	0.422952	0.489498
<i>performance IQ(scaled)</i>	0.271721	0.309194
<i>full scale IQ(scaled)</i>	0.392671	0.451651

Wife variables	PC1	PC2
<i>reading(standard)</i>	0.470387	-0.460293
<i>spelling(standard)</i>	0.480109	-0.442682
<i>arithmetic(standard)</i>	0.356364	0.068955
<i>vocabulary(scaled)</i>	0.07925	0.009375
<i>comprehension(scaled)</i>	0.059798	0.047292
<i>verbal IQ(scaled)</i>	0.396589	0.119958
<i>performance IQ(scaled)</i>	0.315482	0.658417
<i>full scale IQ(scaled)</i>	0.393151	0.370378

PC1 = First principal component. PC2 = Second principal component.

In the PC1 cases for husband variables PC1 has high loadings from spelling (0.488106), reading (0.432491), verbal IQ (0.422952), arithmetic (0.394913), and full scale IQ (0.392671) as the five major significant variables. For wife variables, PC1 has high loadings from reading (0.470387), spelling (0.480109), verbal IQ (0.396589), and full scale IQ (0.393151) as the four major significant variables. In the PC2 cases for husband variables PC2 has high loadings from spelling (-.442378), arithmetic (-.458365), verbal IQ (0.489498), and full scale IQ (0.451651) as the four major significant variables. For wife variables PC2 has high loadings from performance IQ

(0.658417), reading (-.460293), spelling (-.442682), and full scale IQ (0.370378) as the four major significant variables.

To test the assumption that there exists a relationship between spouses, correlation analysis was used to check spousal concordance in PC1 and PC2 values, respectively. Figure 1 showed strong positive relationship between husband and wife PC1 values. Correlation analysis further indicated there was a significant positive correlation between the PC1 values of paired husbands and wives ($r=0.515$, $p<0.0001$, $n=84$). However, for the PC2 the relationship between husbands and wives is weak ($r=0.1952$, $p=0.0752$).

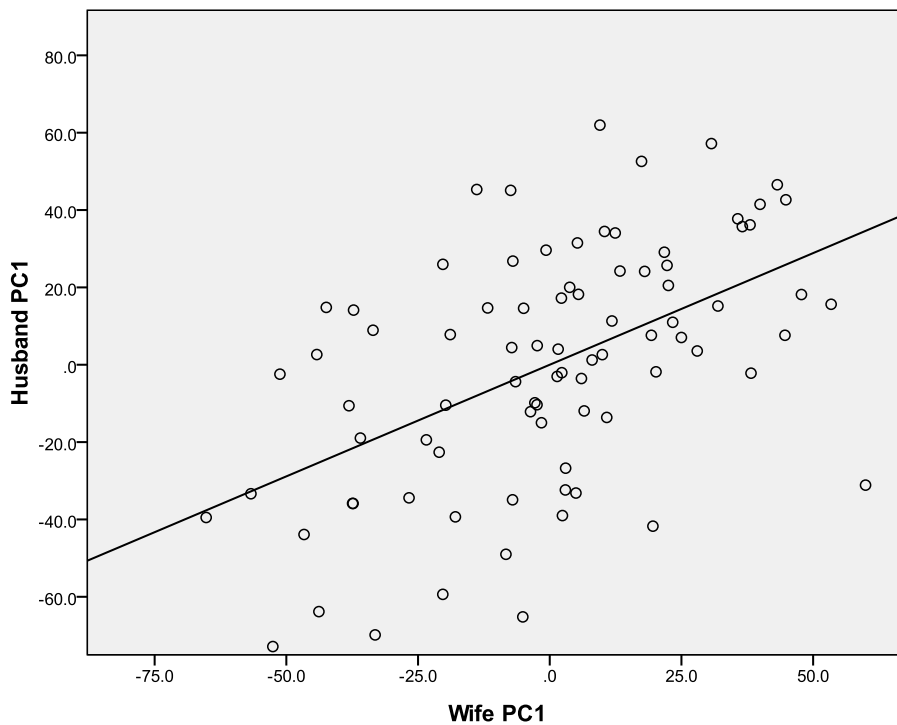


Figure 1. Relationship Between Husband and Wife PC1 Scores
Model regression line is plotted ($\text{Husband PC1} = 5.76 \times 10^{-15} + 0.57728 * \text{Wife PC1}$; $r = 0.515$, $p<0.0001$).

Genetic Association Study for IQ

Genome-Wide Association Analysis in COGA Sample

By testing HWE we removed the SNPs with $p < 10^{-4}$ and those with minor allele frequency (MAF) < 0.01 . Then, there were 10,740 SNPs left in the Affymetrix panel.

For COGA data there was no SNPs reached genome-wide significance ($p < 5 \times 10^{-7}$). There were 20 SNPs that had suggestive associations with FSIQ ($p < 10^{-3}$) (Table 3). A more comprehensive list for the SNPs with p values < 0.01 is presented in APPENDIX C.

In Table 3, nine SNPs are from additive model while 13 SNPs are from dominant model. The most significant associated SNP for additive model is rs1933836 on 6q22 ($p = 0.000417$), while for dominant model is rs0524129 on 4q15 ($p = 0.00000272$). Eight known genes are identified (CDCA7L, ZWINT, NTM, NR3C2, AP3B1, ELMO1, SLC5A8, and DGKK). Table 3 also revealed that most empirical p -values (EMP) are significant ($p < 0.05$).

Table 3.
Affymetrix Panel FBAT- $p < 10^{-3}$ Results and Related Test Results

SNP	Gene band	Position	Gene	Fam#	FBAT-Z	FBAT-p	HWE	MAF	EMP
Ad									
rs1933836	6q22.31	120961539		61	3.529	0.000417	0.3962	0.14	0.0007999
rs1316623	7p15.3	21960185	CDCA7L	100	3.361	0.000777	1	0.289	0.0022
rs1949741	10q21.1	57141137	ZWINT	89	3.682	0.000232	0.0798	0.476	0.00009999
rs1916503	10q21.1	57119488	ZWINT	93	3.499	0.000466	0.4089	0.467	0.0008999
rs1916506	10q21.1	57119180	ZWINT	59	3.442	0.000577	0.00005744	0.476	0.0002
rs0411280	11q25	130897898	NTM	96	3.366	0.000764	0.06248	0.319	0.0023
rs1954130	14q31.3	86035729		43	3.353	0.0008	0.5783	0.094	0.005899
rs2223246	20q13.11	41378557		86	3.291	0.000998	0.301	0.356	0.0023
rs1934189	Xp11.22	50165948	DGKK	67	3.293	0.00099	0.05806	0.335	-
Dom									
rs0524129	4p15.33	12716280		30	-4.691	0.00000272	0.4049	0.267	0.007299
rs2504857	6p24.1	12644328		24	3.86	0.000113	0.2632	0.266	0.07099
rs1074801	4q31.3	155795734		64	-3.825	0.000131	0.8354	0.448	0.0113
rs1933836	6q22.31	120961539		61	3.704	0.000212	0.3962	0.14	0.0007999
rs1848074	18q21.31	52295901		46	3.481	0.0005	0.8137	0.327	0.014
rs0353753	8q12.1	57839091		69	-3.469	0.00052	0.3434	0.218	0.005599
rs1113937	9q21.13	75226175		72	3.426	0.00061	0.8218	0.356	0.0156
rs3846329	4q31.23	149448788	NR3C2	77	3.399	0.000675	0.7714	0.235	0.007499
rs0326798	6p21.1	44649914		80	-3.38	0.000724	0.8355	0.442	0.009299
rs1363235	5q14.1	77456412	AP3B1	45	-3.372	0.000746	0.2101	0.288	0.19
rs1986568	7p14.1	37353349	ELMO1	65	3.327	0.000878	0.09416	0.449	0.0048
rs0724344	12q23.2	100088839	SLC5A8	82	3.327	0.00088	0.4095	0.215	0.02
rs1934189	Xp11.22	50165948	DGKK	60	3.696	0.000219	0.05806	0.335	-

Fam#: number of informative families.

Ad: additive model.

Dom: dominant model.

Position is based on NCBI Genome Build 36.3.

MAF: minor allele frequency of the SNP.

EMP: p-value using permutation test.

HWE: p-value using Hardy-Weinberg Equilibrium Test

FBAT: family based association test

Replication Study in IMAGE Sample

Based on 22 SNPs with $p < 10^{-3}$ in the COGA sample, we selected 2,022 SNPs from IMAGE dataset in order to replicate our results for IQ. For the SNPs in COGA data within known gene we chose all the SNPs within each gene in IMAGE data, while for each SNP in COGA data that are not located in known gene, we chose all SNPs between two flanking genes in the IMAGE dataset. For our output from IMAGE dataset there was no SNPs reached genome-wide significance ($p < 5 \times 10^{-7}$), but there were 13 SNPs that had suggestive associations with IQ ($p < 10^{-3}$) (Table 4). A more comprehensive list for the SNPs with p values < 0.01 is presented in Supplementary APPENDIX D. In Table 4 seven SNPs are from the additive model, while nine SNPs are from the dominant model. The most significant associated SNP for additive model is rs9367203 on 6p21 ($p=0.000079$), while for the dominant model it is rs1546587 on 11q25 ($p=0.000147$). Two known genes are replicated (NTM and NR3C2). Table 4 also revealed that all three SNPs in NR3C2 have significant empirical p -values ($p < 0.01$), while two SNPs (rs12576852, rs4937665) in NTM repeated in additive and dominant models have significant empirical p -values ($p < 0.01$).

Table 4.
IMAGE FBAT- $p < 10^{-3}$ Results and Related Test Results

SNP	Gene band	Position	Gene	Fam#	FBAT-Z	FBAT-p	HWE	MAF	EMP
Ad									
rs9367203	6p21.1	44611945		342	2.61	0.000079	1	0.274	0.00005
rs1546587	11q25	130861460	NTM	129	-3.796	0.000341	0.3115	0.058	0.3134
rs12576852	11q25	130847995	NTM	121	-3.631	0.000599	0.1731	0.054	0.00043
rs13118022	4q31.23	149565037	NR3C2	339	-2.614	0.000659	0.2302	0.389	0.00066
rs4937665	11q25	131239994	NTM	253	-3.48	0.000697	0.7356	0.151	0.00242
rs1994624	4q31.23	149550372	NR3C2	312	-2.603	0.000911	0.00000029	0.404	0.00069
rs1036433	11q25	131261645	NTM	310	1.856	0.000927	0.391	0.496	0.06493
Dom									
rs1546587	11q25	130861460	NTM	129	-3.582	0.000147	0.3115	0.058	0.3134
rs4937672	11q25	131499942	NTM	465	-2.933	0.000275	0.003327	0.426	0.7924
rs12576852	11q25	130847995	NTM	121	-3.432	0.000283	0.1731	0.054	0.00043
rs13137823	4q31.23	149242356	NR3C2	328	2.982	0.000424	0.3807	0.207	0.00211
rs4937665	11q25	131239994	NTM	260	-3.391	0.000502	0.7356	0.151	0.00242
rs7943322	11q25	131532819	NTM	448	-2.706	0.000522	0.3096	0.393	0.144
rs7933020	11q25	130843833	NTM	136	-3.129	0.000627	0.08227	0.061	0.8076
rs7943905	11q25	131270348	NTM	262	-3.108	0.000702	1	0.144	0.8175
rs4937664	11q25	131239876	NTM	263	-3.167	0.000995	0.7376	0.152	0.3955

Fam#: number of informative families.

Ad: additive model.

Dom: dominant model.

Position is based on NCBI Genome Build 36.3.

MAF: minor allele frequency of the SNP.

EMP: p-value using permutation test.

HWE: p-value using Hardy-Weinberg Equilibrium Test

FBAT: family based association test

Haplotype Block and Haplotype Analysis

Using HAPLOVIEW, we identified haplotype blocks for the above two genes (NR3C2 and NTM). LD structures are illustrated in Figures 2 and 3. Two-SNP haplotype analyses for NR3C2 gene (Table 5) revealed that the C-T haplotype inferred from rs16998733 and rs13118022 ($D'=0.99$ and $r^2=0.38$) was associated with IQ ($p=0.000455$) and C-G haplotype from rs4835478 and rs13137823 ($D'=0.99$ and $r^2=0.58$) associated with IQ ($p=0.000457$). For NTM G-T haplotype inferred from rs1546587 and rs4937665 ($D'=0.97$ and $r^2=0.75$) was mostly associated with IQ ($p=0.00000224$) in the additive model while T-G from rs4937672 and rs7480231 ($D'=0.91$ and $r^2=0.50$) mostly associated with IQ in the dominant model ($p=0.000062$). These results showed stronger associations than single-marker analyses.

Table 5.
Haplotype Table for NR3C2 and NTM ($p < 10^{-3}$)

Gene	Model	SNPs	Haplotyp	Hapfreq	N	P	
NR3C2	Ad	rs907620 - rs16998733	T-C	0.607	422	0.00021	
		rs16998733 - rs13118022	C-T	0.608	389	0.000455	
		rs907620 - rs16998733 - rs13118022	T-C-T	0.605	351	0.000629	
	Dom	rs4835478 - rs13137823	C-G	0.204	278	0.000457	
		rs4835478 - rs13142954	T-G	0.688	153	0.000969	
NTM	Ad	rs1546587 - rs4937665	G-T	0.799	321	0.00000224	
		rs12576852 - rs4937665	C-T	0.803	315	0.0000039	
		rs1546587 - rs4937664	G-G	0.799	324	0.00000602	
		rs1546587 - rs7943905	G-G	0.804	323	0.00000609	
		rs12576852 - rs4937664	C-G	0.803	318	0.00001	
		rs12576852 - rs7943905	C-G	0.808	316	0.00001	
		rs1546587 - rs656644	G-T	0.752	346	0.00009	
		rs12576852 - rs656644	C-T	0.755	356	0.000116	
		rs12576852 - rs1546587	C-G	0.94	131	0.000336	
		rs12576852 - rs1036433	C-C	0.474	454	0.000412	
		rs4937665 - rs7943905	T-G	0.844	255	0.000514	
		rs4937665 - rs1036433	C-T	0.137	246	0.000586	
		rs4937664 - rs1036433	C-T	0.138	247	0.000599	
		rs4937664 - rs4937665	C-C	0.147	244	0.000631	
		rs4937664 - rs1036433	G-C	0.483	442	0.000914	
		Dom	rs4937672 - rs7480231	T-G	0.369	321	0.000062
			rs4937665 - rs1036433	C-T	0.137	239	0.000403
	rs4937664 - rs1036433		C-T	0.138	240	0.000417	

Hapfreq: frequency of the haplotype.

N: number of informative families.

Ad: additive model

Dom: dominant model

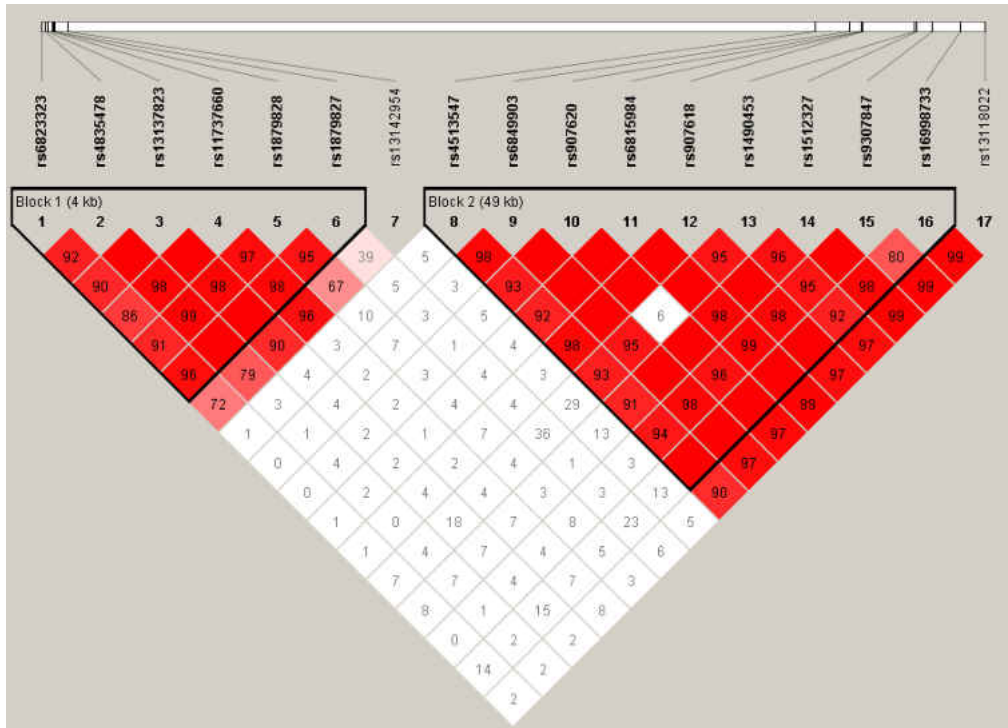


Figure 2. LD Structures for NR3C2

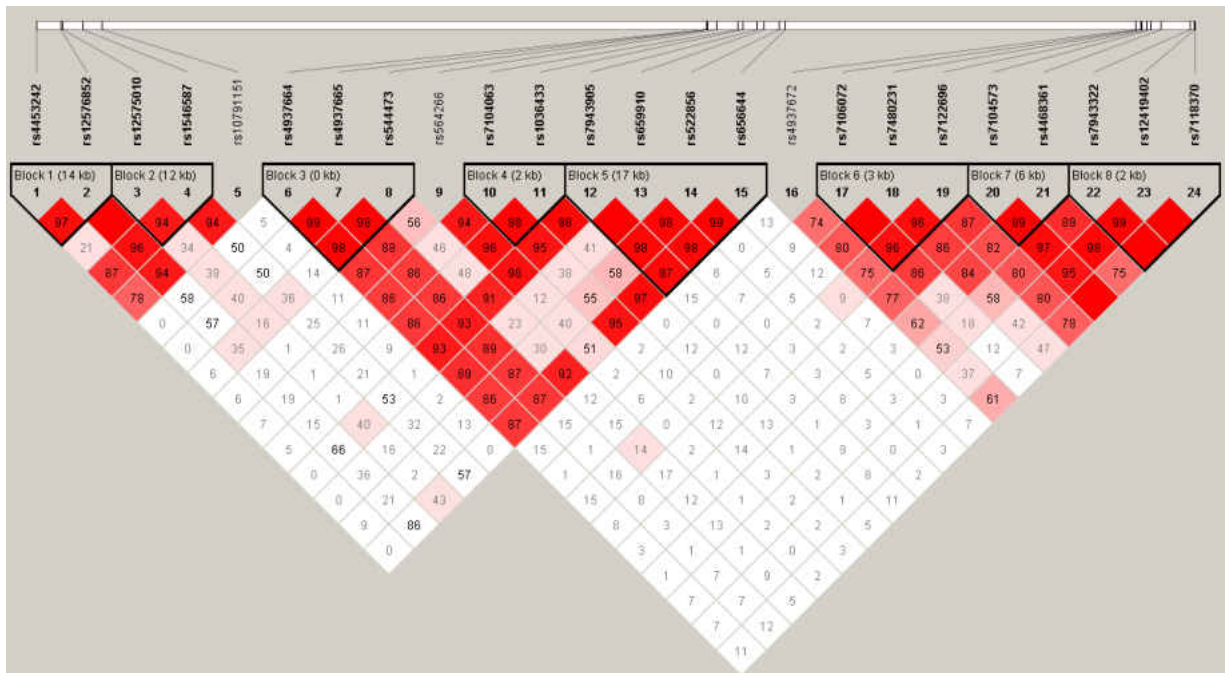


Figure 3. LD Structures for NTM

CHAPTER 4

DISCUSSION

The first part of this study provides evidence of significant spousal concordance in academic achievements and intelligence measured by WAIS-R. Simple correlation analyses showed that six (reading, spelling, arithmetic, vocabulary, verbal IQ, and full scale IQ) of eight traits in academic achievements and intelligence showed evidence of spousal correlation ($p < 0.05$), of them three (reading, spelling, and vocabulary) showed highly significant correlation ($p < 0.0001$), while correlation analysis based on the first principal component score (PC1 value) of eight traits further revealed highly significant spousal resemblance (correlation coefficient = 0.515, $p < 0.0001$).

Academic achievements and intelligence, which considered as an important hereditary factor, have been commonly observed and studied in genetics. Assortative mating by achievement or intelligence traits between spouses has been received much less attention despite its potential importance as an indicator of mutual mate choice (Berninger, Nielsen, Abbott, Wijsman, & Raskind, 2008). It can affect the genetic structure of a population by increasing genetic variance and also homozygosity, although only when few loci are involved. It has been reported that all observed assortative mating in IQ and personal traits might well be due to initial assortment (Mascie-Taylor, 1989). Some indirect evidence is presented that assortative mating may codetermine patterns of affectedness in dyslexia families with regarding to reading and spelling (Wolff & Melngailis, 1994). Another study that measures verbal

and nonverbal intelligence shows that couples are similar in almost all the measured traits even after controlling for age and education level, and there is moderate similarity in education and verbal intelligence possibly due to assortative mating (Watson et al., 2004). Wainwright et al. (2005) used the univariate analysis to indicate a positive phenotypic assortative mating, and the phenotypic and genetic correlations between the Queensland Core Skills Test (QCST) and Verbal IQ (VIQ) were significantly stronger than the phenotypic and genetic correlations between the QCST and Performance IQ (PIQ).

While in the second part of this study, we reported the first GWA study that used family-based association test to approach the relationship between SNPs and IQ. We have identified several SNPs associated with IQ at an allelic p-value less than 0.001 in the GAW14 dataset from COGA. Especially, two genes NTM and NR3C2 that were found in COGA and also well replicated in the IMAGE data attracted our attention.

NTM (neurotrimin or HNT) on 11q25 encodes a member of IgLON (LAMP, OBCAM, Ntm) family of immunoglobulin (Ig) domain-containing glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecules (Sellar et al., 2003). Struyk et al. (1995) cloned the rat neurotrimin gene and found that northern blot analysis of several rat tissues detected expression only in the brain. In situ hybridization of developing rat brain showed neurotrimin expressed at high levels in several developing projection systems. Wilson et al. (1996) reported that molecules

within GP55 family that are related to OBCAM, neurotrimin, LAMP, and CEPU-1 are capable of acting as cell adhesion molecules and inhibitors of neurite outgrowth for chicks. NTM is also largely expressed in a complementary pattern to that of LAMP in the nervous system, with co-expression at a few sites. It is expressed at high levels in sensory-motor cortex and of particular note is transiently expressed in neurons of cortical barrel fields and corresponding thalamic “barreloids.” Binding of a recombinant, soluble form of NTM to CHO cells expressing either NTM or LAMP demonstrates that NTM and LAMP interact both homophilically and heterophilically (Gil et al., 2002). NTM was identified as a positional candidate tumour suppressor gene involved in neuroblastoma. NTM was also found putative functions in neuronal development, axon growth, and synaptic function while showing highly restricted brain expression patterns in the adult mouse brain (Lein et al., 2007) as well as in brain regions where morphological alterations in post-mortem brains of autism patients have been identified (e.g. cerebral cortex, cerebellum, and hippocampus). In another study NTM was identified in the neonatal brain-raft proteome comprises the cell adhesion or recognition molecules for cell-cell communication (Yu et al., 2007). Liu et al. (2007) first reported for chromosome 11q24-25 that there was suggestive evidence of linkage (HLOD=3.29 at marker D11S1320) in a Dutch population study that used genome screen of 103 patients with late-onset Alzheimer disease (AD) that is the most common cause of dementia with 402 microsatellite markers.

NR3C2 on 4q31 encodes the mineralocorticoid receptor (or MR, MLR, MCR). It

is called aldosterone receptor and officially been labeled as nuclear receptor subfamily 3, group C, member 2. NR3C2 mediates aldosterone actions on salt and water balance within restricted target cells. The protein functions as a ligand-dependent transcription factor that binds to mineralocorticoid response elements in order to transactivate target genes. Plomin et al. (Plomin & Craig, 2001) first observed chromosome 4 may include genes responsible for the substantial heritability of general cognitive ability. Defects in this gene are also associated with early onset hypertension with severe exacerbation in pregnancy (Geller et al., 2006). Besides, common NR3C2 polymorphisms have been described and seem to be mostly related to modulation of stress responsiveness. Flores et al. (2003) reported that NR3C2 and GR are regulated by Corticotropin-releasing hormone (CRH) and vasopressin (AVP) that participate in the endocrine, autonomic, immunological, and behavioral response to stress and this gene and the function of CRH and AVP could be relevant to stress-related disorder like major depression. It has been reported that a common polymorphism in MR modulates stress responsiveness (DeRijk et al., 2006).

Besides NTM and NR3C2 we also found significant SNPs that are located within known gene as follows: CCDC30, CDCA7L, ZWINT, AP3B1, ELMO1, SLC5A8, and DGKK that are from chromosome 1p34, 7p15, 10q21, 5q14, 7p14, 12q23, and Xp11.2. For COGA data the most significant SNP from Affymetrix by additive model is rs1933836 ($p=0.000417$) on 6q22 with no known gene while by dominate model is rs0524129 ($p=0.00000272$) on 4p15 with no known gene. Enoch et al. (2008) did a

dense whole genome linkage scan using 3878 unlinked SNPs in a large pedigree derived from a population isolate sample of 328 Plains American Indians and found linkage peaks for EEG power in all three frequency bands converged on chromosome 5q13-14 with genome-wide significant LOD scores of 3.5 (empirical $p < 0.0001$) for alpha and beta power and identified CRH-BP as a significant gene, which suggested a likely role for CRH-BP in stress-related alcoholism and highlight the use of the resting EEG as an intermediate phenotype for arousal-related behaviors such as anxiety and addiction. Cardoso et al. (2009) identified a new syndrome featuring bilateral periventricular heterotopia (PH), mental retardation, and epilepsy mapping to chromosome 5q14.3-q15. PH is an etiologically heterogeneous disorder characterized by nodules of neurons ectopically placed along the lateral ventricles, while most affected patients have seizures and their cognitive level varies from normal to severely impaired. In our study we also identified 5q14.1 as significant gene band that associate with intelligence. Levy et al. (2010) reported that SLC2A1 on chromosome 1p34 to be associated with cognition and intelligence by conducting the study in patients who had severe epilepsy, significant cognitive and motor delay, ataxia, and microcephaly. In our study CCDC30 on Chromosome 1p34 is identified to have significant associations that further confirm 1p34 is important in function of cognition and intelligence.

Among those significant identified genes, we found ZWINT on chromosome 10q21 was identified three times in Affymetrix by additive model with SNPs

rs1949741, rs1916503, rs1916506 (p-value=0.000232, 0.000466, 0.000577). A similar study reported that Fas gene located on chromosome 10q24.1 has been tested to have association with the pathogenesis of Alzheimer's disease (AD) by Feuk et al. (2004). However, later, by doing the case-control association study Rosenmann, Hanna, et al. found no association between this locus and AD. Later, Johansson (2005) reported that CDC2 gene located on chromosome 10q21.1 close to the marker D10S1225 linked to AD. This gene band is also replicated by our study.

On X chromosome it is quite interesting that both additive and dominant (recessive) model pointed to a known gene DGKK rs1934189 (p=0.000219) by Affymetrix) on chromosome Xp11.2. The first study about chromosome X was conducted in 19 cases (12 cases from three different families and 7 nonfamilial cases). Cognitive impairment, psychiatric features, and organic personality change occurred in over half the cases, and more than one third had seizures. Hardie et al. (1991) pointed out that there may be a locus for this disorder on the short arm of the X chromosome associated with intelligence. Later, Petit (1996) also reported X chromosome to be associated with Autism, mental retardation, and behavior disturbances by doing a case-control study. Billuart et al. (1998) reported Chromosome Xq12 for association between cognitive impairment and a defect in a signalling pathway that depends on a Ras-like GTPase. In 2010, Chromosome Xp11.2 is identified as significant gene band for mental retardation (MR) which is characterized by cognitive impairment with an IQ <70. Approximately 30% male

excess suggests that mutations carried on Xp11.2 are disproportionately represented (Rujirabanjerd et al., 2010). From those studies and our significant results of Chromosome Xp11.2, we concluded that this gene band is relevant to the function of intelligence and cognition.

Besides those known genes and the most significant SNPs, we also reported several significant SNPs and Gene band where there are no known genes around those positions. For Affymetrix rs1954130 ($p=0.0008$) on chromosome 14q31, rs2223246 ($p=0.000998$) on chromosome 20q13, rs2504857 ($p=0.000113$) on chromosome 6p24, rs1074801 ($p=0.000131$) on chromosome 4q31, rs0326798 ($p=0.000724$) on chromosome 6p21, rs1848074 ($p=0.0005$) on chromosome 18q21, rs0353753 ($p=0.00052$) on chromosome 8q12, rs1113937 ($p=0.00061$) on chromosome 9q21. Most studies found discussed association of chromosome 6 with intelligence and cognition disease. Pulliam et al. (2003) identified locus at chromosome 6p21 that contains the hereditary hemochromatosis gene HFE is associated with neurodegeneration and oxidative stress in Alzheimer's disease. In another study chromosome 6p21 and MICB are identified to have associations with human herpes virus seropositivity and schizophrenia risk (Shirts et al., 2007). Later, HLA-A on chromosome 6p21 has been identified as possibly being involved in the pathogenesis of AD (Ma et al., 2008). Francks et al. (2004) used association analysis in 223 siblings from the United Kingdom and United States and identified several underlying quantitative trait loci (QTLs) on chromosome 6p22.2 that influence developmental

dyslexia (reading disability). Hallmayer et al. (2005) studied genome scan data and found linkage association to chromosome 6p24 with schizophrenia characterized by pervasive cognitive deficit. Chandler et al. (2010) tested and identified that Neuritin 1 (NRN1), an activity-regulated gene with multiple roles in neurodevelopment and synaptic plasticity located within the 6p24-p25 interval on chromosome 6, to be linked to subtype of schizophrenia (SZ) characterized by pervasive cognitive deficit (CD) by case-control study. In our study we also found several candidate gene band on chromosome 6 including 6p21, 6q22, and 6p24 that suggested chromosome 6 and those gene bands are important for further study for intelligence and cognition. The functions for these genes on IQ need further study.

This study has several strengths. First, we examined eight traits in academic achievements and intelligence and found six of them showed significant spousal correlations. Second, we used PC score to test the relationship for academic achievements and intelligence between spouses. Principal component analysis (PCA) is a useful statistical technique that has found application in fields such as face recognition and image compression and is a common technique for finding patterns in data of high dimension (L. I. Smith, 2002). However, instead of using PCA to study the achievement and intelligence, other methods like univariate analysis has been used to indicate a positive phenotypic assortative mating (Wainwright et al., 2005) or ANCOVA for studying intelligence in childhood (Nolan et al., 2003). To our knowledge, our analysis using PCA represents the first attempt to assess spousal

concordance in achievements and intelligence. It has been suggested that spouse similarity was found for temperament, personality, and psychiatric symptomatology that were largely independent highlights the necessity of simultaneous assessment of psychiatric domains in the search for the underlying characteristics conditioning nonrandom mate selection (Dubuis-Stadelmann, et al., 2001). Till now, there are no research that uses PCA to find the spousal concordance in achievements and intelligence. Comparing with previous results (single variable correlation analysis), our results based on PCA are novel.

For the GWA study, first, our results provided support to the findings of Dick et al. (2006, 2007) who conducted the linkage analysis for intelligence on COGA dataset. We discovered that associations of SNPs including significant results on chromosome 1p34, 6q14, 6p21, 6q22, 6p24, 9q21, and 14q31, which had covered most reported chromosome from Dick's linkage analysis. Second, we performed a family-based, GWA analysis of COGA dataset, and we also used IMAGE project for replication. We focused on the identification of novel genetic variants not only using a more powerful family based method but also dealing with X-chromosome SNPs. In addition, we just used 122 Caucasian pedigrees (292 nuclear families) that have a majority of individuals who self reported to be "white" to reduce the genetic heterogeneity. In our genetic study, we found neither significant genome-wide association ($p < 5 \times 10^{-7}$) nor strong genome-wide association ($p < 10^{-5}$) of SNPs with intelligence, probably due to a small number of SNPs we used (11120 SNPs), thus limiting the coverage of the

genome. However, we have found several SNPs that had suggestive associations with IQ ($p < 10^{-3}$). In those significant SNPs, we found two novel, suggestive genes, NTM and NR3C2 that were not reported by previous studies. These two candidate genes were further proved by replicating family-based analysis using part of IMAGE sample.

The findings of this study also have several limitations. The sample size is not large and the sample analyzed was not a random sample collected with the primary goal of analyzing IQ (Dick, et al., 2006). The COGA data were a sample of multiplex alcoholic families ascertained through alcoholic families ascertained through alcohol dependent probands in treatment centers. However, it's not largely influenced by the ascertainment of the sample because the mean and standard deviation for IQ among the COGA sample and the sibling correlation for the IQ measures do not deviate considerably from published reports on unselected samples. Also, the means and SD for each variable in the subset in this paper are quite similar compared to the means and SD for the COGA data (Dick et al., 2006). Second, limitation is due to time restrictions. Not all subtests of the WAIS were administered. Thus, five verbal subtests (information, similarities, vocabulary, comprehension, and digit span) and four performance subtests (picture completion, block design, object assembly, and digit symbol) are included in the study. Further, many subjects could not be tested due to the time requirements for other parts of the COGA assessment battery (Dick et al., 2006). Third, for GWA study, instead of reaching significant genome-wide association

($p < 5 \times 10^{-7}$), our study only reached suggestive associations with IQ ($p < 10^{-3}$). Thus, replication study is needed in independent samples to further confirm our results.

CHAPTER 5

CONCLUSION

In conclusion the study confirms and extends previous studies relating to the spousal concordance in academic achievements and intelligence between spouses. Regardless of the causes, the presence of spousal concordance on achievement and intelligence aspects has important implications for genetic studies in future research. An analysis of assortative mating for academic achievements and intelligence may help us to understand the complex genetic and environmental contributions to academic achievements and intelligence.

This study also identified several IQ associated genetic variants by using FBAT for COGA dataset. Especially two genes NTM and NR3C2 that were well replicated by IMAGE dataset attracted our attention. To our knowledge this is the first genome wide screen that showed significant association to chromosome 11q25 and 4q31 markers. For these two regions our analysis identified the NTM on 11q25 has been shown in previous study to be candidate tumour suppressor gene involved in neuroblastoma, late-onset Alzheimer disease (AD), and relevant to autism while NR3C2 on 4q31 has been shown to associate with major depression and both type 1 and type 2 diabetes mellitus in humans. These finding may serve as a resource for replication in other populations and provide a foundation for future investigations. Future studies are warranted to verify the strength of association between the genetic factors and IQ and gene-environment interaction on the development of the study of

intelligence.

REFERENCES

- al-Kandari, Y., Crews, D. E., & Poirier, F. E. (2002). Consanguinity and spousal concordance in Kuwait. *Coll Antropol*, *26 Suppl*, 1-13.
- Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics*, *21*, 263-265. doi: 10.1093/bioinformatics/bth457 bth457 [pii]
- Batty, G. D., Deary, I. J., Benzeval, M., & Der, G. (2010). Does IQ predict cardiovascular disease mortality as strongly as established risk factors? Comparison of effect estimates using the West of Scotland Twenty-07 cohort study. *European Journal of Cardiovascular Prevention & Rehabilitation*, *17*(1), 24-27. doi: 10.1097/HJR.0b013e328321311b
- Berninger, V. W., Nielsen, K. H., Abbott, R. D., Wijsman, E., & Raskind, W. (2008). Gender differences in severity of writing and reading disabilities. *J Sch Psychol*, *46*(2), 151-172. doi: S0022-4405(07)00022-2 [pii] 10.1016/j.jsp.2007.02.007
- Billuart, P., Bienvenu, T., Ronce, N., des Portes, V., Vinet, M. C., Zemni, R., et al. (1998). Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. *Nature*, *392*(6679), 923-926. doi: 10.1038/31940
- Bloch, K. V., Klein, C. H., de Souza e Silva, N. A., Nogueira Ada, R., & Salis, L. H. (2003). Socioeconomic aspects of spousal concordance for hypertension, obesity, and smoking in a community of Rio de Janeiro, Brazil. *Arq Bras Cardiol*, *80*(2), 179-186, 171-178. doi: S0066-782X2003000200006 [pii]
- Bouchard, T. J., Jr., & McGue, M. (1981). Familial studies of intelligence: A review. *Science*, *212*(4498), 1055-1059.

- Browning, B. L., & Browning, S. R. (2008). Haplotypic analysis of Wellcome Trust Case Control Consortium data. *Hum Genet*, *123*, 273-280. doi: 10.1007/s00439-008-0472-1
- Cardoso, C., Boys, A., Parrini, E., Mignon-Ravix, C., McMahon, J. M., Khantane, S., et al. (2009). Periventricular heterotopia, mental retardation, and epilepsy associated with 5q14.3-q15 deletion. *Neurology*, *72*, 784-792. doi: 01.wnl.0000336339.08878.2d [pii] 10.1212/01.wnl.0000336339.08878.2d
- Chandler, D., Dragovic, M., Cooper, M., Badcock, J. C., Mullin, B. H., Faulkner, D., et al. (2010). Impact of Neuritin 1 (NRN1) polymorphisms on fluid intelligence in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*, *153B*, 428-437. doi: 10.1002/ajmg.b.30996
- Comings, D. E., Wu, S., Rostamkhani, M., McGue, M., Lacono, W. G., Cheng, L. S., & MacMurray, J. P. (2003). Role of the cholinergic muscarinic 2 receptor (CHRM2) gene in cognition. *Mol Psychiatry*, *8*(1), 10-11. doi: 10.1038/sj.mp.4001095 4001095 [pii]
- DeRijk, R. H., Wust, S., Meijer, O. C., Zennaro, M. C., Federenko, I. S., Hellhammer, D. H., et al. (2006). A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. *J Clin Endocrinol Metab*, *91*(12), 5083-5089. doi: jc.2006-0915 [pii] 10.1210/jc.2006-0915
- Devlin, B., Daniels, M., & Roeder, K. (1997). The heritability of IQ. *Nature*, *388*, 468-471. doi: 10.1038/41319
- Dick, D. M., Aliev, F., Bierut, L., Goate, A., Rice, J., Hinrichs, A., et al. (2006). Linkage analyses of IQ in the collaborative study on the genetics of alcoholism (COGA) sample. *Behav Genet*, *36*(1), 77-86. doi: 10.1007/s10519-005-9009-8

- Dick, D. M., Aliev, F., Kramer, J., Wang, J. C., Hinrichs, A., Bertelsen, S., et al. (2007). Association of CHRM2 with IQ: Converging evidence for a gene influencing intelligence. *Behav Genet*, *37*, 265-272. doi: 10.1007/s10519-006-9131-2
- Dubuis-Stadelmann, E., Fenton, B. T., Ferrero, F., & Preisig, M. (2001). Spouse similarity for temperament, personality and psychiatric symptomatology. *Personality and Individual Differences*, *30*, 1095-1112. doi: 10.1016/s0191-8869(00)00092-1
- Edenberg, H. J., Strother, W. N., McClintick, J. N., Tian, H., Stephens, M., Jerome, R. E., et al. (2005). Gene expression in the hippocampus of inbred alcohol-preferring and -nonpreferring rats. *Genes Brain Behav*, *4*(1), 20-30. doi: GBB091 [pii] 10.1111/j.1601-183X.2004.00091.x
- Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*, *98*, 6917-6922. doi: 10.1073/pnas.111134598 111134598 [pii]
- Enoch, M. A., Shen, P. H., Ducci, F., Yuan, Q., Liu, J., White, K. V., et al. (2008). Common genetic origins for EEG, alcoholism and anxiety: The role of CRH-BP. *PLoS One*, *3*, e3620. doi: 10.1371/journal.pone.0003620
- Farley, F. H., & Davis, S. A. (1977). Arousal, personality, and assortative mating in marriage. *J Sex Marital Ther*, *3*, 122-127.
- Farley, F. H., & Mueller, C. B. (1978). Arousal, personality, and assortative mating in marriage: Generalizability and cross-cultural factors. *J Sex Marital Ther*, *4*(1), 50-53.
- Feng, D., & Baker, L. (1994). Spouse similarity in attitudes, personality, and

- psychological well-being. *Behav Genet*, 24, 357-364.
- Flint, J. (1999). The genetic basis of cognition. *Brain*, 122 (Pt 11), 2015-2032.
- Fountoulakis, K. N. (2010). The emerging modern face of mood disorders: A didactic editorial with a detailed presentation of data and definitions. *Ann Gen Psychiatry*, 9, 14. doi: 1744-859X-9-14 [pii] 10.1186/1744-859X-9-14
- Francks, C., Paracchini, S., Smith, S. D., Richardson, A. J., Scerri, T. S., Cardon, L. R., et al. (2004). A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United Kingdom and from the United States. *Am J Hum Genet*, 75, 1046-1058. doi: S0002-9297(07)60072-X [pii] 10.1086/426404
- Gao, M. C., Bellugi, U., Dai, L., Mills, D. L., Sobel, E. M., Lange, K., & Korenberg, J. R. (2010). Intelligence in Williams Syndrome is related to STX1A, which encodes a component of the presynaptic SNARE complex. *PLoS One*, 5, e10292. doi: 10.1371/journal.pone.0010292
- Geller, D. S., Zhang, J., Zennaro, M. C., Vallo-Boado, A., Rodriguez-Soriano, J., Furu, L., et al. (2006). Autosomal dominant pseudohypoaldosteronism type 1: mechanisms, evidence for neonatal lethality, and phenotypic expression in adults. *J Am Soc Nephrol*, 17, 1429-1436. doi: ASN.2005111188 [pii]10.1681/ASN.2005111188
- Gil, O. D., Zhang, L., Chen, S., Ren, Y. Q., Pimenta, A., Zanazzi, G., et al. (2002). Complementary expression and heterophilic interactions between IgLON family members neurotrimin and LAMP. *J Neurobiol*, 51, 190-204. doi: 10.1002/neu.10050
- Ginsburg, E., Livshits, G., Yakovenko, K., & Kobylansky, E. (1998). Major gene control of human body height, weight and BMI in five ethnically different

- populations. *Ann Hum Genet*, 62(Pt 4), 307-322. doi:
10.1046/j.1469-1809.1998.6240307.x
- Grant, J. D., Heath, A. C., Bucholz, K. K., Madden, P. A., Agrawal, A., Statham, D. J., & Martin, N. G. (2007). Spousal concordance for alcohol dependence: Evidence for assortative mating or spousal interaction effects? *Alcohol Clin Exp Res*, 31, 717-728. doi: ACER356 [pii] 10.1111/j.1530-0277.2007.00356.x
- Guessous, I., Gwinn, M., & Khoury, M. J. (2009). Genome-wide association studies in pharmacogenomics: Untapped potential for translation. *Genome Med*, 1(4), 46. doi: gm46 [pii] 10.1186/gm46
- Hallmayer, J. F., Kalaydjieva, L., Badcock, J., Dragovic, M., Howell, S., Michie, P. T., et al. (2005). Genetic evidence for a distinct subtype of schizophrenia characterized by pervasive cognitive deficit. *Am J Hum Genet*, 77, 468-476. doi: S0002-9297(07)63026-2 [pii] 10.1086/432816
- Halpin, B. (2003). Educational homogamy in Ireland and Britain: Trends and patterns. *Br J Sociol*, 54, 473-496. doi: 10.1080/0007131032000143546
EARY4E6Q60RP0U7Q [pii]
- Hardie, R. J., Pullon, H. W., Harding, A. E., Owen, J. S., Pires, M., Daniels, G. L., et al. (1991). Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. *Brain*, 114 (Pt 1A), 13-49.
- Heun, R., & Maier, W. (1993). Morbid risks for major disorders and frequencies of personality disorders among spouses of psychiatric inpatients and controls. *Compr Psychiatry*, 34, 137-143. doi: 0010-440X(93)90059-D [pii]
- Hoffmann, T., & Lange, C. (2006). P2BAT: A massive parallel implementation of PBAT for genome-wide association studies in R. *Bioinformatics*, 22, 3103-3105. doi: btl507 [pii] 10.1093/bioinformatics/btl507

- Horvath, S., Xu, X., & Laird, N. M. (2001). The family based association test method: strategies for studying general genotype--phenotype associations. *Eur J Hum Genet*, 9, 301-306. doi: 10.1038/sj.ejhg.5200625
- Hugin-Flores, M. E., Steimer, T., Schulz, P., Vallotton, M. B., & Aubert, M. L. (2003). Chronic corticotropin-releasing hormone and vasopressin regulate corticosteroid receptors in rat hippocampus and anterior pituitary. *Brain Res*, 976, 159-170. doi: S000689930302585X [pii]
- Hur, Y. M. (2003). Assortive mating for personaltiy traits, educational level, religious affiliation, height, weight, adn body mass index in parents of Korean twin sample. *Twin Res*, 6, 467-470.
- Johansson, A., Zetterberg, H., Hampel, H., Buerger, K., Prince, J. A., Minthon, L., et al. (2005). Genetic association of CDC2 with cerebrospinal fluid tau in Alzheimer's disease. *Dement Geriatr Cogn Disord*, 20(6), 367-374. doi: DEM2005020006367 [pii] 10.1159/000088634
- Laird, N. M., & Lange, C. (2006). Family-based designs in the age of large-scale gene-association studies. *Nat Rev Genet*, 7, 385-394. doi: nrg1839 [pii]10.1038/nrg1839
- Laird, N. M., & Lange, C. (2009). The role of family-based designs in genome-wide association studies. *Statist. Sci*, 24, 388-397.
- Lein, E. S., Hawrylycz, M. J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., et al. (2007). Genome-wide atlas of gene expression in the adult mouse brain. *Nature*, 445, 168-176. doi: nature05453 [pii] 10.1038/nature05453
- Levy, B., Wang, D., Ullner, P. M., Engelstad, K., Yang, H., Nahum, O., et al. (2010). Uncovering microdeletions in patients with severe Glut-1 deficiency syndrome using SNP oligonucleotide microarray analysis. *Mol Genet Metab*, 100,

- 129-135. doi: S1096-7192(10)00098-3 [pii] 10.1016/j.ymgme.2010.03.007
- Liu, F., Arias-Vasquez, A., Sleegers, K., Aulchenko, Y. S., Kayser, M., Sanchez-Juan, P., et al. (2007). A genomewide screen for late-onset Alzheimer disease in a genetically isolated Dutch population. *Am J Hum Genet*, *81*, 17-31. doi: S0002-9297(07)62813-4 [pii] 10.1086/518720
- Lott, D. F. (1979). A possible for generally adaptive features in the mate selection and sexual stimulation. *Psychol. Report*, *45*, 539-546.
- Low, N., Cui, L., & Merikangas, K. R. (2007). Spousal concordance for substance use and anxiety disorders. *J Psychiatr Res*, *41*, 942-951. doi: S0022-3956(06)00241-X [pii] 10.1016/j.jpsychires.2006.11.003
- Lunetta, K. L., Faraone, S. V., Biederman, J., & Laird, N. M. (2000). Family-based tests of association and linkage that use unaffected sibs, covariates, and interactions. *Am J Hum Genet*, *66*, 605-614. doi: S0002-9297(07)63434-X [pii] 10.1086/302782
- Luo, S., & Klohnen, E. C. (2005). Assortative mating and marital quality in newlyweds: A couple-centered approach. *J Pers Soc Psychol*, *88*, 304-326.
- Ma, S. L., Tang, N. L., Tam, C. W., Lui, V. W., Suen, E. W., Chiu, H. F., & Lam, L. C. (2008). Association between HLA-A alleles and Alzheimer's disease in a southern Chinese community. *Dement Geriatr Cogn Disord*, *26*, 391-397. doi: 000164275 [pii] 10.1159/000164275
- Maes, H. H., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., et al. (1998). Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychol Med*, *28*, 1389-1401.
- Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a

- test of prefrontal cognition. *Am J Psychiatry*, 159, 652-654.
- Mascie-Taylor, C. G. (1989). Spouse similarity for IQ and personality and convergence. *Behav Genet*, 19, 223-227.
- Mascie-Taylor, C. G., & Boldsen, J. L. (1984). Assortative mating for IQ: A multivariate approach. *J Biosoc Sci*, 16, 109-117.
- Mascie-Taylor, C. G., & Vandenberg, S. G. (1988). Assortative mating for IQ and personality due to propinquity and personal preference. *Behav Genet*, 18, 339-345.
- McGue, M., Jr., T. J. B., Iacono, W. G., & Lykken, D. T. (1993). *Behavioral genetics of cognitive ability: a life-span perspective, in nature, nurture, and psychology*. Washington, DC: American Psychological Association.
- Merikangas, K. R. (1982). Assortative mating for psychiatric disorders and psychological traits. *Arch Gen Psychiatry*, 39, 1173-1180.
- Merikangas, K. R., & Brunetto., W. (1996). Assortative mating and psychiatric disorders. *Balliere's Clinical Psychiatry International Practice and Research* 2, 175 - 185.
- Nolan, M. A., Redoblado, M. A., Lah, S., Sabaz, M., Lawson, J. A., Cunningham, A. M., et al. (2003). Intelligence in childhood epilepsy syndromes. *Epilepsy Res*, 53, 139-150. doi: S0920121102002619 [pii]
- Pawlowski, B. (2003). Variable preferences for sexual dimorphism in height as a strategy for increasing the pool of potential partners in humans. *Proc Biol Sci*, 270, 709-712. doi: 10.1098/rspb.2002.2294
- Payton, A., Holland, F., Diggle, P., Rabbitt, P., Horan, M., Davidson, Y., et al. (2003). Cathepsin D exon 2 polymorphism associated with general intelligence in a healthy older population. *Mol Psychiatry*, 8(1), 14-18. doi:

10.1038/sj.mp.4001239 4001239 [pii]

Petit, E., Herault, J., Raynaud, M., Cherpi, C., Perrot, A., Barthelemy, C., et al. (1996).

X chromosome and infantile autism. *Biol Psychiatry*, 40, 457-464. doi:

0006-3223(96)85270-X [pii] 10.1016/0006-3223(96)85270-X

Petrill, S. A. (2002). The case for general intelligence: A behavioral genetic perspective. *The general factor of intelligence: How general is it?*, Robert J. S.,

& Elena, G. Mahwah, NJ: *Psychology Press*. ISBN: 978-1-4106131-6-5

Plomin, R., & Craig, I. (2001). Genetics, environment and cognitive abilities: review and work in progress towards a genome scan for quantitative trait locus

associations using DNA pooling. *Br J Psychiatry Suppl*, 40, s41-48.

Plomin, R., Turic, D. M., Hill, L., Turic, D. E., Stephens, M., Williams, J., et al.

(2004). A functional polymorphism in the succinate-semialdehyde

dehydrogenase (aldehyde dehydrogenase 5 family, member A1) gene is

associated with cognitive ability. *Mol Psychiatry*, 9, 582-586. doi:

10.1038/sj.mp.4001441 4001441 [pii]

Pulliam, J. F., Jennings, C. D., Kryscio, R. J., Davis, D. G., Wilson, D., Montine, T. J., et al. (2003). Association of HFE mutations with neurodegeneration and

oxidative stress in Alzheimer's disease and correlation with APOE. *Am J Med*

Genet B Neuropsychiatr Genet, 119B(1), 48-53. doi: 10.1002/ajmg.b.10069

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., et al.

(2007). PLINK: A tool set for whole-genome association and population-based

linkage analyses. *Am J Hum Genet*, 81, 559-575. doi: S0002-9297(07)61352-4

[pii] 10.1086/519795

Reich, T. (1996). A genomic survey of alcohol dependence and related phenotypes:

results from the collaborative study on the genetics of alcoholism (COGA).

Alcohol Clin Exp Res, 20(8 Suppl), 133A-137A.

Rosenmann, H., Meiner, Z., Kahana, E., Aladjem, Z., Friedman, G., Ben-Yehuda, A., et al. (2004). The Fas promoter polymorphism at position -670 is not associated with late-onset sporadic Alzheimer's disease. *Dement Geriatr Cogn Disord*, 17, 143-146. doi: 10.1159/000076347 DEM2004017003143 [pii]

Ruano, D., Abecasis, G. R., Glaser, B., Lips, E. S., Cornelisse, L. N., de Jong, A. P., et al. (2010). Functional gene group analysis reveals a role of synaptic heterotrimeric G proteins in cognitive ability. *Am J Hum Genet*, 86, 113-125. doi: S0002-9297(09)00567-9 [pii] 10.1016/j.ajhg.2009.12.006

Rujirabanjerd, S., Nelson, J., Tarpey, P. S., Hackett, A., Edkins, S., Raymond, F. L., et al. (2010). Identification and characterization of two novel JARID1C mutations: Suggestion of an emerging genotype-phenotype correlation. *Eur J Hum Genet*, 18, 330-335. doi: ejhg2009175 [pii] 10.1038/ejhg.2009.175

Sellar, G. C., Watt, K. P., Rabiasz, G. J., Stronach, E. A., Li, L., Miller, E. P., et al. (2003). OPCML at 11q25 is epigenetically inactivated and has tumor-suppressor function in epithelial ovarian cancer. *Nat Genet*, 34, 337-343. doi: 10.1038/ng1183 ng1183 [pii]

Shirts, B. H., Kim, J. J., Reich, S., Dickerson, F. B., Yolken, R. H., Devlin, B., & Nimgaonkar, V. L. (2007). Polymorphisms in MICB are associated with human herpes virus seropositivity and schizophrenia risk. *Schizophr Res*, 94, 342-353. doi: S0920-9964(07)00186-7 [pii] 10.1016/j.schres.2007.04.021

Smith, C. A., & Farrington, D. P. (2004). Continuities in antisocial behavior and parenting across three generations. *J Child Psychol Psychiatry*, 45, 230-247.

Smith, L. I. (2002). A tutorial on Principal Components Analysis. Retrieved April 12, 2010. From

<http://www.cs.toronto.edu/~fleet/courses/D11/fall09/Handouts/pca-smithTutorial.pdf>.

Struyk, A. F., Canoll, P. D., Wolfgang, M. J., Rosen, C. L., D'Eustachio, P., & Salzer, J. L. (1995). Cloning of neurotrimin defines a new subfamily of differentially expressed neural cell adhesion molecules. *J Neurosci*, *15*(3 Pt 2), 2141-2156.

Sutton, G. C. (1980). Assortative marriage for smoking habits. *Ann Hum Biol*, *7*, 449-456.

Wainwright, M. A., Wright, M. J., Geffen, G. M., Luciano, M., & Martin, N. G. (2005). The genetic basis of academic achievement on the Queensland Core Skills Test and its shared genetic variance with IQ. *Behav Genet*, *35*, 133-145. doi: 10.1007/s10519-004-1014-9

Wainwright, M. A., Wright, M. J., Luciano, M., Geffen, G. M., & Martin, N. G. (2005). Multivariate genetic analysis of academic skills of the Queensland core skills test and IQ highlight the importance of genetic g. *Twin Res Hum Genet*, *8*, 602-608. doi: 10.1375/183242705774860259

Watson, D., Klohnen, E. C., Casillas, A., Simms, E. N., Haig, J., & Berry, D. S. (2004). Match makers and deal breakers: Analyses of assortative mating in newlywed couples. *J Pers*, *72*, 1029-1068. doi: 10.1111/j.0022-3506.2004.00289.x JOPY289 [pii]

Wechsler, D. (1981). *Wechsler adult intelligence scale-revised*. San Antonio, TX: Psychological.

Wechsler, D. (1997). *Wechsler adult intelligence scale-III*. San Antonio, TX: Psychological.

Wellcome Trust Case Control Consortium. (2007), Retrieved April 12, 2010, from <http://www.wtccc.org.uk/>

- Wilson, D. J., Kim, D. S., Clarke, G. A., Marshall-Clarke, S., & Moss, D. J. (1996). A family of glycoproteins (GP55), which inhibit neurite outgrowth, are members of the Ig superfamily and are related to OBCAM, neurotrimin, LAMP and CEPU-1. *J Cell Sci*, 109 (Pt 13), 3129-3138.
- Wilson, S. E. (2002). The health capital of families: an investigation of the inter-spousal correlation in health status. *Soc Sci Med*, 55, 1157-1172.
- Wolanski, N. (1974). The stature of offspring and the assortative mating of parents. *Hum Biol*, 46(4), 613-619.
- Wolff, P. H., & Melngailis, I. (1994). Family patterns of developmental dyslexia: Clinical findings. *Am J Med Genet*, 54, 122-131. doi: 10.1002/ajmg.1320540207
- Yu, H., Wakim, B., Li, M., Halligan, B., Tint, G. S., & Patel, S. B. (2007). Quantifying raft proteins in neonatal mouse brain by 'tube-gel' protein digestion label-free shotgun proteomics. *Proteome Sci*, 5, 17. doi: 1477-5956-5-17 [pii] 10.1186/1477-5956-5-17

APPENDICES

APPENDIX A: Data Sources

The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB, Principal Investigator: T. Reich, Washington University, Co-Principal Investigator) includes nine centers where data collection, analysis, and/or storage take place. The nine sites and Principal Investigator and Co-Investigators are: Indiana University (T.-K. Li, J. Nurnberger Jr., P.M. Conneally, H.J. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego (M. Schuckit); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (B. Porjesz, H. Begleiter); Washington University in St. Louis (T. Reich, C. R. Cloninger, J. Rice, A. Goate); Rutgers University (J. Tischfield); and Southwest Foundation (L. Almasy). This national collaborative study is supported by NIH grant U10AA08403 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The National Institute of General Medical Sciences has provided continuous funding for the Genetic Analysis Workshops (GAW) since 1982, through grant R01 GM31575 to Jean MacCluer (Southwest Foundation for Biomedical Research). The GAW14 data was kindly provided by Jean MacCluer (Southwest Foundation for Biomedical Research). We also acknowledge the contributions of the COGA, supported by NIH Grants U10AA08401 and U10AA08403 (NIAAA) and the contributions of all scientists who have provided genotyping data to the Wave I and/or Wave II--Genetic Analysis Data.

We also acknowledge the database for replication study. The dataset from the GAIN Database found is obtained at <http://www.ncbi.nlm.nih.gov/projects/gap/> through the dbGAP accession number phs000016.v1.p1. The International Multi-Center ADHD Genetics Project (IMAGE) project is a multi-site, international effort supported by NIH grants R01MH081803 and R01MH62873 to Stephen V. Faraone. Site Principal Investigators are Philip Asherson, Tobias Banaschewski, Jan Buitelaar, Richard P. Ebstein, Stephen V. Faraone, Michael Gill, Ana Miranda, Robert D. Oades, Herbert Roeyers, Aribert Rothenberger, Joseph Sergeant, Edmund Sonuga-Barke, and Hans-Christoph Steinhausen; senior coinvestigators are Ian Craig, Peter McGuffin, Robert Plomin, Pak Sham, Eric Taylor, Iris Manor, Jacques Eisenberg and Margaret Thompson. Chief Investigators are Evi Bitsakou, Marieke Altink, Wai Chen, Hanna Christiansen, Barbara Franke, Rafaela Marco, UMueller, Fernando Mulas, Lamprini Psychogiou, Nanda Rommelse, Aisling Mulligan and Henrik Uebel. Other investigators are Cathelijne Buschgens, Frits Boer, Alysa Doyle, Ellen Fliers, Alexander Heise and Ruud Minderaa. The genotyping of samples was provided through the Genetic Association Information Network (GAIN). Samples and associated phenotype data for The International Multi-Center ADHD Genetics Project (IMAGE) project were provided by Dr Stephen V. Faraone. We thank all the families who kindly participated in this research.

This thesis is part of project “Genetic analysis of alcohol dependence and alcohol-related phenotypes in the COGA sample” approved by IRB, East Tennessee State University.

APPENDIX B: Glossary

<p>Additive genetic model</p>	<p>In a disease association study, if the risk conferred by an allele is increased r-fold for heterozygotes and $2r$-fold for homozygotes, this corresponds to additive model (Lewis, 2002). These data are best analyzed using Armitage trend test for genotype frequencies or by logistic regression in which the genotypes are represented as (-1), 0, (+1).</p>
<p>Alleles</p>	<p>Alternative forms of a genetic <i>locus</i>; a single allele for each locus is inherited separately from each parent (e.g., at a locus for eye color the allele might result in blue or brown eyes).</p>
<p>Genetic Association</p>	<p>Association refers to a concurrence greater than predicted by chance between a specific allele and another trait (for example, a disease) that may or may not have a genetic basis. Evaluation of association requires the study of unrelated individuals. Association studies may prove useful in identifying a genetic factor in a disease. Except when linkage disequilibrium exists, association is not due to genetic linkage and should not be confused with it.</p>
<p>Dominant model</p>	<p>A genetic association analysis mode that examines association</p>

	<p>with a dominant allele. The comparison groups are wild-type homozygous genotypes vs allele positivity (combining heterozygotes and homozygotes for the variant).</p>
Gene	<p>The fundamental physical and functional unit of heredity. A <i>gene</i> is an ordered sequence of <i>nucleotides</i> located in a particular position on a particular <i>chromosome</i> that encodes a specific functional product (i.e., a <i>protein</i> or <i>RNA molecule</i>).</p>
Genetic epidemiology	<p>Genetic epidemiology is the epidemiological evaluation of the role of inherited causes of disease in families and in populations; it aims to detect the inheritance pattern of a particular disease, localize the gene and find a marker associated with disease susceptibility. Gene-gene and gene-environment interactions are also studied in genetic epidemiology of a disease. In its broad context, genetic epidemiology includes family studies, molecular epidemiologic studies with genetic components, and more traditional cohort and case-control studies with family history components.</p>
Genetic heterogeneity	<p>Presence of several different genotypes contributing to the genetic component of a disease on their own. In clinical settings</p>

	<p>genetic heterogeneity refers to the presence of a variety of genetic defects which cause the same disease, which may be the mutations at different positions on the same gene, a finding common to many human diseases (including Alzheimer's disease, cystic fibrosis, lipoprotein lipase and polycystic kidney disease).</p>
Genome	<p>All of the genes carried by a single gamete; the DNA content of an individual, which includes all 44 autosomes, 2 sex chromosomes, and the mitochondrial DNA.</p>
Genotype	<p>The two alleles inherited at a specific locus. If the alleles are the same, the genotype is homozygous, if different, heterozygous. In genetic association studies, genotypes can be used for analysis as well as alleles or haplotypes.</p>
Haplotype blocks	<p>A chromosomal region with high linkage disequilibrium and low haplotype diversity. Probably flanked by recombinational hotspots, haplotype blocks are shorter in African populations (average 11kb) than in other populations (average 22kb) (Gabriel, 2002).</p>

Haplotype	The particular combination of alleles in a linked group encoded by genes in close vicinity on the same chromosome.
Hardy-Weinberg equilibrium (HWE)	In an infinitely large population, gene and genotype frequencies remain stable as long as there is no selection, mutation, or migration. For a bi-allelic locus where the gene frequencies are p and q : $p^2+2pq+q^2 = 1$. HWE should be assessed in controls in a case-control study and any deviation from HWE should alert for genotyping errors (Gomes, 1999; Lewis, 2002) but see also Zou and Donner, 2006. Relying only on HWE tests to detect genotyping errors is not recommended as this is a low power test (Leal, 2005). (Online HWE Analysis; HWE and Association Testing for SNPs in Case-Control Studies; HWE Tutorial in Life, 7 th Ed; Basic Population Genetics).
Heritability	The proportion of the phenotypic variability due to genetic variance [(narrow-sense) $h^2 = (\text{additive}) \text{ genetic variance} / \text{total phenotypic variance}$]. Can be locus-specific or for all loci combined. A high h^2 does not mean that the trait cannot be influenced by environment. In a different environment the same h^2 may not be that high. Heritability does not indicate the degree to which a trait is genetic; it measures the proportion of

	phenotypic variance that is the result of genetic factors.
Homozygote and heterozygote	A heterozygote is an individual having two different alleles at a genetic locus; a homozygote is an individual having two copies of the same allele at a locus.
Linkage disequilibrium (LD)	Two alleles at different loci that occur together on the same chromosome (or gamete) more often than would be predicted by random chance. It is a measure of co-segregation of alleles in a population. Also called population 'gametic association' and may be defined as 'nonzero' if multilocus gamete frequencies are different from the product of allele frequencies at each locus.
Linkage	The tendency of 'genes' on the same chromosome to segregate together. This means that linked genes are transmitted to the same gamete more than 50% of the time. Genetic linkage reflects a lack of meiotic crossovers between two genes one of which is usually a latent/unknown disease locus.
LOD score	The LOD score method for testing linkage was first proposed by Morton in 1955 (Morton, 1955). Stands for the logarithm of

	<p>odds but it is <i>not</i> the logarithm of the odds for linkage but the logarithm of the likelihood ratio for a particular value of the recombination fraction vs. free recombination ($r = 0.5$) (Elston, 1998; Borecki, 2001). Thus, the LOD score serves as a test of the null hypothesis of free recombination versus the alternative hypothesis of linkage. It is a statistical measure of the likelihood that two genetic markers occur together on the same chromosome and are inherited as a single unit of DNA.</p> <p>Determination of LOD scores requires pedigree analysis and a score of $>+3$ is traditionally taken as evidence for linkage (and -2 may mean the opposite).</p>
Permutation Test	<p>A statistical approach to examine statistical significance of associations based on Monte Carlo methods that accounts for multiple comparisons issue (McIntyre, 2000; Becker & Knapp, 2004; Becker, 2005). Haploview and UNPHASED (ref) can do permutation test (both require data in linkage format). WHAP and BEAGLE are also a freely available software packages that can analyze multiallelic markers.</p>
Population stratification	<p>An example of 'confounding by ethnicity' in which the co-existence of different disease rates and allele frequencies</p>

	<p>within population sub-sections leads to a spurious association at the population level. Differing allele frequencies in ethnically different strata in a single population may lead to a spurious association or 'mask' an association by artificially modifying allele frequencies in cases and controls when there is no real association (for this to happen, the subpopulations should differ not only in allele frequencies but also in baseline risk to the disease being studied) (Mark, 1996; Altshuler, 1998).</p>
<p>Single nucleotide polymorphism (SNP)</p>	<p>A single nucleotide variation in the DNA code. It is the most common type of stable genetic variation and usually bi-allelic. SNPs may be silent -no change in phenotype- (sSNP), may cause a change in phenotype (cSNP) or may be in a regulatory region (rSNP) with potential to change phenotype. Thus the effects of SNPs, if any, are generally on gene expression or protein structure (Williams, 2007).</p>

APPENDIX C:

Affymetrix Panel FBAT- $p < 0.01$ Results and Related Test Results

TSC	SNP	Gene band	Position	Fam#	Z	FBAT-p	HWE-p	MAF	EMP
tsc0052828	rs0952035	1	108130229	56	2.989	0.002801	0.5315	0.187	0.0015
tsc0999660	rs1934369	1	48899795	104	2.826	0.004715	0.626	0.318	0.0134
tsc0218512	rs2003346	1	7001081	71	2.824	0.004743	0.00887	0.274	0.0172
tsc0648117	rs1434365	1	99513464	56	-2.65	0.008059	0.5563	0.139	0.0032
tsc0246331	rs0705695	1	7012409	92	2.642	0.008248	0.4381	0.298	0.0175
tsc0523528	rs1371552	2	222388815	97	-3.182	0.001464	0.00537	0.264	0.0013
tsc0549290	rs1384924	2	52850837	111	-3.106	0.001896	1	0.407	0.0148
tsc0570933	rs1395324	2	28197971	84	3.105	0.001902	1	0.236	0.0164
tsc0063067	rs2018909	2	50914962	36	2.992	0.00277	0.4583	0.091	0.0269
tsc0058930	rs0726085	2	67864317	75	-2.915	0.00356	0.7319	0.177	0.015
tsc0515188	rs1583118	2	7336224	95	-2.733	0.006277	0.0204	0.469	0.0156
tsc0056028	rs1112919	2	54803045	97	2.725	0.006424	0.1098	0.277	0.0128
tsc0053184	rs0723504	2	12216475	106	2.695	0.007042	0.5238	0.386	0.011
tsc0048708	rs0721357	2	222389134	103	2.652	0.007991	0.00439	0.347	0.0117
tsc0049862	rs1807844	3	32778283	85	2.704	0.006851	0.2025	0.159	0.0188
tsc0974772	rs1920116	3	166847358	98	2.666	0.007684	0.07745	0.263	0.005
tsc0459389	rs0524129	4	12949175	81	-3.158	0.00159	0.4049	0.267	0.0073
tsc0046635	rs3846329	4	150038301	87	3.099	0.001941	0.7714	0.235	0.0075
tsc0065126	rs0763366	4	32467596	106	3.073	0.002122	1	0.428	0.007
tsc0045058	rs0719776	4	33664764	47	2.946	0.003216	0.5523	0.102	0.0262
tsc0530051	rs1374530	4	106923103	76	2.781	0.005425	1	0.206	0.005
tsc1762383	rs2889670	4	191037857	78	2.657	0.007893	0.2993	0.289	0.0034
tsc0998766	rs1933836	6	120692147	61	-3.529	0.000417	0.3962	0.14	0.0008
tsc0058146	rs0952884	6	46615143	18	3.216	0.001301	1	0.036	0.0004
tsc0052474	rs1074195	6	120031275	63	-3.056	0.002241	0.02053	0.13	0.0038
tsc0039821	rs0717388	6	114144104	110	3.046	0.002318	0.149	0.499	0.0025
tsc0944551	rs1902066	6	81288771	113	-2.971	0.002967	0.05704	0.415	0.002
tsc0271696	rs0965323	6	47710490	92	-2.922	0.003478	1	0.331	0.0014
tsc1292475	rs2225766	6	8466831	107	2.891	0.003842	0.8141	0.367	0.0152
tsc0052238	rs0723054	6	16728540	108	2.88	0.003978	0.8354	0.451	0.0205
tsc0194305	rs0326798	6	44544015	103	-2.859	0.004255	0.8355	0.442	0.0093
tsc0058362	rs0725819	6	23799374	34	-2.851	0.004362	0.01008	0.134	0.0493
tsc1396432	rs2327068	6	8503769	50	-2.816	0.004869	0.6077	0.118	0.0395
tsc0042299	rs0718502	6	8512498	108	2.781	0.005415	0.8212	0.368	0.0186
tsc1395270	rs2326584	6	5274204	93	2.77	0.005612	1	0.277	0.0187
tsc0039822	rs0717389	6	114144158	106	-2.742	0.006115	0.1449	0.474	0.004
tsc1292474	rs2225765	6	8466783	99	-2.703	0.006876	0.3047	0.354	0.0359
tsc0076377	rs1962252	6	66486629	66	-2.657	0.007889	0.7037	0.181	0.0199
tsc0044031	rs0719316	6	16730399	108	-2.654	0.007944	0.8354	0.451	0.0408

tsc0042301	rs0718504	6	8512610	98	-2.592	0.009539	0.8062	0.372	0.0167
tsc1241272	rs1316623	7	21638203	100	-3.361	0.000777	1	0.289	0.0022
tsc0040987	rs1073158	7	131808721	76	3.129	0.001755	1	0.169	0.016
tsc0051248	rs1986568	7	37033584	103	-2.921	0.003488	0.09416	0.449	0.0048
tsc0060076	rs0028179	7	31731918	65	-2.827	0.004702	0.6311	0.123	0.036
tsc0051247	rs1986567	7	37033410	104	-2.811	0.004943	0.08634	0.443	0.0075
tsc0057389	rs0725349	7	79877337	75	2.677	0.007427	0.4106	0.196	0.0047
tsc0447090	rs1974769	7	64590600	97	-2.649	0.008072	0.2422	0.387	0.0025
tsc0260049	rs0958408	7	131483640	89	-2.585	0.009738	0.292	0.199	0.1064
tsc0547537	rs1384037	8	13476761	115	3.004	0.002666	0.8327	0.496	0.004
tsc1367193	rs2262337	8	56848785	81	-2.958	0.003096	0.3434	0.218	0.0056
tsc0274978	rs0967411	8	14810172	85	-2.954	0.003134	0.2192	0.223	0.0004
tsc0559877	rs1390049	8	15035716	82	-2.846	0.004422	0.7708	0.306	0.006
tsc0574630	rs1396976	8	130522651	77	-2.817	0.004843	1	0.18	0.0067
tsc1766192	rs2891346	8	73142189	64	2.754	0.005887	0.06651	0.145	0.0137
tsc0054504	rs0724112	8	52326998	60	2.753	0.005913	1	0.175	0.0009
tsc0040292	rs0717583	8	134945075	101	2.621	0.008755	0.8183	0.333	0.0198
tsc0547781	rs1384185	8	121575717	110	2.592	0.009555	0.6801	0.441	0.05159
tsc0056583	rs4128166	9	112396402	91	-2.657	0.00788	0.0245	0.494	0.0047
tsc0063364	rs0728086	9	107246346	80	-2.641	0.008264	1	0.285	0.0359
tsc1027490	rs1949741	10	56287305	89	-3.682	0.000232	0.0798	0.476	0.0001
tsc0968864	rs1916503	10	56265656	93	3.499	0.000466	0.4089	0.467	0.0009
tsc0968867	rs1916506	10	56265348	59	3.442	0.000577	0.00006	0.476	0.0002
tsc1698580	rs0582661	10	104738427	105	2.931	0.00338	0.598	0.315	0.0366
tsc0943990	rs1786912	10	66532698	59	-2.927	0.003418	1	0.124	0.0019
tsc1686293	rs2422070	10	93459605	101	2.807	0.004998	0.8087	0.308	0.05389
tsc0609025	rs1414043	10	25589033	106	2.725	0.006424	0.03602	0.44	0.0054
tsc0149855	rs0956368	10	82491271	44	-2.702	0.006885	0.7309	0.22	0.08329
tsc0414849	rs0835236	10	93647411	51	-2.645	0.008169	1	0.26	0.1351
tsc0049777	rs3886738	10	62360873	40	2.62	0.0088	1	0.093	0.0278
tsc0045694	rs0411280	11	133393101	96	-3.366	0.000764	0.06248	0.319	0.0023
tsc0047236	rs4128561	11	130415550	116	-2.804	0.00504	0.1401	0.431	0.0108
tsc0275383	rs1116375	11	27924442	79	-2.739	0.00616	0.1734	0.223	0.007
tsc0945688	rs1902765	12	52295105	107	-3.17	0.001524	0.5185	0.496	0.0003
tsc0055034	rs0724344	12	100703667	85	3.074	0.002109	0.4095	0.215	0.02
tsc0958665	rs1910773	12	126424698	48	2.876	0.004026	0.5698	0.1	0.05269
tsc0552462	rs1386493	12	72135948	64	2.797	0.005164	0.2233	0.145	0.0074
tsc0065975	rs0763875	12	95854998	29	2.757	0.005828	0.4583	0.066	0.0007
tsc1211377	rs2173446	12	64169692	112	2.717	0.006585	0.05511	0.495	0.0093
tsc0046031	rs3851661	12	126324837	102	-2.711	0.006709	0.4072	0.422	0.0136
tsc1117623	rs2114919	12	100324232	77	-2.682	0.007314	0.2723	0.128	0.0015
tsc0552461	rs1386492	12	72143034	65	2.65	0.008045	0.1906	0.149	0.0079
tsc1034888	rs1954130	14	84471548	43	3.353	0.0008	0.3151	0.094	0.0059
tsc0048032	rs0721070	14	57011147	70	-2.984	0.002845	0.5123	0.229	0.0026

tsc0051743	rs0722816	14	67861421	48	2.956	0.003118	0.6747	0.165	0.0183
tsc1571468	rs2383633	14	32285638	46	-2.918	0.00352	0.2473	0.113	0.0041
tsc0534396	rs1376837	14	38859249	75	-2.807	0.005003	0.3829	0.212	0.0286
tsc1035624	rs2022666	14	60154702	71	-2.695	0.00704	0.3969	0.221	0.0495
tsc0685758	rs1454985	15	28656752	113	-2.687	0.007208	0.3846	0.41	0.0028
tsc0275730	rs0967899	16	50937116	103	3.278	0.001044	0.06104	0.483	0.0011
tsc0520638	rs028168	16	47348829	94	3.246	0.00117	0.3822	0.49	0.0024
tsc0101255	rs0205425	16	27508353	96	3.139	0.001697	0.1453	0.5	0.0063
tsc0574962	rs1397148	16	46481059	107	3.04	0.002365	0.5219	0.449	0.0045
tsc0050837	rs0028168	16	47348829	91	-2.798	0.005142	0.3532	0.499	0.0069
tsc0533075	rs1376203	16	46481612	103	-2.752	0.005915	0.6807	0.49	0.0196
tsc0544512	rs1382361	16	46666593	105	2.734	0.006263	0.8354	0.491	0.0229
tsc0520315	rs1369790	16	50987827	92	2.702	0.0069	0.2765	0.318	0.0036
tsc0059939	rs0403070	16	74653574	75	2.596	0.009419	0.1509	0.379	0.05069
tsc0231046	rs0918174	18	3656906	102	-2.96	0.003076	1	0.336	0.0012
tsc0481569	rs1350551	18	30052427	44	-2.785	0.005347	0.592	0.123	0.0042
tsc0756536	rs1848074	18	54233842	96	2.644	0.008189	0.8137	0.327	0.014
tsc1016228	rs1943889	18	70942183	106	2.635	0.008405	1	0.453	0.0281
tsc1288669	rs2223246	20	41673628	86	3.291	0.000998	0.301	0.356	0.0023
tsc0834119	rs3904864	20	4367143	108	3.018	0.002546	0.5288	0.465	0.0041
tsc0067300	rs0725862	20	19619278	97	-2.729	0.006354	0.1519	0.354	0.0054
tsc1164652	rs2145168	20	19642137	93	2.665	0.007689	1	0.26	0.0059
tsc0054435	rs0724084	20	7263740	103	-2.623	0.008716	0.0961	0.493	0.0031
tsc1086516	rs2027715	21	20194814	109	-3.095	0.001971	0.8199	0.398	0.0099
tsc0846433	rs1858821	22	28372502	93	-2.682	0.007312	1	0.282	0.0188
tsc0999365	rs1934189	chrX	SNP_A-1516213	67	3.293	0.00099	0.05806	0.335	-
tsc0619548	rs1419303	chrX	SNP_A-1514989	20	-2.704	0.006855	0.1314	0.109	-
dom									
tsc0571381	rs1395548	1	162948311	78	-3.09	0.001999	0.2719	0.398	0.05659
tsc1509722	rs2362815	1	120520746	92	2.978	0.002906	0.8156	0.327	0.007
tsc0064386	rs3122425	1	40572503	24	2.933	0.003362	1	0.264	0.07199
tsc1680828	rs2419988	1	69027483	18	2.719	0.006542	0.2698	0.179	0.4604
tsc0662006	rs1441834	1	29900884	24	2.711	0.006702	0.03237	0.249	0.4329
tsc0218512	rs2003346	1	7001081	51	-2.685	0.007249	0.00887	0.274	0.0172
tsc0648117	rs1434365	1	99513464	56	-2.653	0.007978	0.5563	0.139	0.0032
tsc0549290	rs1384924	2	52850837	56	-3.06	0.002214	1	0.407	0.0148
tsc0052017	rs0722944	2	161947310	11	2.973	0.002946	0.2293	0.271	0.8903
tsc0570933	rs1395324	2	28197971	75	-2.918	0.003518	1	0.236	0.0164
tsc0063067	rs2018909	2	50914962	34	2.9	0.003733	0.4583	0.091	0.0269
tsc0523528	rs1371552	2	222388815	90	2.889	0.003862	0.00537	0.264	0.0013
tsc0552514	rs1386515	2	185142598	56	-2.878	0.003998	0.7539	0.18	0.0133
tsc1250703	rs2197804	2	33882990	22	-2.832	0.00462	0.09896	0.202	0.06979
tsc0515188	rs1583118	2	7336224	55	-2.803	0.005059	0.0204	0.469	0.0156
tsc0058930	rs0726085	2	67864317	68	2.771	0.005588	0.7319	0.177	0.015

tsc0053635	rs0952167	2	52020837	13	-2.717	0.006592	0.3434	0.162	0.2246
tsc0784977	rs1851186	2	210646849	43	2.683	0.0073	0.6094	0.366	0.0454
tsc0149464	rs0956133	2	213985790	63	-2.663	0.007745	0.53	0.458	0.08389
tsc0976906	rs1196155	2	181128483	24	2.589	0.009621	1	0.253	0.06699
tsc0537907	rs1378794	3	154253501	82	-2.951	0.003168	1	0.255	0.172
tsc0183073	rs0904827	3	20025987	21	-2.863	0.004194	0.7871	0.237	0.1922
tsc0557051	rs1388699	3	159065057	74	2.687	0.007205	1	0.404	0.0119
tsc1051947	rs2036999	3	128426229	74	2.637	0.008368	0.4824	0.335	0.0305
tsc0588516	rs1403635	3	2218428	19	2.63	0.008527	0.1386	0.23	0.469
tsc0055873	rs0816491	3	38895165	60	-2.626	0.008648	0.4728	0.19	0.0224
tsc0974772	rs1920116	3	166847358	89	-2.596	0.009428	0.07745	0.263	0.005
tsc0459389	rs0524129	4	12949175	30	4.691	0.000003	0.4049	0.267	0.0073
tsc0059698	rs1074801	4	156425301	64	3.825	0.000131	0.8354	0.448	0.0113
tsc0046635	rs3846329	4	150038301	77	-3.399	0.000675	0.7714	0.235	0.0075
tsc0086499	rs1008277	4	48215016	43	-3.069	0.002145	0.824	0.363	0.0455
tsc0547043	rs1383718	4	67702503	14	3.043	0.00234	0.4509	0.169	0.08219
tsc0057873	rs0725594	4	20595373	12	-3.043	0.002342	1	0.167	0.9266
tsc0555770	rs1388070	4	156149955	43	-3.003	0.002671	0.8241	0.363	0.0227
tsc0530051	rs1374530	4	106923103	70	-2.813	0.004908	1	0.206	0.005
tsc0043198	rs0718913	4	173628985	41	-2.788	0.005302	0.03784	0.3	0.0039
tsc0303948	rs0985892	4	79864746	67	-2.713	0.00667	0.2751	0.314	0.0326
tsc0046630	rs1073671	4	190772142	70	2.701	0.006916	0.09565	0.424	0.1501
tsc0043524	rs0950657	4	122194133	25	2.684	0.007282	0.5972	0.28	0.02
tsc0045058	rs0719776	4	33664764	45	2.68	0.007363	0.5523	0.102	0.0262
tsc0047778	rs0951299	4	99843682	91	-2.592	0.009549	0.351	0.324	0.0353
tsc0507037	rs1363235	5	76226446	45	3.372	0.000746	0.2101	0.288	0.19
tsc0051954	rs1074152	5	75779133	29	2.785	0.005345	0.2183	0.36	0.0096
tsc0170010	rs0896386	5	175528608	81	-2.69	0.007135	0.5839	0.247	0.09459
tsc0313571	rs0173282	5	75910391	77	-2.674	0.007501	0.8206	0.433	0.1959
tsc0522426	rs1583679	5	110099572	62	2.651	0.008036	1	0.131	0.0132
tsc0040204	rs0256853	5	123293731	51	2.646	0.008156	0.6785	0.413	0.1575
tsc0513033	rs1366236	5	151353418	73	-2.589	0.009616	1	0.497	0.3351
tsc0067408	rs2504857	6	12593888	24	-3.86	0.000113	0.2632	0.266	0.07099
tsc0998766	rs1933836	6	120692147	61	-3.704	0.000212	0.3962	0.14	0.0008
tsc0194305	rs0326798	6	44544015	80	3.38	0.000724	0.8355	0.442	0.0093
tsc0058146	rs0952884	6	46615143	18	3.216	0.001301	1	0.036	0.0004
tsc0052474	rs1074195	6	120031275	61	-3.137	0.001704	0.02053	0.13	0.0038
tsc1314243	rs2092296	6	145516851	57	-3.06	0.00221	0.5219	0.418	0.06219
tsc1331647	rs2103633	6	145517188	57	-2.997	0.002729	0.5253	0.418	0.07929
tsc0613382	rs1416207	6	143512442	43	-2.965	0.003024	0.6499	0.363	0.8316
tsc0042299	rs0718502	6	8512498	47	2.866	0.004156	0.8212	0.368	0.0186
tsc1292475	rs2225766	6	8466831	47	2.866	0.004156	0.8141	0.367	0.0152
tsc0041579	rs0718174	6	108208652	42	-2.83	0.004652	0.6499	0.319	0.2552
tsc0042301	rs0718504	6	8512610	43	2.812	0.004922	0.8062	0.372	0.0167

tsc1269202	rs2210798	6	8466520	47	2.797	0.005151	0.8167	0.373	0.0249
tsc0058362	rs0725819	6	23799374	31	-2.752	0.005927	0.01008	0.134	0.0493
tsc1484946	rs2355205	6	108174724	38	-2.742	0.006112	0.4912	0.312	0.394
tsc0271696	rs0965323	6	47710490	73	2.72	0.006531	1	0.331	0.0014
tsc0179242	rs0902370	6	129264612	43	-2.717	0.006582	1	0.289	0.1232
tsc0214432	rs0879831	6	44561732	67	2.69	0.007135	0.2119	0.49	0.0252
tsc1396996	rs2327212	6	132502412	10	-2.647	0.008109	1	0.143	0.4908
tsc0883414	rs1995688	6	86578654	31	2.643	0.008228	0.6164	0.297	0.544
tsc0042280	rs0052484	6	23622004	58	2.628	0.008582	0.4069	0.443	0.0157
tsc0159829	rs0578994	6	124420644	83	2.611	0.009039	0.1519	0.277	0.0172
tsc0844988	rs0791856	6	86628176	33	2.608	0.009105	0.8076	0.303	0.5146
tsc0052238	rs0723054	6	16728540	70	2.597	0.009411	0.8354	0.451	0.0205
tsc0051248	rs1986568	7	37033584	65	-3.327	0.000878	0.09416	0.449	0.0048
tsc0620722	rs1419970	7	125997067	27	-3.106	0.001894	0.44	0.255	0.4146
tsc0044034	rs0719319	7	124190540	48	-3.044	0.002335	0.3649	0.379	0.047
tsc1467706	rs2349775	7	8362452	78	3.038	0.00238	0.5783	0.229	0.07179
tsc0462989	rs1569095	7	48093371	84	-2.9	0.003734	0.4801	0.342	0.0358
tsc0057389	rs0725349	7	79877337	71	-2.859	0.004255	0.4106	0.196	0.0047
tsc1242664	rs0037981	7	7665012	67	2.782	0.005399	0.517	0.465	0.0384
tsc0051247	rs1986567	7	37033410	61	-2.754	0.00589	0.08634	0.443	0.0075
tsc1241272	rs1316623	7	21638203	89	2.66	0.007822	1	0.289	0.0022
tsc0791034	rs1524339	7	144926978	26	2.616	0.008892	0.2787	0.283	0.5773
tsc0040576	rs0717699	7	8038756	13	-2.588	0.00965	0.1631	0.181	0.9768
tsc1367193	rs2262337	8	56848785	69	-3.469	0.000522	0.3434	0.218	0.0056
tsc0065449	rs0763552	8	31350133	47	-2.971	0.002972	0.01434	0.448	0.09269
tsc0459391	rs1566835	8	113006384	61	-2.834	0.00459	0.8205	0.403	0.07019
tsc0274978	rs0967411	8	14810172	78	-2.801	0.005088	0.2192	0.223	0.0004
tsc0547537	rs1384037	8	13476761	66	-2.799	0.005123	0.8327	0.496	0.004
tsc0550862	rs1385720	8	25594961	88	2.744	0.006068	0.5181	0.447	0.06459
tsc0049315	rs0710616	8	129885999	63	-2.705	0.00682	0.8373	0.493	0.08509
tsc1767065	rs2891799	8	123886572	43	-2.62	0.008797	1	0.5	0.2666
tsc0574630	rs1396976	8	130522651	71	2.62	0.008803	1	0.18	0.0067
tsc0149336	rs1113937	9	67080681	72	3.426	0.000612	0.8218	0.356	0.0156
tsc0614355	rs1416738	9	62832253	53	-3.243	0.001184	0.2053	0.443	0.0214
tsc0049761	rs0721832	9	83563618	10	2.7	0.006943	0.03202	0.162	0.0244
tsc0988681	rs1928415	9	684198	45	2.671	0.007554	1	0.102	0.2024
tsc0597247	rs1408113	9	107541029	18	2.64	0.008298	0.00655	0.422	0.05449
tsc0063364	rs0728086	9	107246346	19	2.589	0.009638	1	0.285	0.0359
tsc1495550	rs2358839	10	20125974	40	-3.106	0.001898	0.08547	0.317	0.525
tsc0058588	rs0952965	10	107090319	64	3.08	0.002071	0.3957	0.441	0.0383
tsc1027490	rs1949741	10	56287305	52	2.931	0.003381	0.0798	0.476	0.0001
tsc1698580	rs0582661	10	104738427	89	2.921	0.003488	0.598	0.315	0.0366
tsc0060577	rs0726804	10	111478983	23	-2.862	0.004216	0.2142	0.448	0.0323
tsc0039992	rs0950129	10	105163606	44	-2.817	0.004855	0.8322	0.38	0.2686

tsc1688990	rs2437871	10	89159930	68	-2.786	0.005334	0.6691	0.435	0.06729
tsc0943990	rs1786912	10	66532698	58	2.737	0.006195	1	0.124	0.0019
tsc0935380	rs1896404	10	122160973	37	-2.733	0.006268	0.1539	0.396	0.05649
tsc0968864	rs1916503	10	56265656	54	2.722	0.006494	0.4089	0.467	0.0009
tsc0968867	rs1916506	10	56265348	38	-2.718	0.006577	0.00006	0.476	0.0002
tsc0060216	rs2014307	10	123237035	70	2.708	0.006762	0.05495	0.322	0.2894
tsc0968864	rs1916503	10	56265656	61	-2.685	0.007243	0.4089	0.467	0.0009
tsc0609024	rs1414042	10	25588945	70	2.678	0.007416	0.08897	0.426	0.0268
tsc0049777	rs3886738	10	62360873	40	2.657	0.007879	1	0.093	0.0278
tsc1027490	rs1949741	10	56287305	58	-2.633	0.008469	0.0798	0.476	0.0001
tsc0609025	rs1414043	10	25589033	67	2.617	0.008859	0.03602	0.44	0.0054
tsc0597718	rs1408344	10	101541987	48	-2.607	0.009124	0.8284	0.416	0.3127
tsc0149855	rs0956368	10	82491271	36	-2.595	0.00945	0.7309	0.22	0.08329
tsc0054458	rs0724095	11	136394458	11	3.187	0.001437	1	0.189	0.209
tsc0045694	rs0411280	11	133393101	82	3.039	0.002376	0.06248	0.319	0.0023
tsc0563913	rs1392065	11	37644017	17	-2.982	0.00286	0.609	0.146	0.157
tsc1013853	rs1942518	11	106733523	79	2.97	0.002975	0.6785	0.436	0.1145
tsc0019847	rs0883505	11	106757760	78	2.956	0.003118	0.6785	0.436	0.1128
tsc0296033	rs0980804	11	28401542	76	-2.916	0.003543	1	0.449	0.05229
tsc1009167	rs1939990	11	128809488	19	-2.915	0.003552	0.5839	0.237	0.5608
tsc1009168	rs1939991	11	128809551	19	-2.915	0.003552	0.5839	0.237	0.5283
tsc1009169	rs1939992	11	128810179	19	-2.915	0.003552	0.5839	0.236	0.5548
tsc0047236	rs4128561	11	130415550	83	-2.906	0.003661	0.1401	0.431	0.0108
tsc0164649	rs0892951	11	31746638	48	-2.759	0.005806	0.5328	0.426	0.05009
tsc0275383	rs1116375	11	27924442	74	-2.728	0.006365	0.1734	0.223	0.007
tsc0108927	rs1079598	11	115649148	12	-2.717	0.006583	1	0.136	0.3801
tsc0108926	rs1079597	11	115649160	12	-2.662	0.007775	0.684	0.137	0.5975
tsc0055034	rs0724344	12	100703667	82	3.327	0.000878	0.4095	0.215	0.02
tsc1211377	rs2173446	12	64169692	76	2.917	0.003537	0.05511	0.495	0.0093
tsc0552462	rs1386493	12	72135948	61	-2.881	0.00396	0.2233	0.145	0.0074
tsc0945688	rs1902765	12	52295105	61	-2.76	0.005776	0.5185	0.496	0.0003
tsc0046372	rs0951062	12	20448720	36	2.753	0.005905	0.7857	0.265	0.4711
tsc0589357	rs1404124	12	70585140	58	2.738	0.00619	0.6465	0.134	0.031
tsc0958665	rs1910773	12	126424698	48	-2.703	0.006866	0.5698	0.1	0.05269
tsc0065975	rs0763875	12	95854998	29	-2.684	0.007282	0.4583	0.066	0.0007
tsc1159942	rs2141859	12	104029030	74	2.671	0.007563	0.2991	0.481	0.05709
tsc0055014	rs0952392	12	75861581	85	2.667	0.007651	0.5089	0.201	0.06479
tsc1539790	rs2373358	12	100278816	65	2.635	0.008411	0.05537	0.46	0.1789
tsc1109907	rs2109097	12	4461262	79	2.588	0.009641	1	0.279	0.06629
tsc0273111	rs0966218	13	21321360	75	2.636	0.00839	0.5047	0.376	0.273
tsc1034888	rs1954130	14	84471548	43	3.056	0.002242	0.3151	0.094	0.0059
tsc0534396	rs1376837	14	38859249	72	2.907	0.003644	0.3829	0.212	0.0286
tsc0048032	rs0721070	14	57011147	64	2.889	0.003861	0.5123	0.229	0.0026
tsc0906621	rs1887496	14	31236799	62	-2.849	0.004391	0.6734	0.466	0.046

tsc0056196	rs1074501	14	71494883	82	2.748	0.005996	0.6609	0.355	0.2467
tsc1571468	rs2383633	14	32285638	46	2.576	0.009987	0.2473	0.113	0.0041
tsc0523226	rs1371386	15	86427482	84	-2.837	0.004561	0.8321	0.38	0.0428
tsc0055180	rs0724408	15	91110486	91	-2.835	0.004577	1	0.38	0.0063
tsc0511035	rs1365225	15	23146307	68	-2.72	0.006533	0.7902	0.318	0.1189
tsc0059178	rs0953065	15	85742162	49	-2.585	0.009744	0.5155	0.387	0.0457
tsc0189790	rs0909003	16	55402808	61	3.034	0.002415	1	0.447	0.0419
tsc0101255	rs0205425	16	27508353	58	-3.006	0.002645	0.1453	0.5	0.0063
tsc0520638	rs28168	16	47348829	64	2.914	0.003572	0.3822	0.49	0.0024
tsc0533075	rs1376203	16	46481612	67	2.757	0.005835	0.6807	0.49	0.0196
tsc0574962	rs1397148	16	46481059	64	2.738	0.006173	0.5219	0.449	0.0045
tsc0544512	rs1382361	16	46666593	69	2.702	0.006898	0.8354	0.491	0.0229
tsc0275730	rs0967899	16	50937116	70	2.647	0.008133	0.06104	0.483	0.0011
tsc0520315	rs1369790	16	50987827	36	-2.597	0.009412	0.2765	0.318	0.0036
tsc0845765	rs1858466	17	50856651	57	-2.776	0.00551	0.684	0.123	0.0285
tsc0076378	rs0955770	17	51387721	50	2.761	0.005766	0.01582	0.136	0.0407
tsc0756536	rs1848074	18	54233842	46	3.481	0.0005	0.8137	0.327	0.014
tsc0046696	rs0720513	18	71190700	43	3.134	0.001722	0.00304	0.374	0.1201
tsc0481569	rs1350551	18	30052427	41	3.019	0.002535	0.592	0.123	0.0042
tsc0399836	rs1477489	18	70447135	13	-2.862	0.004204	0.3745	0.195	0.336
tsc0541703	rs1380833	18	41800842	70	2.805	0.005037	0.5349	0.456	0.1446
tsc0231046	rs0918174	18	3656906	84	-2.775	0.005521	1	0.336	0.0012
tsc0856122	rs1863605	18	30052486	45	2.633	0.008457	0.5977	0.126	0.0067
tsc1790867	rs2903017	19	30268224	32	-2.685	0.007252	0.8013	0.307	0.34
tsc0079667	rs1004246	19	16950128	32	-2.586	0.009704	0.5741	0.266	0.07159
tsc1288669	rs2223246	20	41673628	69	-3.055	0.002254	0.301	0.356	0.0023
tsc0834119	rs3904864	20	4367143	67	-2.908	0.003633	0.5288	0.465	0.0041
tsc0054435	rs0724084	20	7263740	66	-2.757	0.005825	0.0961	0.493	0.0031
tsc0537821	rs0234693	21	40980671	18	2.999	0.00271	0.1674	0.224	0.375
tsc1268219	rs2210254	21	26663009	11	-2.739	0.006167	0.5124	0.155	0.0196
tsc0054099	rs0723929	21	19571803	16	-2.61	0.009041	0.0336	0.186	0.8553
tsc1086516	rs2027715	21	20194814	81	-2.589	0.009635	0.8199	0.398	0.0099
tsc0045394	rs0719925	22	42394082	54	-2.927	0.003418	0.1739	0.485	0.0238
tsc1293972	rs2226519	22	13456557	26	2.917	0.003529	0.7888	0.367	0.0113
tsc0846433	rs1858821	22	28372502	77	-2.733	0.006285	1	0.282	0.0188
tsc0999365	rs1934189	chrX	SNP_A-1516213	60	3.696	0.000219	0.05806	0.335	-
tsc0999365	rs1934189	chrX	SNP_A-1516213	62	-3.212	0.001318	0.05806	0.335	-
tsc0045533	rs0719989	chrX	SNP_A-1509419	66	3.2	0.001373	1	0.431	-
tsc0999364	rs1934188	chrX	SNP_A-1516174	54	3.134	0.001727	0.1544	0.329	-
tsc0619548	rs1419303	chrX	SNP_A-1514989	15	2.697	0.006989	0.1314	0.109	-
tsc0058981	rs0726107	chrX	SNP_A-1517523	26	2.599	0.00934	0.08853	0.159	-
tsc0042798	rs1986444	chrX	SNP_A-1516790	30	2.586	0.009715	0.2712	0.175	-

Fam#: number of informative families.

Ad: additive model.

Dom: dominant model.

Position is based on NCBI Genome Build 36.3.
MAF: minor allele frequency of the SNP.
EMP: p-value using permutation test.
HWE: p-value using Hardy-Weinberg Equilibrium Test
FBAT: family based association test

APPENDIX D:

IMAGE FBAT-p<0.05 Results and Related Test Results

SNP	Gene band	Position	Gene	Fam#	Z	FBAT-p	HWE-p	MAF	EMP
Ad									
rs11945798	4p15.33	12378330		83	2.14	0.032329	0.677	0.036	0.03596
rs1973655	4p15.33	12647036		416	2.106	0.03518	0.1338	0.303	0.03816
rs17310924	4p15.33	12663699		417	-2.502	0.012359	0.6119	0.351	0.02276
rs12649713	4p15.33	12733566		255	-1.968	0.049027	0.05063	0.161	0.05578
rs10017077	4p15.33	12769886		289	2.425	0.015289	0.5489	0.17	0.01274
rs6845865	4q31.23	149194052	NR3C2	272	2.392	0.016747	1	0.163	0.01846
rs1021956	4q31.23	149198624	NR3C2	313	-2.163	0.030557	0.346	0.187	0.03228
rs2276932	4q31.23	149203771	NR3C2	142	-2.241	0.024997	0.2317	0.064	0.02105
rs12641157	4q31.23	149206745	NR3C2	360	-2.79	0.005272	0.938	0.242	0.00584
rs7660368	4q31.23	149207422	NR3C2	434	-2.715	0.006634	0.4294	0.375	0.00742
rs6823323	4q31.23	149240208	NR3C2	380	2.349	0.018835	0.6151	0.279	0.01883
rs4835478	4q31.23	149241706	NR3C2	382	2.851	0.00436	0.6209	0.286	0.00549
rs13137823	4q31.23	149242356	NR3C2	328	2.982	0.002863	0.3807	0.207	0.00211
rs13142954	4q31.23	149249477	NR3C2	353	2.486	0.012936	0.0833	0.225	0.00928
rs11099678	4q31.23	149272300	NR3C2	419	2.341	0.019215	0.9498	0.348	0.01897
rs3846300	4q31.23	149315756	NR3C2	367	2.454	0.014138	0.0000808	0.243	0.00783
rs7693077	4q31.23	149339274	NR3C2	258	-2.772	0.005574	0.1679	0.155	0.0049
rs4260521	4q31.23	149425972	NR3C2	406	2.145	0.031965	0.7934	0.314	0.03937
rs17484454	4q31.23	149428458	NR3C2	403	2.234	0.025475	0.6939	0.313	0.03203
rs907620	4q31.23	149522434	NR3C2	383	-2.467	0.013629	0.3296	0.284	0.01569
rs1490453	4q31.23	149540796	NR3C2	268	-2.516	0.011877	0.137	0.163	0.00999
rs1512327	4q31.23	149541829	NR3C2	435	2.658	0.00787	0.4551	0.465	0.00708
rs1994624	4q31.23	149550372	NR3C2	379	-3.317	0.000911	0.00000029	0.404	0.00069
rs17582031	4q31.23	149551098	NR3C2	196	-2.261	0.023775	0.2747	0.105	0.02464
rs16998733	4q31.23	149556858	NR3C2	206	-2.667	0.007648	0.371	0.11	0.00809
rs13118022	4q31.23	149565037	NR3C2	422	-3.406	0.000659	0.2302	0.389	0.00066
rs6536024	4q31.3	155762819		432	2.433	0.014977	0.01578	0.457	0.0271
rs7654093	4q31.3	155764522		354	-2.984	0.002843	0.02297	0.254	0.00356
rs17374025	4q31.3	155831099		213	2.381	0.017263	0.002185	0.125	0.01278
rs4704496	5q14.1	77660704	SCAMP1	318	2.192	0.02841	0.5418	0.208	0.02813
rs9367203	6p21.1	44611945		376	3.949	0.000079	1	0.274	0.00005
rs1535518	6p21.1	44621377		230	3.241	0.001189	0.2029	0.13	0.00129
rs4141996	6p21.1	44622585		282	3.194	0.001402	0.8304	0.16	0.00173
rs6923763	6p21.1	44611148		201	-2.905	0.003675	1	0.11	0.00673
rs1322658	6p21.1	44635848		194	-2.73	0.006326	0.6195	0.1	0.01434
rs16872008	6p21.1	44584757		130	2.61	0.009051	1	0.062	0.01029
rs1885663	6p21.1	44617244		321	2.518	0.011818	0.3915	0.21	0.00974
rs9349292	6p21.1	44607781		277	2.426	0.01528	0.4489	0.156	0.01203

rs2146347	6p21.1	44597692		412	2.34	0.019297	0.6458	0.315	0.01983
rs477011	6p21.1	44743718		413	2.302	0.021346	0.1371	0.366	0.01801
rs12191328	6p21.1	44745757		390	2.256	0.024083	0.06144	0.315	0.01637
rs2396258	6p21.1	44596736		451	2.255	0.024162	0.4757	0.4	0.02935
rs6922821	6p21.1	44711480		128	-2.177	0.02951	0.6254	0.064	0.02038
rs1283917	6p21.1	44695769		348	-2.045	0.040898	2.73E-23	0.192	0.01223
rs9472290	6p21.1	44597785		362	2.042	0.041115	0.5728	0.229	0.04091
rs932679	6p21.1	44609668		313	-1.976	0.048164	0.4686	0.197	0.05832
rs10249209	7p14.1	37325626	ELMO1	293	-2.923	0.003472	0.4227	0.172	0.00238
rs6947058	7p14.1	37326734	ELMO1	402	2.851	0.004356	0.469	0.319	0.00239
rs17136677	7p14.1	37381813	ELMO1	73	-2.544	0.010956	0.6269	0.029	0.00649
rs2893061	7p15.3	21960292	CDCA7L	72	-2.54	0.011085	0.1675	0.05	0.00977
rs4722069	7p15.3	21911302	CDCA7L	348	-2.232	0.025609	0.2325	0.215	0.0364
rs2724003	7p14.1	37324120	ELMO1	300	-2.082	0.037344	0.289	0.181	0.02556
rs1420422	7p14.1	37186278	ELMO1	262	-2.028	0.042534	0.9107	0.151	0.0429
rs2463940	10q21.1	57076231	ZWINT	451	2.814	0.0049	0.2761	0.469	0.00751
rs2243510	10q21.1	57087819	ZWINT	438	2.032	0.042118	0.4255	0.366	0.04513
rs2461911	10q21.1	57078480	ZWINT	386	2.022	0.043209	0.6712	0.273	0.06135
rs1546587	11q25	130861460	NTM	129	-3.582	0.000341	0.3115	0.058	0.3134
rs12576852	11q25	130847995	NTM	121	-3.432	0.000599	0.1731	0.054	0.00043
rs4937665	11q25	131239994	NTM	260	-3.391	0.000697	0.7356	0.151	0.00242
rs1036433	11q25	131261645	NTM	453	3.312	0.000927	0.391	0.496	0.06493
rs4937664	11q25	131239876	NTM	263	-3.167	0.001539	0.7376	0.152	0.3955
rs7933020	11q25	130843833	NTM	136	-3.129	0.001752	0.08227	0.061	0.8076
rs7943905	11q25	131270348	NTM	262	-3.108	0.001883	1	0.144	0.8175
rs505595	11q25	131420821	NTM	438	3.043	0.002341	0.6391	0.418	1
rs2037784	11q25	131218550	NTM	236	-2.943	0.003256	0.8967	0.126	0.7556
rs4937672	11q25	131499942	NTM	465	-2.933	0.003361	0.003327	0.426	0.7924
rs554928	11q25	131424270	NTM	439	-2.927	0.003427	0.819	0.48	0.1446
rs726371	11q25	131388635	NTM	443	2.916	0.003546	0.5616	0.435	0.161
rs7112023	11q25	130855991	NTM	441	-2.897	0.00377	0.9526	0.406	0.03925
rs1939380	11q25	131383113	NTM	413	2.875	0.004036	0.6938	0.315	0.223
rs7943322	11q25	131532819	NTM	448	-2.706	0.006812	0.3096	0.393	0.144
rs656644	11q25	131287579	NTM	318	-2.629	0.008555	0.8568	0.199	0.0234
rs7104063	11q25	131258973	NTM	431	-2.61	0.009058	0.1644	0.499	0.3988
rs10894536	11q25	131718194	NTM	174	-2.587	0.009685	0.2602	0.087	0.5579
rs1790181	11q25	131459357	NTM	462	-2.576	0.009991	0.2082	0.481	0.00189
rs11222930	11q25	131483352	NTM	460	-2.568	0.010238	0.08581	0.485	0.3018
rs564266	11q25	131246136	NTM	463	-2.556	0.010584	0.1824	0.438	0.05943
rs11222627	11q25	130831003	NTM	171	-2.555	0.010619	0.5854	0.085	0.08996
rs12421680	11q25	130856178	NTM	426	-2.531	0.011376	0.5278	0.348	0.02365
rs11222927	11q25	131481961	NTM	398	2.507	0.012191	0.4083	0.292	0.07244
rs542216	11q25	131427861	NTM	399	2.468	0.013588	0.4056	0.286	0.2516
rs487303	11q25	131293427	NTM	392	2.434	0.014941	0.4168	0.261	0.1354

rs10894453	11q25	131193607	NTM	468	-2.426	0.015253	0.188	0.478	0.5374
rs496368	11q25	131318317	NTM	454	-2.419	0.015551	0.8189	0.476	0.3342
rs9943476	11q25	130867911	NTM	435	-2.399	0.016421	0.7655	0.406	0.2983
rs10791144	11q25	130817549	NTM	90	2.373	0.017659	0.0716	0.042	0.07073
rs10791172	11q25	131185006	NTM	419	-2.354	0.018565	0.1701	0.322	0.7572
rs12577076	11q25	130854126	NTM	423	-2.353	0.018633	0.1598	0.34	1
rs11222862	11q25	131382649	NTM	374	2.348	0.018863	0.454	0.255	0.5684
rs497747	11q25	131301922	NTM	447	-2.336	0.019507	0.8638	0.479	0.7373
rs600097	11q25	131308589	NTM	437	2.306	0.021099	0.504	0.377	0.7217
rs1547898	11q25	131451891	NTM	319	2.254	0.024209	0.003151	0.209	0.0101
rs476378	11q25	131304735	NTM	402	2.251	0.024373	0.3738	0.297	0.9185
rs7101483	11q25	131556078	NTM	434	2.229	0.02581	0.731	0.481	0.8929
rs483097	11q25	131195776	NTM	380	-2.214	0.026845	0.6581	0.264	0.2838
rs10894447	11q25	131165583	NTM	463	2.205	0.027431	0.06262	0.43	0.7585
rs10791184	11q25	131321152	NTM	408	2.171	0.029965	0.6498	0.328	0.1697
rs2846797	11q25	131375703	NTM	449	-2.16	0.030809	0.6808	0.421	0.1306
rs11222798	11q25	131170693	NTM	447	-2.146	0.031878	0.4173	0.449	0.2466
rs7925725	11q25	130954575	NTM	358	-2.132	0.033039	0.000000412	0.424	0.4062
rs1349092	11q25	130846582	NTM	465	2.124	0.033679	0.2297	0.48	0.2621
rs9633924	11q25	131325896	NTM	175	2.11	0.034894	0.8488	0.083	0.9419
rs621452	11q25	131853952	NTM	233	2.101	0.035603	0.06969	0.136	0.4893
rs10894478	11q25	131348613	NTM	409	2.091	0.036485	0.2626	0.352	0.2298
rs11222859	11q25	131375406	NTM	380	2.082	0.037372	0.5805	0.287	0.08078
rs1784808	11q25	131401580	NTM	455	2.042	0.041157	0.36	0.472	0.2472
rs1040099	11q25	130958741	NTM	291	2.04	0.04137	0.7577	0.165	0.9081
rs7950545	11q25	130830006	NTM	434	1.989	0.046749	0.3317	0.379	0.1393
rs2442100	11q25	130804925	NTM	102	1.978	0.04793	0.3451	0.048	0.06121
rs11222903	11q25	131452383	NTM	266	1.975	0.048265	0.7458	0.152	0.2848
rs16922585	11p13	31881910		305	1.97	0.048813	0.443	0.18	0.5421
rs1375102	11q25	130866605	NTM	182	1.969	0.048915	0.5924	0.086	0.3552
rs12897286	14q31.3	86057602		451	2.84	0.004507	0.415	0.434	0.00299
rs2373256	14q31.3	86204160		467	2.766	0.005672	0.4235	0.483	0.00711
rs2022630	14q31.3	86013060		150	2.753	0.005912	0.8358	0.075	0.00438
rs12881958	14q31.3	86155057		400	-2.432	0.015021	0.5445	0.3	0.02527
rs17122593	14q31.3	86192767		426	-2.315	0.020619	0.5641	0.329	0.02554
rs11624137	14q31.3	86335520		239	2.159	0.030834	0.4496	0.13	0.02521
rs12897379	14q31.3	86057520		450	2.157	0.030991	0.01162	0.433	0.0175
rs1954132	14q31.3	86029385		173	2.105	0.035259	0.1434	0.083	0.03407
rs12891883	14q31.3	86229607		404	-2.029	0.042446	0.6338	0.296	0.0616
rs1903173	18q21.31	52255331		130	-2.852	0.004341	0.213	0.063	0.00451
rs1626571	18q21.31	51998525		388	-2.299	0.021494	0.4402	0.286	0.02497
rs2191692	18q21.31	51997766		375	-2.013	0.044067	0.3968	0.283	0.05026
rs13039861	20q13.11	41338072		163	-2.198	0.027935	0.5683	0.08	0.0375
rs6030819	20q13.11	41449455		309	2.605	0.009193	0.2042	0.199	0.0112

rs8116375	20q13.11	41450487		218	-2.067	0.038707	0.3353	0.143	0.02941
rs2904404	20q13.2	53210038		130	2.894	0.003806	1	0.061	0.00371
rs2148694	20q13.2	53214464		177	2.985	0.002837	0.1757	0.091	0.00144
rs6014310	20q13.2	53215688		132	2.969	0.002987	1	0.061	0.00259
rs11086499	20q13.2	53405071		429	-2.082	0.037305	0.8171	0.444	0.04303
rs56840	20q13.2	53480643		453	-2.044	0.040943	3.53E-25	0.302	0.01245
rs11696400	20q13.2	53608133		205	2.64	0.008298	1	0.104	0.01136
rs17304222	20q13.2	53610608		205	2.651	0.008028	0.8773	0.104	0.01035
rs3848692	20q13.2	53613263		39	-2.17	0.03004	1	0.017	0.02607
rs6024454	20q13.2	53826840		335	-2.152	0.031398	0.5911	0.196	0.03304
rs6513132	20q13.2	53829419		337	-2.11	0.034868	0.2854	0.199	0.03105
rs2870678	20q13.2	53833175		440	2.454	0.014113	0.6855	0.45	0.01285
rs6069417	20q13.2	53843024		443	2.184	0.028931	0.8183	0.466	0.02575
rs5915330	Xp11.22	50108660	CCNB3	303	2.512	0.012017	-	0.413	-
rs5961171	Xp11.22	50123486		303	2.911	0.003602	-	0.412	-
dom									
rs13137823	4q31.23	149242356	NR3C2	312	3.524	0.000424	0.3807	0.207	0.00211
rs7693077	4q31.23	149339274	NR3C2	251	-2.978	0.002904	0.1679	0.155	0.0049
rs3846300	4q31.23	149315756	NR3C2	347	2.674	0.007497	0.0000808	0.243	0.00783
rs13118022	4q31.23	149565037	NR3C2	339	-2.614	0.00895	0.2302	0.389	0.00066
rs1994624	4q31.23	149550372	NR3C2	312	-2.603	0.00924	0.00000029	0.404	0.00069
rs10017077	4p15.33	12769886		278	2.6	0.009324	0.5489	0.17	0.01274
rs907620	4q31.23	149522434	NR3C2	338	-2.593	0.00952	0.3296	0.284	0.01569
rs7654093	4q31.3	155764522		320	-2.511	0.012026	0.02297	0.254	0.00356
rs2276932	4q31.23	149203771	NR3C2	141	-2.45	0.014275	0.2317	0.064	0.02105
rs1512327	4q31.23	149541829	NR3C2	315	2.443	0.01457	0.4551	0.465	0.00708
rs16998733	4q31.23	149556858	NR3C2	203	-2.394	0.016667	0.371	0.11	0.00809
rs12641157	4q31.23	149206745	NR3C2	338	-2.339	0.019353	0.938	0.242	0.00584
rs13143512	4p15.33	12493999		350	2.264	0.023591	0.4881	0.293	0.08741
rs13142954	4q31.23	149249477	NR3C2	335	2.257	0.024004	0.0833	0.225	0.00928
rs17374025	4q31.3	155831099		208	2.234	0.025455	0.002185	0.125	0.01278
rs1021956	4q31.23	149198624	NR3C2	304	-2.221	0.026365	0.346	0.187	0.03228
rs1490453	4q31.23	149540796	NR3C2	258	-2.195	0.028142	0.137	0.163	0.00999
rs11945798	4p15.33	12378330		83	2.138	0.032554	0.677	0.036	0.03596
rs12649713	4p15.33	12733566		250	-2.134	0.03281	0.05063	0.161	0.05578
rs6845865	4q31.23	149194052	NR3C2	263	2.073	0.038209	1	0.163	0.01846
rs939367	4p15.33	12336095		301	2.062	0.03923	0.7315	0.495	0.1955
rs907618	4q31.23	149522813	NR3C2	317	-2.039	0.041477	0.07823	0.23	0.1297
rs17581570	4q31.23	149433693	NR3C2	314	-2.038	0.041554	0.1823	0.218	0.08678
rs4513547	4q31.23	149506946	NR3C2	319	-2.008	0.044695	0.06014	0.237	0.1258
rs9307847	4q31.23	149546971	NR3C2	312	-1.991	0.046464	0.03871	0.232	0.1356
rs4704496	5q14.1	77660704	SCAMP1	299	2.22	0.026438	0.5418	0.208	0.02813
rs4141996	6p21.1	44622585		275	3.115	0.001841	0.8304	0.16	0.00173
rs1535518	6p21.1	44621377		227	3.023	0.002502	0.2029	0.13	0.00129

rs6923763	6p21.1	44611148		198	-2.726	0.00641	1	0.11	0.00673
rs1322658	6p21.1	44635848		194	-2.695	0.007043	0.6195	0.1	0.01434
rs9367203	6p21.1	44611945		342	2.61	0.00906	1	0.274	0.00005
rs12191328	6p21.1	44745757		336	2.566	0.0103	0.06144	0.315	0.01637
rs10948152	6p21.1	44730276		306	2.411	0.01591	0.0297	0.292	0.2477
rs16872008	6p21.1	44584757		129	2.371	0.017749	1	0.062	0.01029
rs2146347	6p21.1	44597692		357	2.334	0.019585	0.6458	0.315	0.01983
rs1283917	6p21.1	44695769		348	-2.285	0.022296	2.73E-23	0.192	0.01223
rs2504855	6p24.1	12736724		364	-2.236	0.025372	0.2753	0.302	0.09007
rs1885663	6p21.1	44617244		301	2.176	0.02955	0.3915	0.21	0.00974
rs1021129	6p21.1	44735522		343	2.147	0.03177	0.2785	0.276	0.07479
rs927485	6p21.1	44646117		363	-2.073	0.038203	0.1338	0.262	0.09423
rs12205124	6p21.1	44793705		163	-2	0.045542	0.3356	0.08	0.06667
rs477011	6p21.1	44743718		339	1.983	0.047387	0.1371	0.366	0.01801
rs687878	6p21.1	44814768		340	1.976	0.048146	0.549	0.251	0.1784
rs9349292	6p21.1	44607781		273	1.961	0.049837	0.4489	0.156	0.01203
rs4723651	7p14.1	37437683	ELMO1	351	2.698	0.006975	0.2647	0.421	0.2254
rs17136677	7p14.1	37381813	ELMO1	73	-2.606	0.009161	0.6269	0.029	0.00649
rs2893061	7p15.3	21960292	CDCA7L	72	-2.535	0.011238	0.1675	0.05	0.00977
rs1420422	7p14.1	37186278	ELMO1	253	-2.307	0.021041	0.9107	0.151	0.0429
rs11973001	7p14.1	37323478	ELMO1	329	-2.299	0.021494	0.8728	0.23	0.06797
rs6947058	7p14.1	37326734	ELMO1	351	2.264	0.023563	0.469	0.319	0.00239
rs10249209	7p14.1	37325626	ELMO1	280	-2.214	0.026805	0.4227	0.172	0.00238
rs4722069	7p15.3	21911302	CDCA7L	331	-1.977	0.048078	0.2325	0.215	0.0364
rs2153137	10q21.1	57253933	ZWINT	356	-2.541	0.011056	0.8111	0.398	0.2432
rs2243510	10q21.1	57087819	ZWINT	360	2.488	0.01286	0.4255	0.366	0.04513
rs2461911	10q21.1	57078480	ZWINT	344	2.268	0.02331	0.6712	0.273	0.06135
rs2463940	10q21.1	57076231	ZWINT	331	2	0.045552	0.2761	0.469	0.00751
rs1546587	11q25	130861460	NTM	129	-3.796	0.00015	0.3115	0.058	0.3134
rs4937672	11q25	131499942	NTM	361	-3.637	0.000275	0.003327	0.426	0.7924
rs12576852	11q25	130847995	NTM	121	-3.631	0.00028	0.1731	0.054	0.00043
rs4937665	11q25	131239994	NTM	253	-3.48	0.0005	0.7356	0.151	0.00242
rs7943322	11q25	131532819	NTM	359	-3.469	0.000522	0.3096	0.393	0.144
rs7933020	11q25	130843833	NTM	136	-3.42	0.000627	0.08227	0.061	0.8076
rs7943905	11q25	131270348	NTM	254	-3.389	0.000702	1	0.144	0.8175
rs4937664	11q25	131239876	NTM	256	-3.292	0.000995	0.7376	0.152	0.3955
rs11222627	11q25	130831003	NTM	169	-3.032	0.00243	0.5854	0.085	0.08996
rs2037784	11q25	131218550	NTM	230	-3.001	0.002687	0.8967	0.126	0.7556
rs4468361	11q25	131515327	NTM	369	-2.925	0.003444	0.1382	0.331	0.2155
rs7480231	11q25	131503601	NTM	331	-2.899	0.003749	0.4193	0.454	0.06545
rs7104063	11q25	131258973	NTM	285	-2.83	0.004656	0.1644	0.499	0.3988
rs564266	11q25	131246136	NTM	344	-2.764	0.005715	0.1824	0.438	0.05943
rs600097	11q25	131308589	NTM	353	2.745	0.006044	0.504	0.377	0.7217
rs7110535	11q25	130991544	NTM	315	-2.628	0.008587	0.4151	0.431	0.778

rs9633924	11q25	131325896	NTM	173	2.619	0.008817	0.8488	0.083	0.9419
rs1547898	11q25	131451891	NTM	295	2.568	0.010215	0.003151	0.209	0.0101
rs7112023	11q25	130855991	NTM	347	-2.553	0.010694	0.9526	0.406	0.03925
rs7932411	11q25	131737742	NTM	340	-2.523	0.011635	0.6535	0.337	0.5391
rs1793258	11q25	132089658	NTM	296	-2.484	0.013003	0.03037	0.155	0.6559
rs7925725	11q25	130954575	NTM	286	-2.483	0.013014	0.000000412	0.424	0.4062
rs11222862	11q25	131382649	NTM	343	2.449	0.014307	0.454	0.255	0.5684
rs505595	11q25	131420821	NTM	340	2.428	0.015175	0.6391	0.418	1
rs542216	11q25	131427861	NTM	359	2.412	0.015853	0.4056	0.286	0.2516
rs554928	11q25	131424270	NTM	321	-2.4	0.016386	0.819	0.48	0.1446
rs726371	11q25	131388635	NTM	335	2.394	0.016665	0.5616	0.435	0.161
rs1375102	11q25	130866605	NTM	181	2.391	0.016785	0.5924	0.086	0.3552
rs1939380	11q25	131383113	NTM	360	2.38	0.017327	0.6938	0.315	0.223
rs656644	11q25	131287579	NTM	303	-2.374	0.017606	0.8568	0.199	0.0234
rs10791144	11q25	130817549	NTM	90	2.352	0.018662	0.0716	0.042	0.07073
rs7104573	11q25	131509038	NTM	248	-2.25	0.02442	0.07606	0.154	0.7227
rs10750491	11q25	131200642	NTM	354	-2.221	0.026326	0.6242	0.371	0.9881
rs4128348	11q25	132194365	NTM	290	-2.209	0.027189	0.09632	0.473	NA
rs12577076	11q25	130854126	NTM	371	-2.208	0.027245	0.1598	0.34	1
rs11222930	11q25	131483352	NTM	320	-2.144	0.032048	0.08581	0.485	0.3018
rs10894447	11q25	131165583	NTM	343	2.13	0.033148	0.06262	0.43	0.7585
rs633040	11q25	131236636	NTM	349	-2.13	0.03315	0.5336	0.358	0.178
rs10894536	11q25	131718194	NTM	173	-2.121	0.033937	0.2602	0.087	0.5579
rs1547895	11q25	131452190	NTM	311	-2.107	0.035147	0.3102	0.245	0.3357
rs3925045	11q25	131494847	NTM	295	2.103	0.035484	0.03028	0.173	0.2039
rs7937519	11q25	131522577	NTM	178	-2.082	0.037368	0.123	0.09	0.1896
rs6590640	11q25	131921807	NTM	291	-2.077	0.037809	0.5682	0.487	0.5207
rs11222798	11q25	131170693	NTM	328	-2.063	0.039135	0.4173	0.449	0.2466
rs11222871	11q25	131407253	NTM	237	-2.059	0.039454	0.4787	0.142	0.1514
rs12421680	11q25	130856178	NTM	368	-2.045	0.040864	0.5278	0.348	0.02365
rs12286374	11q25	131733839	NTM	344	-1.989	0.046657	0.4971	0.3	0.6236
rs10791184	11q25	131321152	NTM	350	1.985	0.047115	0.6498	0.328	0.1697
rs11222629	11q25	130831513	NTM	340	1.978	0.047958	0.404	0.249	0.00078
rs12272290	11q25	130774138	NTM	318	-1.968	0.049067	0.00266	0.325	0.7519
rs2442100	11q25	130804925	NTM	102	1.965	0.049469	0.3451	0.048	0.06121
rs7937152	11q25	131441704	NTM	326	-1.963	0.049654	0.3132	0.4	0.0113
rs12897286	14q31.3	86057602		339	2.593	0.009525	0.415	0.434	0.00299
rs2022630	14q31.3	86013060		150	2.541	0.011064	0.8358	0.075	0.00438
rs2373256	14q31.3	86204160		317	2.397	0.016545	0.4235	0.483	0.00711
rs11624137	14q31.3	86335520		239	2.354	0.018562	0.4496	0.13	0.02521
rs12897379	14q31.3	86057520		344	2.296	0.021674	0.01162	0.433	0.0175
rs12881958	14q31.3	86155057		348	-2.19	0.028519	0.5445	0.3	0.02527
rs1959307	14q31.3	86133887		300	1.96	0.04994	0.1597	0.202	0.1815
rs4800940	18q21.31	52058223		349	-2.752	0.005922	0.2192	0.42	0.05331

rs1903173	18q21.31	52255331		129	-2.69	0.007136	0.213	0.063	0.00451
rs4801018	18q21.31	52079434		322	-2.251	0.02437	0.000811	0.438	0.1381
rs1789570	18q21.31	52009049		353	2.063	0.039067	0.6723	0.384	0.08072
rs17205646	18q21.31	52096196		226	-2.045	0.040827	0.5147	0.125	0.03651
rs4619678	20q13.2	53245444		324	-2.957	0.003103	0.2031	0.445	0.1054
rs6014310	20q13.2	53215688		131	2.8	0.005114	1	0.061	0.00259
rs2148694	20q13.2	53214464		175	2.744	0.006068	0.1757	0.091	0.00144
rs2904404	20q13.2	53210038		129	2.721	0.006507	1	0.061	0.00371
rs6023943	20q13.2	53241567		334	-2.545	0.01094	0.07636	0.421	0.1726
rs6513132	20q13.2	53829419		322	-2.494	0.012625	0.2854	0.199	0.03105
rs6024454	20q13.2	53826840		321	-2.486	0.012905	0.5911	0.196	0.03304
rs6023940	20q13.2	53239401		339	-2.461	0.013839	0.3422	0.407	0.1132
rs11696400	20q13.2	53608133		202	2.459	0.013914	1	0.104	0.01136
rs17304222	20q13.2	53610608		202	2.454	0.014133	0.8773	0.104	0.01035
rs6127423	20q13.2	53240850		329	-2.426	0.015263	0.2987	0.452	0.1613
rs6024378	20q13.2	53769588		332	-2.419	0.015574	1	0.406	0.2536
rs2426554	20q13.2	53300235		346	-2.395	0.016635	0.4609	0.371	0.1528
rs11086499	20q13.2	53405071		334	-2.362	0.018198	0.8171	0.444	0.04303
rs3848692	20q13.2	53613263		39	-2.302	0.021341	1	0.017	0.02607
rs2749796	20q13.2	53576499		328	-2.204	0.027524	0.8717	0.229	0.2119
rs8116375	20q13.11	41450487		210	-2.143	0.032086	0.3353	0.143	0.02941
rs2244651	20q13.2	53586892		320	-2.123	0.033765	0.6852	0.229	0.1907
rs6069152	20q13.2	53211922		344	-2.075	0.037993	0.1346	0.395	0.1174
rs4812708	20q13.11	41442583		329	-2.027	0.042648	0.6398	0.428	0.1364
rs2118231	20q13.2	53976926		321	-2.002	0.045306	0.3309	0.481	0.05068
rs5915330	Xp11.22	50108660	CCNB3	282	2.661	0.007799	-	0.413	-
rs5961171	Xp11.22	50123486		282	3.082	0.002054	-	0.412	-

Fam#: number of informative families.

Ad: additive model.

Dom: dominant model.

Position is based on NCBI Genome Build 36.3.

MAF: minor allele frequency of the SNP.

EMP: p-value using permutation test.

HWE: p-value using Hardy-Weinberg Equilibrium Test

FBAT: family based association test

VITA

YUE PAN

- Education: B.S. Mathematics, Shandong Normal University
Jinan, ShanDong, China, 2008
M.S. Mathematical Science, East Tennessee State
University Johnson City, Tennessee, 2010
- Professional Experience: Graduate Assistant, East Tennessee State
University, Johnson City, Tennessee, 2008–2010
- Publications: Yue Pan and Ke-sheng Wang, “Spousal Concordance
in Academic Achievements and Intelligence,”
Genetics and Molecular Biology (submitted),
(2010)
Yue Pan and Ke-sheng Wang, “ Family-based
association studies identified novel loci associated
with intelligence,”
Brain, Behavior and Immunity (will be submitted),
(2010)