A POSTERIOR PROBABILITY OF LINKAGE & ASSOCIATION STUDY OF 111 AUTISM CANDIDATE GENES

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ABSTRACT OF THE DISSERTATION

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Autism is a neurodevelopmental disorder with a complex genetic basis. In this study we investigated the possible involvement of 111 candidate genes in autism by studying 386 patient families from the Autism Genetic Resource Exchange (AGRE). These genes were selected based on their functions that relate to the neurotransmission or central developmental system. In phase 1 of the study, 1497 tagSNPs were selected to efficiently capture the haplotype information of each gene and were genotyped in 265 AGRE nuclear families. The cleaned genotype data were analyzed through the Kelvin program to compute values of Posterior Probability of Linkage (PPL) and Posterior Probability of LD given linkage (PPLD), which directly measure the probability of linkage and/or association. Consistent supportive evidence for linkage was observed for EPHB6-EPHA1 locus at the 7q34 region by two- and multi-point PPL analysis. Some evidence for association was obtained from the intronic SNP rs2242601 of the EPHA1 gene (PPLD = 10.4%), and multiple SNPs from the MECP2 gene at Xq28 (PPLD range

from 5~9%). Using a subset of the newly released AGRE genotype data from the Affymetrix 5.0 high-density SNP array, further evidence for association was obtained for 6 markers located 90kb distal of EPHA1 gene (PPLD range from 21% to 40%).

In phase 2 of this study, in an attempt to conduct fine mapping as well as to replicate our phase 1 results in a set of 123 additional AGRE family samples, additional SNPs were selected from the EPHA1 and MECP2 gene region for fine-scale analysis. Strong support of association with autism was observed for the markers downstream of the EPHA1 gene using the original families, with the SNP rs7801889 showing a high PPLD value of 62%. Markers from the MECP2 gene region remained moderately associated with PPLD values around 8%. Nonetheless, none of the SNPs showed any support for association in the additional family samples. These mixed preliminary results suggested the polymorphisms within and downstream of the Ephrin receptor A1 gene as potential novel susceptibility loci for autism. Limited support for the role of MECP2 in autism etiology was also observed.

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DEDICATION

To my parents Kun Chen and Jialun Tang

for their unconditional love through all my life.

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Chapter 1. Introduction

As a childhood-onset neurodevelopmental and neuropsychiatric disorder, autism causes severe impairment in communication and social function, as well as repetitive/stereotyped behaviors. Studies have shown that genetic factors contribute strongly to autism. In recent years, investigations such as genome-wide scans and other approaches have identified multiple chromosomal regions that show linkage to autistic phenotypes. Due to the moderate resolution of such approaches, however, there are still hundreds of genes under the linkage peaks that need to be examined to assess their potential role in autism. Studies on phenotypic abnormalities of autism have suggested a number of neurobiological pathways, such as certain neurotransmitter systems, that may be involved in autism, although the precise mechanism of involvement for these functional pathways remains to be elucidated.

Given the complex and polygenic nature of the genetic contribution to autism, we proposed to identify associated polymorphism markers by employing a large-scale candidate gene approach to study the genetics of autism:

Aim 1: Use published neurobiological as well as genome-wide linkage studies as the basis to select candidate genes that are likely to be related to autism. We have selected 111 target genes from a large set of candidate genes that were judged to be likely candidate for autism.

Aim 2: Analyze samples from the comprehensive collection of autism families that the autism research community has studied in the past several years, and which are stored in the Rutgers University Cell and DNA Repository (RUCDR). Hundreds of nuclear and extended families have already been collected with at least two autistic children, this DNA sample collection serves as a precious resource for genetics studies.

Aim 3: Simultaneously determine the genotypes of markers in each of the 111 candidate genes in selected families (two parents plus two or more autistic children for each family). The genotyping markers in our study will be the most common type of genetic markers in the human genome --- single nucleotide polymorphisms (SNP). Because of the large-scale nature of the candidate genes in the study, and because these candidate genes encompass the known genetic scan signals as well as the neurobiological pathways likely to be involved, multiple genetic markers are expected to be identified that correlate with the phenotype of autism.

Aim 4: The preliminary result from this pilot study will allow Rutgers scientists to further ascertain and extend the initial “hits” from this project. It is expected that the follow up studies will allow us to focus on novel autism-related loci and genes, and to attract funding from the National Institutes of Health to study these autism genes to elucidate their underlying mechanism.

Chapter 2. Background

2.1 Autism

Autism (MIM209850) is an early onset pervasive developmental disorder with a complex etiology. As defined in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association 1994), the three main characteristics of autism are impairments in social interaction, impairments in communication, restricted and repetitive behavior. The diagnosis of autism is usually made in children before age of three, using a combination of standardized protocols, such as a semi-structured parent interview using the Autism Diagnostic Interview–Revised (ADI-R), and observation and interactions with the child using the Autism Diagnostic Observation Schedule (ADOS). Autism is part of a group of conditions known as autism spectrum disorders (ASD). This is a wide spectrum of developmental disorders of the brain including autistic disorder, Asperger disorder, childhood disintegrative disorder (CDD) and pervasive developmental disorder-not otherwise specified (PDD-NOS). In Asperger disorder, affected individuals are characterized by difficulties in social interaction and by restricted, stereotyped patterns of behavior, interests and activities, although having no general delay in language or cognitive development. CDD is a condition in which young children develop normally until age 3 or 4, but then demonstrate a severe loss of social, communication and other skills.

There is persuasive evidence that autism is a heritable complex genetic disorder. Twin studies show the concordance rate among monozygotic (MZ) twins is between 60 and 90%, while among dizygotic (DZ) twins this rate is 0% to 10%. This high MZ concordance rate indicates that genetic inheritance is the predominant cause (Steffenburg,

Gillberg et al. 1989). Epidemiologic studies report an ASD prevalence of 3 to 6/1000, with a male to female ratio of 4:1 (Shao, Wolpert et al. 2002; Fombonne 2003; Yeargin-Allsopp, Rice et al. 2003). This ratio remains unexplained despite the contribution of a few well characterized X-linked disorders (e.g., Fragile X Syndrome, Rett syndrome), and male-to-male transmission in a number of families rules out X-linkage as the prevailing mode of inheritance (Shao, Wolpert et al. 2002; Yonan, Alarcon et al. 2003). Other than the strong genetic basis, some influence of environmental factors is also likely to be involved in the etiology of ASD. These factors may include toxic exposures (Goldman and Koduru 2000), teratogens (Miyazaki, Narita et al. 2005), perinatal insults (Laviola, Adriani et al. 2004), and a possible and controversial link to the MMR vaccine (Casiday, Cresswell et al. 2006).

There is marked phenotypic diversity in autism, with disease symptoms varying greatly between individuals. One well-accepted explanation is that wide phenotypic variability is likely due to the effect of multiple genes and the interactions among them. It has been estimated that about 2 to 15 genes with various effects may contribute to autism susceptibility (Risch, Spiker et al. 1999). Another possible model considers the underlying effects of epigenetic mechanisms such as DNA methylation and post-translational modification. Because such changes may be due to mutation, maternal exposures, or postnatal experiences, the modulation of gene expression can be the result of environmental factors and parent of origin effects (Chen, Sharma et al. 2002; Abdolmaleky, Smith et al. 2004). Support for a role of epigenetic mechanisms in the etiology of ASD is provided by the case of Rett syndrome. This single gene disorder commonly associated with autism arises because of mutation in MeCP2, a key regulator

of gene expression through modulation of chromatin structure (LaSalle, Hogart et al. 2005).

Although autism is a heterogeneous disorder with respect to etiology, scientists have identified certain pathophysiological features shared among affected individuals. For example, increased brain size appears to be the most consistent morphometric observations reported in autism. A recent clinical study found that a head circumference at or above 75th percentile is associated with more impaired adaptive behaviors and with less impairment in IQ measures and motor and verbal language development (Sacco, Militerni et al. 2007). Neuroimaging studies have also demonstrated an overall enlargement of brain volume associated with increased subcortical white matter in the frontal lobe, and abnormal patterns of growth in the cerebral cortex and hippoccampal formations. The cerebellum, a structure that is important in modulating a variety of cognitive and motor functions, has also been consistently reported to be involved in the pathophysiology of autism. The cerebellar abnormalities include general hypoplasia and a reduced number of Purkinje cells. (Kemper and Bauman 1998; Lee, Martin-Ruiz et al. 2002; Vargas, Nascimbene et al. 2005). One of the most recent studies found 40% lower expression of GAD67 mRNA in the cerebellar Purkinje cells of individuals with autism when compared to unaffected (Yip, Soghomonian et al. 2007). In addition, results from functional MRI studies have also shown that the cerebellum is active during activities like language generation, attention, and problem solving (Allen and Courchesne 2003; Corina, San Jose-Robertson et al. 2003; McDermott, Petersen et al. 2003).

2.2 Linkage screen

The main goal of the whole-genome linkage screens is to find regions with possible susceptibility genes for further fine mapping by association studies and detailed candidate gene screening. Genome wide Linkage analysis aims to look throughout the entire genome for cosegregation between disease loci and polymorphic markers within families. Increased allele sharing among affected family members, or the alleles that segregate in a pattern that fits specific disease models are identified statistically and provide clues for determining the location of disease susceptibility loci.

Beginning in 1998, there have been 15 genome-wide linkage screens for autism and ASD (IMGSAC 1998; Barrett, Beck et al. 1999; Philippe, Martinez et al. 1999; Risch, Spiker et al. 1999; Buxbaum, Silverman et al. 2001; IMGSAC 2001; Liu, Nyholt et al. 2001; Alarcon, Cantor et al. 2002; Auranen, Vanhala et al. 2002; Shao, Wolpert et al. 2002; Yonan, Alarcon et al. 2003; McCauley, Li et al. 2005; Lauritsen, Als et al. 2006; Ylisaukko-oja, Alarcon et al. 2006; Allen-Brady, Miller et al. 2008). Most of these screens used independent samples, though there is some overlap due to the availability of shared sample collections to the investigators. These studies reported 8 loci from chromosome locations at 1p, 2q, 7q and 13q meet the standard of significant linkage (LOD>3.3). Three of the most interesting regions with frequent and strong suggestive evidence of linkage between studies are located on 2q, 7q, and 16p. However, the linked regions span a relatively large genetic distance and contain hundreds of genes. Some other regions have also been reported in more than one study. These include regions on 1p, 4q, 5p, 6q, 10q, 10p, 13q, 15q, 17q, 19p, 19q, and Xq. The variable results between

studies are likely the result of sample heterogeneity by use of different classification criteria or sample population.

Although the gender difference in the prevalence of autism is considerable, most studies assessing the X-chromosome for linkage have been unsuccessful (Hallmayer, Pintado et al. 1994; Hallmayer, Spiker et al. 1996). Alternative approaches have been utilized to explore the skewed gender distribution. For example, independent genome scan studies using male only sib-pair samples disclose suggestive linkage findings on chromosome locations at 7q, 16q, and two significant hits at 17q (Stone, Merriman et al. 2004; Cantor, Kono et al. 2005).

2.3 Cytogenetic analysis

Cytogenetic assessments have long been used to identify chromosomal abnormalities in patients with autism. A number of cytogenetic defects such as translocations, duplications, and deletions have been described for some single cases (Castermans, Wilquet et al. 2004; Vorstman, Staal et al. 2006). Although it was estimated that only 3-5% of the cases of autism are associated with gross chromosomal abnormalities, integration of data from linkage analyses and reports of chromosomal abnormalities are helpful to narrow down the genomic regions where candidate genes may be found as potentially involved in the pathogenesis of autism.

The most prevalent cytogenetic abnormality is found at the 15q11-q13 locus with a frequency of 1-4% (Vorstman, Staal et al. 2006). Studies from multiple populations have identified duplications, deletions, and inversions at this locus. This region includes a number of γ -amino butyric acid (*GABA*) receptor subunit genes (*GABRB3*, *GABRA5* and

GABRG3). These genes are involved in the excitatory neural pathways and their malfunctions have been suggested to relate to pathology for autism. Linkage and association studies also provide supportive evidence to the involvement of *GABA* receptors, with the most common positive linkage finding being within the *GABRB3* gene (Menold, Shao et al. 2001; Ashley-Koch, Mei et al. 2006).

Deletions of chromosome region 2q37 and translocation of 7q22-q33 have also been reported to be relevant for the development of autism. Two studies have reported associations between autism and a terminal 2q deletion with the breakpoint within 2q37 (Gallagher, Becker et al. 2003; Lukusa, Vermeesch et al. 2004). The protein reelin (*RELN*), which the coded gene has been localized to a chromosomal translocation region at 7q22, is a large secreted glycoprotein possibly involved in neural migration during development. It has been implicated in the pathogenesis of several psychiatric disorders, and this protein has been found to be expressed significantly less in patients of schizophrenia and psychotic bipolar disorder than in controls (Fatemi, Earle et al. 2000).

2.4 Association study

When specific alleles in neighboring loci tend to be inherited together in the family, or they exist together in certain population, this non-random association of alleles at two or more loci is called Linkage Disequilibrium (LD). Genetic association studies are performed to determine whether a genetic variant is in LD with a disease or trait. By comparing the genotype of genetic variants in affected individuals and in unaffected controls (or unaffected family members), association can be detected if the polymorphism genotype or haplotype exist more often than expected by chance in an individual carrying

the trait. It is believed that the power of association analysis to detect genetic contributions to complex disease is greater than that of linkage studies with equivalent sample size (Risch 2000).

In 2006, a low-density genome-wide association (GWA) study in autism was published (Lauritsen, Als et al. 2006). In this study, samples from 12 subjects with childhood autism and related pervasive developmental disorders (PDDs) and 44 matched controls were collected from the Faroe Islands, a group of islands northwest of Scotland. A total of 601 microsatellite markers distributed throughout the human genome with an average distance of 5.8 cM were genotyped. This study identified 18 that loci passed the significance level of $p \leq 0.01$, which are located on 2q, 3p, 6q, 15q, 16p, and 18q. Notably, locus positions at 2q31.1, 3p25.3, 6q14.3, 12q24.23, and 16p13.3 overlap with previously identified regions from the genome-wide linkage studies.

2.5 Candidate gene study

Candidate genes are genes selected based on their involvement in pathways related to neurodevelopment and/or pathophysiological processes (functional candidates), or genes within the chromosomal interval identified by linkage analysis and/or close to cytogenetic rearrangements associated with the disorder (positional candidates). The purpose of this kind of study is to identify heritable genetic mutations in candidate genes that are associated with the disease. Once candidate genes have been identified, experimental approaches such as real-time PCR can be performed to further identify the RNA product level of the gene. In addition, the creation of animal models through

targeted gene knock-out or mutation provides a complementary approach to assess the role of the candidate risk allele in the pathophysiology of the disorder.

The Homeobox transcription factor gene EN2 on chromosome 7 is a developmental control gene that plays an important role in both the embryonic and post-natal development of the mouse cerebellum. A number of autopsy reports, histological and imaging studies have suggested its involvement in mouse cerebellar pattern formation in the pathophysiology of autism. EN2 mouse mutants have displayed deficits in social behavior across maturation that include decreased play, reduced social sniffing, and less aggressive behavior (Cheh, Millonig et al. 2006). Experiments show that knockout and transgenic mutant mice have a hypoplastic cerebellum with a decrease in the number of Purkinje cells, indicating that EN2 misregulation negatively impacts cerebellar development. It has been observed in multiple datasets that the autism phenotype is strongly associated with two SNPs from the intron of EN2 (Gharani, Benayed et al. 2004; Benayed, Gharani et al. 2005). Two other studies also indicate that these 2 intronic SNPs contribute to autism susceptibility in Han Chinese populations (Wang, Jia et al. 2007; Yang, Lung et al. 2008). Three studies from two independent genome scans also provide some evidence for linkage to this gene region. In a study of the Finnish population, suggestive linkage (LOD = 2.02) to a combined phenotype of ASD and dysphasia was obtained from a marker 170 kb distal of *EN2* (Auranen, Vanhala et al. 2002). Two other studies using subsets of the Autism Genetic Resource Exchange (AGRE) families carried out fine mapping analysis of the region and reported a LOD score of 2.13 and a p value of 0.001 at markers 5.5Mb and 1Mb away from EN2 (Liu, Nyholt et al. 2001; Alarcon, Cantor et al. 2002). Together, these results suggest that EN2 and other genes with similar

functions might affect human cerebellar development and contribute to the etiology of autism.

The GABA receptor gene clusters (*GABRB3*, *GABRA5*, *GABRG3*) have also been considered as possible candidates for ASD. As a primary inhibitory neurotransmitter, GABA is a key regulator of excitability in the mammalian central nervous system. Intracerebroventricular injections of GABA agonists leads to decrease in arterial blood pressure (BP), heart rate (HR), and peripheral sympathetic nerve activity (Antonaccio, Kerwin et al. 1978). Disruption of development of GABAergic interneurons in mice leads to complex neurodevelopmental effects including deficits in socialization, seizures and anxiety (Levitt 2005). Two separate studies by Blatt et al. (2001) and Samaco et al. (2005) have shown a significant decrease in $GABA_A$ receptor binding sites and $GABA_A$ receptor β3 (GABRB3) subunit protein level in multiple brain tissues of subjects with autism when compared with controls. Evidence from autism association and linkage studies have also support for a role of GABA receptor genes on 15q11-q13 in autism samples (Martin, Menold et al. 2000; Menold, Shao et al. 2001; McCauley, Olson et al. 2004; Ma, Whitehead et al. 2005). In a recent study, fourteen known GABA receptor subunit genes were analyzed to look for the genes associated with autism and their possible interactions using a complex modeling system designed to reveal epistatic relationships. SNP markers from four autosomal regions were screened in 470 Caucasian families with autism. Although there was no significant evidence for interaction among the three genes at the 15q12 region, extension of these analyses to GABA receptor genes on other chromosomes revealed significant association between alleles for *GABRA4* and *GABRB1* on chromosome 4 and autism (Ma, Whitehead et al. 2005). In addition, deletion

or duplication of GABR genes also occurs in multiple human neurodevelopmental disorders including Prader-Willi syndrome (PWS) and Angelman syndrome (AS), both of which have behavioral overlap with autism.

Another one of the most extensively studied genes is the serotonin transporter gene (SLC6A4) that is responsible for the active transport of serotonin into neurons, enterochromaffin cells, platelets, and other cells. In the brain, serotonin transporters are located both in perisynaptic membranes of nerve terminals and in dendritic arbors close to serotonin-containing cell bodies in the midbrain. They mediate removal and recycling of released serotonin after neuronal stimulation. Thus, serotonin transporters are essential in the regulation of the magnitude, duration, and spatial distribution of signals reaching serotonin receptors (Murphy, Li et al. 2001). One study has shown a more than 30% increase in platelet serotonin levels in some individuals with autism (Coutinho, Oliveira et al. 2004). Furthermore, serotonin specific reuptake inhibitors (SSRIs), which target SLC6A4, are a major class of antidepressant drugs. This class of drugs has been shown to be effective in reducing hyperactivity, compulsive, and stereotyped behaviors in autism (Hollander, Phillips et al. 2003). The SLC6A4 gene region 17q11 was identified in a genome scan of 345 AGRE families as the strongest linkage finding (P = .00029) (Yonan, Alarcon et al. 2003). The short allele in *SLC6A4* promoter region was also demonstrated to associate with autism markers by Cook et al (1997). Several other groups reported similar evidence but with the long promoter allele (Yirmiya, Pilowsky et al. 2001; Kim, Cox et al. 2002), which indicates a possible higher risk allele from nearby. Nevertheless, negative results were also reported by several groups who found no proof of overtransmission of the gene (IMGAC. 1998) (Persico, Militerni et al. 2000). These

results may reflect the effect of differences in genetic and environmental factors among these studies.

Since it was suggested that postnatal synaptic plasticity might be disrupted in developmental disorders, such as the autism and Rett syndrome, several studies have implicated involvement of synaptic cell-adhesion molecules in autism. These include the genes encoding neuroligins (NLGNs), their binding partners neurexins (NRXNs) and SHANK. Synapses are specialized intercellular junctions dedicated to the transfer of information from a neuron to its target cell. Dysfunction of synaptic cell-adhesion molecules may impair the properties of synapses and disrupts neural networks. In an early study of 2003 (Jamain, Quach et al.), researchers examined the chromosomal region Xp22.3 and found that evidence of mutations in NLGN3 and NLGN4 are involved in ASD. Since then, a number of different mutations, including frameshifts, missense and internal deletions in the NLGN4 gene and the Arg451Cys substitution in the NLGN3 gene, have been observed in autism patients (Feng, Schroer et al. 2006; Kim, Kishikawa et al. 2008; Yan, Noltner et al. 2008; Zahir, Baross et al. 2008). SHANK proteins have been proposed as master organizers of postsynaptic density because of their ability to nucleate multimeric protein complexes in dendritic spines. SHANK3 is a synaptic protein that can bind neuroligins. A study by Durand et al (2007) identified two alterations in SHANK3 in subjects with an ASD but not observed in control individuals. In another report, the authors studied the frequency of DNA sequence and copy-number variants in this gene in 400 Canadian ASD patients. They also found one mutation and two deletions from the SHANK3 gene in a small portion of affected subjects (Moessner, Marshall et al. 2007)

Three studies have assessed the wingless-type mouse mammary tumour virus integration site family member 2 (*WNT2*) gene on chromosome 7. This gene codes for an evolutionarily conserved glycoprotein that is part of a developmentally important signaling pathway. It was shown that mice with a WNT2 protein signaling defect display reduced social interaction and aberrant behaviors similar to phenotype of autism (Cadigan and Nusse 1997). One study reported a nominal association of a 3'UTR 783C>T SNP detected by mutation analysis from two affected siblings with autistic disorder (Wassink, Piven et al. 2001). However, studies from two other groups could not repeat this finding (McCoy, Shao et al. 2002; Li, Nguyen et al. 2004).

In total more than 90 positional or functional candidate genes for autism have been analyzed, but thus far no clear functional effect of any gene has been demonstrated. This might be the result of allelic heterogeneity, sample heterogeneity, small sample sizes, or ethnically distinct backgrounds. In the summary given by Yang and Gill (2007), 17 of these candidate genes are shown to be associated with ASD (markers have $p < 0.05$), 59 genes show no association, and 13 genes give inconsistent result from different publications. The associated genes were reported at 24 separate chromosomal regions and 13 of them are thought to be involved in the development of human brain. These genes are DLX2, TBR1, NEUROD1, HOXA1, DLX6, PTPRZ1, BDNF, NCAM1, DRD2, RELN, UBE3A, EN2, and NRCAM. Among them, DLX2, DLX6, BDNF and UBE3A are also on our autism candidate gene list.

2.6 Gene expression

Gene expression studies aim to identify genes that are differentially expressed in the relevant tissue between patients and controls. It is widely used as an effective way to identify potential candidate genes for further genetic and biological analysis.

Differential gene expression patterns on DNA microarrays in lymphoblastoid cell lines (LCLs) from MZ twins discordant with respect to severity of and/or language impairment were first shown by Hu et al. (2006). Using 3 sets of discordant twin samples from the Autism Genetic Resource Exchange (AGRE) repository, Hu et al. found totally 25 out of 58 pathway network focus genes to be up-regulated at least 1.5-fold in the more severely affected twin relative to the other twin and 19 genes were down-regulated by at least 1.5-fold. They also showed that many of these genes are present in pathways critical to the development and function of the nervous system, and that approximately half of them map to previously-reported chromosomal regions containing autism susceptibility genes or quantitative trait loci. Another genome-wide expression study compared the mRNA expression profile in LCLs from males with autism due to a fragile X mutation, or due to a 15q11–q13 duplication, with non-autistic controls (Nishimura, Martin et al. 2007). They were able to identify 68 genes that were dysregulated in both types of autism patients compared to controls. Although LCL is a blood derived cell line, many genes identified overlap with linkage and association studies supporting utility of this tissue as a potential surrogate for brain.

2.7 Copy number variation

A number of autistic individuals with unaffected family members may result from copy number variations (CNVs) — gains and losses of large chunks of DNA sequence, including deletions, insertions, duplications and complex multi-site variants. Sporadic cases have been examined to identify candidate genetic loci involved in autism. Sebat et al. (2007) performed comparative genomic hybridization (CGH) on the genomic DNA of 264 patient families and 99 control families to detect CNVs associated with autism. They found *de novo* CNVs exist in 12 out of 118 (10%) patients with sporadic autism. While some of these altered loci had been identified in previous studies, many were unique to the sporadic cases examined in this study. Another interesting result came from the Autism Genome Project Consortium who assessed the effects of CNV while performing large scale linkage scan using the Affymetrix 10K SNP arrays on 1,168 autistic families. Their hypothesis is that rare *de novo* CNVs could be a source of noise or heterogeneity to heritable autism and decreases performance in linkage analyses. Thus, linkage signals from major loci could be amplified if the subset of families with rare CNV risk alleles were removed. After taking out 102 such "CNV families" from 739 complete family set, they detected increased linkage signal from two suggestive regions at chromosomes 15q and 11p (Szatmari, Paterson et al. 2007).

Although many tests using genetic linkage, association, and expression methods have been carried out in autism samples, there are still no definitive trait loci or genes identified as causes of the disorder. This may be due to various reasons, including use of different genetic markers, variations in the statistical methods employed, diverse ethnic

populations, varying power of each sample, sample heterogeneity, and other confounding factors. Despite the discrepant results from previous publications, efforts have been made to find a pattern that points to specific genes and/or genome regions that are likely to contain risk variants. In a recent comprehensive review of linkage, association, and expression studies in autism, the authors performed a literature search using the PubMed database trying to find evidence of convergence (Yang and Gill 2007). Fig.1 shows their distributive diagram of loci or genes that may be correlated with autism. By studying the pattern of all these results, they suggested seven regions of the genome that can be the emphasis for future research: 7q21.2–q36.2, 16p12.1–p13.3, 6q14.3–q23.2, 2q24.1–q33.1, 17q11.1–q21.2, 1q21–q44 and 3q21.3–q29.

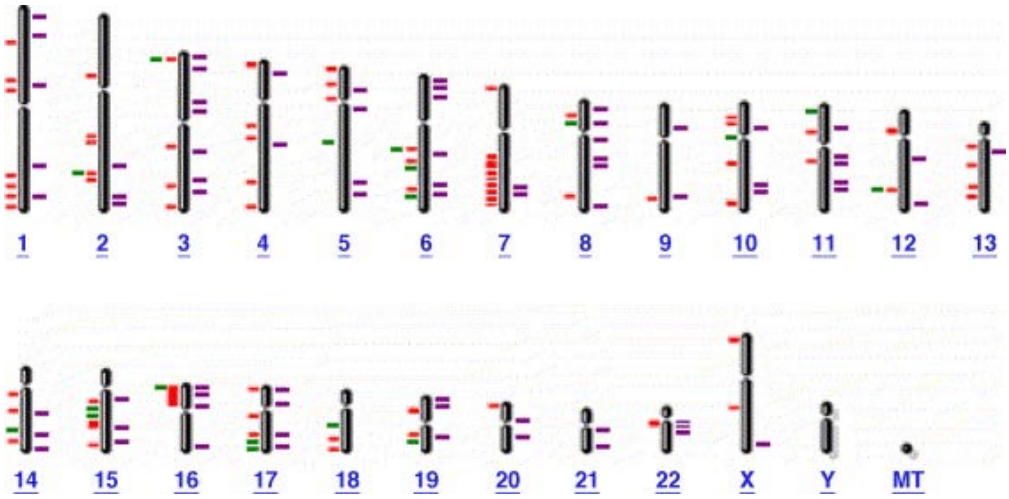

Fig 2.1 Diagram of gene or loci on each chromosome that may be related to autism. Red bars indicate the position of significant or suggestive linkage. Green bars represent the position of markers from genome-wide scan association studies with $p \leq 0.01$. Violet bars on the right side of the chromosomes show the location of genes whose expression is altered compared to controls with a fold change ≥1.0 (Yang and Gill 2007).

2.8 Sampling strategy

Two fundamentally different designs are used in genetic association studies: case-control and family-based studies. The case-control study has been the most widely applied strategy of association, in which allele or genotype frequencies in patients are compared with frequencies in an unaffected control population. However, for this type of analysis it is essential to minimize the confounding effect that occurs when the cases and controls are not drawn from the same backgrounds. In contrast, the family-based association study not only prevents the false-positive associations due to population stratification, but also allows simultaneous testing of linkage and association. In this type of association study, the observed distribution of genotypes within family members is compared with the expected frequency given the familial relationships under the assumption of no association. The transmission disequilibrium test (TDT) is the most commonly used approach in family-based design. It tests whether the frequency of transmission of an allele from heterozygous parents to affected offspring deviates from what is expected by chance. When certain genetic maker is associated with disease, the heterozygous parents will have a higher chance of transmitting specific alleles of that marker to their affected offspring. The detected associated polymorphic marker is either affecting the disease risk directly or in LD with another genetic variant that affects the risk. The simplest TDT approach only uses genotype data from trios that consist of affected offspring and two parents. Extensions to the basic TDT method have been applied to handle more complicated situations such as missing parents and extended families (Dudbridge, Koeleman et al. 2000; Ashley-Koch, Mei et al. 2006).

2.9 Selection of markers for candidate gene testing

The completion of the human genome sequence and the initiation of the International HapMap Project have identified more than six million SNP markers. Development of rapid high-throughput methods to genotype SNPs, and to understand the correlations between neighboring SNPs, together with new analytic techniques now permit comprehensive, genome-wide association studies to survey for variants that contribute to disease susceptibility. But due to the relatively high cost of genotyping, it is still unrealistic to genotype all SNPs within target genes.

Multiple methods have been developed to select subsets of markers based on different underlying algorithms, such as multiple linear regression (He and Zelikovsky 2006), principal components analysis (Lin and Altman 2004), Bayesian networks (Lee and Shatkay 2006), and the Monte Carlo methods (Liu, Lin et al. 2006). One of the most popular approaches is to assay the variation that can best "represent" neighboring markers in a gene or region of interest by using LD to guide the selection. Because most of the genome falls within blocks of strong LD, within which most variants are strongly correlated, it is possible to determine the LD patterns and then select a small fraction of SNPs that tag most of the remaining variants (Johnson, Esposito et al. 2001; Gabriel, Schaffner et al. 2002). In contrast to the direct tests of association between a putatively functional variant and disease risk, this indirect approach tests disease association under the assumption that the potential risk polymorphism is in strong LD with one of the genotyped tagSNPs. The advantage of this indirect association analysis is that it does not require prior determination of which SNP might be functionally important.

The primary goal of the International HapMap Project is to facilitate identification of appropriate sets of tagSNPs that span the human genome to be used in this efficient, LD-based approach. Computer programs such as Tagger have been developed for the selection and evaluation of tag SNPs from this genetic variation resource (de Bakker, Yelensky et al. 2005). Tagger can effectively search for marker predictors to capture the haplotype information specified by the investigator. It selects a minimal set of markers such that all alleles to be represented are in the same LD bin given a user-defined threshold. Its output is a list of tagSNPs and corresponding LD parameters for captured variants of interest.

The degree of LD between alleles at two loci can be described in terms of the metric r^2. An r^2 of 1 indicates perfect LD between two alleles, and there is no loss of power when using a tagSNP marker instead of directly genotyping the disease causal variant. In contrast, an r^2 of 0 means there is no correlation between two markers. Studies have shown that an r^2 of 0.8 or greater is usually sufficient for tagSNP mapping to obtain a good coverage of untyped SNPs without losing much power (de Bakker, Yelensky et al. 2005).

2.10 TagSNP transferability

With the completion of phase II of the HapMap project, more than three million SNPs have been genotyped in four HapMap populations: Yoruba from Ibadan, Nigeria (YRI), Japanese from Tokyo, Japan (JPT), Han Chinese from Beijing, China (CHB), and Utah residents with northern and western European ancestry (CEU). Although these data provide a precious resource for researchers to select tagSNPs to cut costs from redundant

genotyping while maintaining sufficient power to capture complete haplotype information, it is known that LD patterns and haplotype blocks may vary across different populations (Gonzalez-Neira, Ke et al. 2006; Gu, Pakstis et al. 2007). It has been suggested by earlier studies that tagSNPs should be evaluated in each individual population (Weale, Depondt et al. 2003; Carlson, Eberle et al. 2004). So by comparing the similarity of haplotypes in separate populations and whether tagSNPs can capture most of the variants in these populations, we are able to assess the effectiveness of tagSNPs selected from HapMap populations. There is no consensus of quantitative measures of transferability in the literature, but the measures usually relate to comparing the LD structure between populations and can be roughly classified into 3 types: 1) percentage of SNPs captured by tagSNPs with r^2 over a threshold; 2) average of adjacent pairwise LD ; and 3) average of pairwise LD with tagSNPs (Gu, Yu et al. 2008).

Several studies have shown a generally good performance of tagSNPs transferability when the tagSNPs are picked for populations similar to a corresponding HapMap reference subset (Mueller, Lohmussaar et al. 2005; Lim, Kim et al. 2006; Ribas, Gonzalez-Neira et al. 2006). According to a study from de Bakker et al. (2006), the standard tagging approach in the four HapMap population samples can effectively capture common variation in many other independent samples, regardless of diverse LD structure between populations. The observed loss in coverage and power are largely due to fluctuations in allele frequency and r^2 estimates from sampling variation.

2.11 Parametric and non-parametric linkage analysis

Parametric (model-based) linkage analysis is to test the cosegregation of genetic loci within members of pedigrees. When two loci on the same chromosome are physically located far from each other, there is a higher possibility that a recombination event can occur that disrupt their cosegregation at meiosis than if they are close. The probability of such recombination events between two loci are indicated by the recombination fraction θ.

The degree of linkage is usually reported as a LOD score, which was first presented by Morton in 1955 (Morton 1955). It is a function of the recombination fraction θ or chromosomal distance between markers measured in cM. The supportive evidence in favor of linkage is indicated by large positive LOD scores, and negative scores show evidence against linkage. In the parametric linkage study, model parameters need to be specified for a certain disease. The parameters of model include: marker allele frequencies, disease penetrance, mode of inheritance (dominant or recessive), and the genetic map of chromosomes. Two-point linkage analysis is used to estimate the recombination fraction between a marker locus and the disease locus, while multipoint analysis is used to find the position of the disease locus relative to a set of other known markers. The best estimate of θ or genetic position is that which maximizes the lod score function (maximum likelihood method).

As for the complex diseases, since more than one gene as well as environmental factors might contribute to disease risk, there is not a single specific mode of inheritance that describe the disease. Therefore various methods have been developed to investigate linkage without the need to include explicit model parameters. Such methods are referred

to as non-parametric (model-free) analyses. One of the most common applications of this type of method is the sib-pair study, in which the excess sharing of segments of chromosome that carries disease loci between affected siblings is determined. In this case there is no need to assign a model of inheritance. Thus non-parametric methods have been mainly used in seeking genes responsible for complex diseases including various psychiatric disorders.

2.12 Bayesian inference and PPL

Bayesian inference is a statistical method that uses evidence or observations to update and calculates a numerical estimate of the degree of belief in the hypothesis. The main feature is that both model parameters and data are random variables with a joint probability distribution that is specified by a probabilistic model -- the data are the observed variables while the model parameters are the unobserved variables. The joint distribution is a product of the likelihood and the prior probability as shown in equation (1) below. The prior probability incorporates presumptive values of a parameter before the evidence (data) is available. The likelihood is a conditional distribution that specifies the probability of the observed data given any particular values for the parameters and is based on a model of the underlying process. Together, these two functions combine all available information about the parameters. Thus, the main aim of Bayesian inference is to calculate the posterior distribution of the parameters, i.e., the conditional distribution of parameters given the data (Beaumont and Rannala 2004).

The Posterior Probability of Linkage, or PPL (Vieland 1998) is a straightforward application of Bayesian theorem, which provides a direct measure of the probability that

a marker is linked to a disease gene. Assuming a prior probability distribution of recombination rate θ as f(θ) and the genotype data as D, the prior distribution can be transformed into a posterior distribution f(θ|D). This can be used to calculate the PPL. Let H_L represent the hypothesis that a trait locus and a given marker are linked, then the PPL is defined as a definite integral as in equation (2).

$$f(\theta|D) \triangleq \frac{f(D|\theta)f(\theta)}{\int_{0\le\theta\le\frac{1}{2}} f(D|\theta)f(\theta)\,d\theta} = \frac{f(D|\theta)f(\theta)}{f(D)} \tag{1}$$

$$PPL \triangleq P(H_L|D) = \int_{0\le\theta<1/2} f(\theta|D)d\theta = \int_{0\le\theta<1/2} \left[\frac{f(D|\theta)f(\theta)}{\int_{0\le\theta\le1/2} f(D|\theta)f(\theta)\,d\theta}\right] d\theta \tag{2}$$

f (θ|D) : the posterior probability of θ given D;

f (θ): the prior probability of θ;

f (D|θ): the conditional probability of seeing D under condition of parameter θ;

f (D): the marginal probability of D (sum of the product of all probabilities of any complete set of mutually exclusive hypotheses and corresponding conditional probabilities). (Vieland 1998)

An alternative formulation of the Bayesian theorem is that the posterior odds can be deduced from the product of the prior odds and the likelihood ratio, which allowing the PPL be calculated from the regular LOD score. The resulting equation combines Bayesian and non-Bayesian methods and presents a new method to process the model parameters. Different from other methods that based on the likelihood as a function of the

trait model, the PPL method utilizes a grid of nuisance parameters instead of specific values from fixed models to test the evidence for linkage. In effect, the PPL is determined by the average value of evidence through the complete set of genetic models, with the weight given to different portions of the parameter space being controlled by the priors (Vieland, Wang et al. 2001). Thus, this method may be considered as "model-free."

The PPL itself is a probability scale, ranging from 0 when there is lack of evidence for linkage to 1 when there is complete support for linkage. According to calculations from Elston and Lange (1975), the prior probability of linkage for two random loci is 2%, so a PPL greater than 0.02 shows evidence in favor of linkage while PPL less than 0.02 shows evidence against linkage. Unlike the more familiar p value statistic, there is no definitive threshold for "significant" or "highly significant" in the results of PPL analysis. So users must decide for themselves whether a PPL result is "interesting" or not. To help indicate the relative scale of PPL, Logue et al. conducted a simulation of 10,000 data replicates under the null hypothesis (no trait gene at the location being tested) using genotype data from microsatellite markers. The simulation showed that the PPL values of 5%, 25%, and 80% were associated with Type 1 error probabilities of 0.02, 0.0009, and 0.0001, respectively (Logue, Vieland et al. 2003).

The PPL has many inherent advantages over other likelihood-based linkage methods. First, it includes integration over unknown 'nuisance' parameters of the trait model without inflation of scores due to maximization over large numbers of parameters. Second, it has a natural and effective mechanism to accumulate evidence for or against linkage across multiple, potentially heterogeneous, data sets via the Bayesian technique of sequential updating. Third, it is capable of incorporating prior genomic information,

such as unequal male and female recombination fractions, into linkage analysis. Recently, the PPL method has been improved to include multipoint calculation (Wang, Huang et al. 2001; Logue, Goedken et al. 2003; Logue, Brzustowicz et al. 2006); quantitative traits (Bartlett and Vieland 2005); and allowance for linkage disequilibrium, in a manner that also permits estimation of the location and degree of LD between a marker and a putative disease-susceptibility mutation (Yang, Huang et al. 2005).

When analyzing multiple datasets divided into subgroups, the PPL passes forward the posterior distribution for the recombination fraction (2-point analysis) or genomic location (multi-point analysis) derived from one dataset as the prior distribution for the analysis of the next. This process can be repeated as each new dataset is incorporated into the analysis. In this way, the PPL allows for heterogeneity within subsets, as well as for differences across subsets, while accumulating the total evidence for and against linkage based on data from all families. Because PPL does not involve maximum-likelihood estimation or maximization of linkage statistics across subsets, there is no inflation of the PPL inherent in either updating across data subsets or subsetting on the basis of genetically irrelevant factors. In another study, Bartlett et al. reanalyzed the AGRE collection of families by dividing original data into six clinically defined subsets and updating the PPL sequentially over the subsets (Bartlett, Goedken et al. 2005). Their results indicate a substantial probability of linkage to chromosome 1, which had been previously overlooked. This analysis illustrates that the way in which heterogeneity is addressed in linkage analysis can dramatically affect the overall conclusions of a linkage study.

The Bayesian methods including PPL are capable of incorporating prior genomic information, such as unequal male and female recombination fractions, into linkage analysis. Genetic map distance varies along different regions of chromosomes between males and females, and a detailed measurements of the two distances are now available across the genome (Matise, Chen et al. 2007). Theoretically, more precise results should be expected from calculation when the prior information of the sex-specific recombination is considered. However simulation studies showed that sex-averaged PPL, which ignores sex specific recombination rates, indicate little difference compared to the sex-specific PPL even in the presence of a large male/female difference (Bartlett, Flax et al. 2002; Yang, Huang et al. 2005). So it is recommended that the sex-averaged form of PPL be used in studying a target genomic region.

After the development and evaluation of two-point PPL, several versions of multipoint PPL have also been implemented that allow for simultaneous use of data from multiple markers. The initial version by Wang et al. (Wang, Huang et al. 2001) calculated multipoint PPL by integrating the density over a ‘window’ extending across the region of detectable linkage to form the posterior density along the chromosome. As this window moved down the chromosome, the value of multipoint PPL was recalculated for each new placement of the interval. In this approach, the trait model was examined at one dominant and one recessive model. Logue et al. (Logue, Goedken et al. 2003) later modified this method by changing the way the trait model parameters are dealt with while keeping the concept of the moving window. They removed the need to fix the trait model by placing priors on the parameters and then integrating over the set of possible trait model values. However, one drawback of this moving window multipoint PPL is that it is not on the

same scale as the 2-point PPL, so it is impossible to compare the strength of linkage from flanking markers with evidence from a single marker. Therefore, Logue and Vieland (2004) designed a new approach to calculate multipoint PPL. In this approach, the PPL is computed at any given map position based on the posterior density at that position alone, using an imputation procedure which is calibrated to the scale of the 2-point analysis. This provides a basis for calibrating the multipoint PPL to the 2-point PPL, so that any appreciable differences in magnitude between the 2-point and multipoint PPLs can be interpreted as reflecting differences due to marker information. A recent study re-analyzed the dataset that previously identified a promising schizophrenia candidate region on 1q23 with a maximum 2-point HLOD of 5.8 (Logue, Brzustowicz et al. 2006). This study showed supportive evidence of the previously observed linkage, with an estimated multipoint PPL of 99.7%. Furthermore, their study found a second peak on chromosome 1 at 1p13 with a multipoint PPL of 70% and a third chromosome 17 marker with a multipoint PPL of 44%.

One assumption made by the original two-point PPL method is the existence of linkage equilibrium between alleles at the trait locus and the marker locus. However, when LD is present between the two loci, the expected LOD score is higher when LD is taken into consideration (Clerget-Darpoux 1982). In 2005, Huang et al. (Yang, Huang et al. 2005) implemented LD-PPL that allows for LD by incorporating variable phase probabilities into the underlying linkage likelihood. This approach not only keeps the advantage of having nuisance parameters integrated out of the trait model and allowing for heterogeneity between data subset, but also includes a new vector of LD parameters that makes detecting association (D') between a trait and marker locus possible. Huang et

al.'s simulation results showed that when there is positive evidence of linkage, the value of LD-PPL is larger than PPL under different testing conditions; while when there is a lack of linkage and LD, the value of LD-PPL becomes smaller than PPL. They showed that while the estimation of LD is less likely to be affected by violations of Hardy-Weinberg equilibrium at the marker, the incorrect value of marker allele frequencies does lead to over- or under-estimation the value of D'. They also pointed out that even with substantial misspecification of the parameters, the estimates still lead to the right direction of whether LD is low or high. Based on this method, a new extension of the LD-PPL, the Posterior Probability of LD given Linkage (PPLD), was later developed capable of directly measuring the evidence for (or against) LD conditional on linkage. Because the PPL and the PPLD are on the same scale, it is possible to sequentially update the posterior map (of potential trait-gene locations) obtained from linkage analyses with LD evidence obtained from fine-mapping or WGA data, in a mathematically rigorous manner.

Chapter 3. Methods

3.1 Subjects

Samples used in this project are part of the Autism Genetics Resource Exchange (AGRE) and are provided by the Rutgers University Cell and DNA Repository (RUCDR). AGRE is a central repository of family DNA samples created by the Cure Autism Now Foundation and the Human Biological Data Interchange. These families contain subjects with a diagnosis of Autism according to the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter et al. 1994). Families included in this collection have at least two affected siblings, one or both parents and additional affected and unaffected siblings where available. Information from ADI-R interview and pedigree configurations are available for all families from AGRE. In addition, detailed birth, medical, psychological, neurological and cytogenetic analyses are available on most probands as well as some family members.

Our aim was to analyze a phenotypically well defined and homogeneous set of families with the hopes that this would reduce possible genetic heterogeneity and thus increase our power to detect etiological genetic variations. In addition, we have selected, where possible, quad-families of two affected siblings and their parents. This family structure allows both family-based association as well as linkage analysis and provides increased power for haplotype construction and genotype error checking. We have used the following selection and exclusionary criteria:

1) First we excluded all probands with possible non-idiopathic causes of autism (e.g. cases with Fragile X syndrome, karyotypic abnormalities or with other known neurological, medical or psychiatric disorder).

2) To help ensure sample homogeneity, only male probands with a narrow definition of autism based on ADI-R were selected.
3) In addition we used data from the language acquisition component of the ADI-R to select only probands defined as having significant phrase speech delay after 36 months.

For the Phase 1 of our study, two separate genotype datasets with overlapping family samples were analyzed in two steps, Phase 1a and Phase 1b. The Phase 1a analysis includes 265 Phase 1a family set from the total of 682 families that were available in AGRE at the time of sample selection. Among them, 174 families are Caucasian, 49 families are Hispanic (22 of them are mixed), and the remaining 42 families are unknown or from other mixed races. The subjects are from 225 quad-families with both parents and affected siblings, and 40 trio-families with both parents and one affected child. DNA samples extracted from immortalized lymphoblast cell lines were standardized to 100ng/µl. The Phase 1b dataset included the Phase 1a dataset plus a subset of the high-density SNP (Affymetrix 5.0 array) data on 777 AGRE families contributed by the Autism Consortium (www.agre.org). This subset contained genotypes of 243 AGRE families that are overlapping with the Phase 1a family set.

For the Phase 2 follow-up study, we used both the Phase 1a family set for the fine-mapping study, and a newly selected Phase 2 family set for a replication study, which included 123 additional families chosen by similar criteria to the updated AGRE database,. Among the Phase 2 family set, 72 families are Caucasian, 25 families are Hispanic, and 26 families are other or with unknown ethnicity. We wanted to have

enough sample size for this follow-up study but there is only limited number of new family samples available from the updated AGRE database. To ensure we have sufficient power in our analysis, the Phase 2 family set contained families that have female probands (20 families) and with extended pedigree structures in addition to the trio- and quad- families. In total, the additional subjects are from 5 trio-families, 42 quad- families and 76 families with 5 or more family members.

3.2 Candidate gene selection

The goal of this project was to test biologically relevant candidate genes for genetic association with autism. We selected genes based upon the following criteria:

1) Previous research has demonstrated that the homeobox transcription factor, *ENGRAILED 2* (*EN2*), is consistently and significantly associated with ASD (518 families, *P*=0.000000427) (Gharani, Benayed et al. 2004; Benayed, Gharani et al. 2005). This group has also demonstrated that En2 knockout mice display subtle cerebellar neuropathological changes similar to what has been observed in the ASD brain (Cheh, Millonig et al. 2006). These studies are consistent with *EN2* being an ASD susceptibility gene (ASD [MIM 608636]; *EN2* [MIM 131310]). For this reason, other genes that perform similar functions as EN2 have been selected for analysis.

2) Genes important for serotonin and GABA neurotransmission have also been selected for analysis. Serotonin is an important regulator of mood and behavior. Physiological, pharmacological and genetic studies have consistently suggested that defects in the serotonin pathway are correlated with autism. For example, elevated platelet serotonin has been reported in 20-25% of individuals with autism and their

first-degree relatives (Cook, Arora et al. 1993) and selective serotonin reuptake inhibitors (SSRIs) have been effective in treating some of the maladaptive behaviors associated with ASD (Posey and McDougle 2000).

GABA function is necessary for higher cortical functions. Several physiological and genetic studies have suggested a possible role in ASD. For example, three GABA (A) receptors are deleted in the most common cytogenic abnormality observed in ASD (15q11-q13) and elevated GABA levels have been reported in affected children (Cook, Lindgren et al. 1997; Dhossche, Applegate et al. 2002).

3) Finally, Dr. Brzustowicz's laboratory has previously identified genomic regions that display significant association with ASD. Developmentally important genes near these markers have been selected for analysis.

We selected 111 candidate genes to study their possible correlation with autism. These genes are scattered over 21 human chromosomes with average gene size of 79kb. Most of them have never been studied/reported before to be directly related to autism or other psychiatric disorders.

Chr	Candidate genes
1	GABRD, HTR6, S100A6
2	POMC, OTX1, HTR5B, EN1, SCTR, SCN3A, GAD1, DLX2, CREB1, EPHA4
3	SLC6A1, CCK, ZIC4, HTR3D, OXTR
4	CCKAR, GABRG1, GABRA2, GABRA4, GABRB1, FGF5, PRKG2, FGF2, NUDT6, SPRY1, GRID2
5	GDNF, SLC12A2, HTR4, GABRB2, GABRA6, GABRA1, GABRG2, FGF18
6	GABBR1, MLN, HTR1B, GABRR1, GABRR2, L3MBTL3, SAMD3, OPRM1

7	DLX6, DLX5, EPHB4, ACHE, SYPL, WNT2, EPHB6, EPHA1, HTR5A, SHH, GRM8
8	FGF20, FGF17, PENK, CALB1, GLI4
10	ANK3, HTR7, PAX2, FGF8
11	SCT, TH, CCKBR, TPH1, BDNF, PAX6, HTR3B, HTR3A
12	WNT1, CSAD, RARG, GLI, TPH2
13	MAB21L1, HTR2A, SPRY2
14	OTX2, AKAP5
15	UBE3A, GABRB3, GABRA5, GABRG3, SLC12A6
17	GABARAP, FGF11, KCNAB3, SLC6A4, RARA, NGFR, DLX4, DLX3
19	FGF22, CACNA1A, GRIK5
20	OXT, AVP
21	PCP4
22	COMT, WNT7B
X	SYP, NLGN3, FMR1, GABRE, GABRA3, GABRQ, MECP2

Table 3.1 List of autism candidate genes of our study

3.3 Selection of TagSNPs

In Phase 1 of the study, tagSNPs across each gene region plus 5kb at both up- and down-stream of each candidate gene were selected to efficiently represent all variation in each gene region. The tagSNPs were chosen by the following procedure:

a. Determine the physical coordinates of genes

The physical coordinates (NCBI Build36) of all candidate genes were retrieved through Ensemble BioMart (http://www.ensembl.org/biomart/index.html). Then +/- 5kb were added to the start and end position of each gene attempt to include regulatory elements.

b. Obtain design score from Illumina Inc.

The Illumina BeadChip platform was used in Phase 1 genotyping. Their GoldenGate Custom Panel system provides complete information on all HapMap validated SNPs. A design score ranging from 0 to 1.1 indicates how well the specific SNP markers perform on their customized genotyping platform. A score above 0.6 is preferred to ensure genotyping quality. Illumina provided us with design score of all SNP markers within the coordinates of candidate genes.

c. Select tagSNPs for genotyping

We employed the program Tagger (http://www.broad.mit.edu/mpg/tagger/) to select tagSNPs from each of our candidate gene regions. We applied 3 rounds of selection in this process. In the first round, we applied the aggressive multi-marker tagging mode in deriving the most efficient set of tagSNPs. Parameters were set as $r^2 \geq 0.8$, minor allele frequency (MAF) ≥ 0.05, design score ≥ 0.4. After this selection, there were 8 genes for which no tagSNPs were chosen. In the second round, we loosened the selection criteria by using MAF ≥ 0.02 and pairwise tagging mode. After this round, 3 genes remained with no tagSNPs. We then examined the HapMap database and found there are no HapMap genotyped SNPs within the region of these genes. Therefore in the last round, we manually selected 2 GoldenGate validated SNPs for each of the 3 genes. Furthermore, to make sure we would have credible result for each gene, one more GoldenGate validated SNP was also selected for those genes that only had one tagSNP selected by Tagger.

By this process, we selected 1536 tagSNPs from 111 autism candidate gene regions for our phase 1 study (see Appendix 1 for detailed list). On average, each gene is covered

by about 14 tagSNPs, and the average physical distance between each pair of SNPs is 6.4kb. About 98% of tagSNPs have a minor allele frequency greater than 0.05 (Figure3.1).

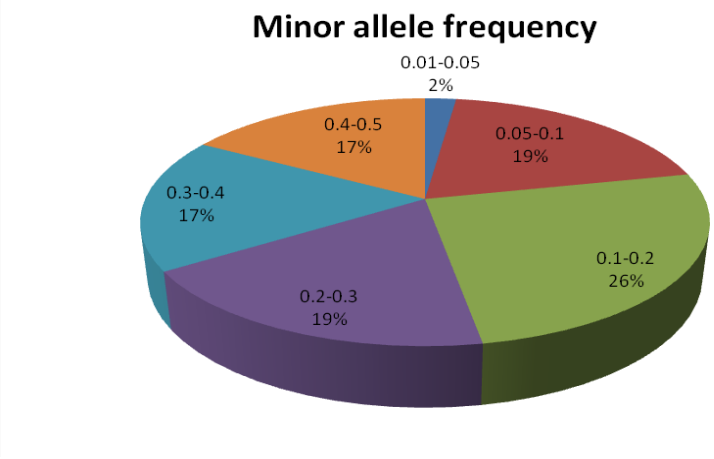

Figure 3.1 Minor allele frequency of selected tagSNPs from phase 1 study

For the Phase 2 study, the tagSNPs that passed our suggestive significance threshold in the Phase 1 study plus additional SNP markers from their LD bins were selected for genotyping and further analysis. To pick the additional markers, we downloaded the HapMap LD dataset (Hapmap data release 22, dbSNP build 36) for the EPHA1 and MECP2 gene regions and chose all the markers that have $r^2 > 0.6$ with our suggestive markers. There are 21 SNPs from chromosome 7 and 14 SNPs from the X chromosome selected for the Phase 2 study. Figure3.2 and 3.3 show the LD plot of these markers from the HapMap CEPH population.

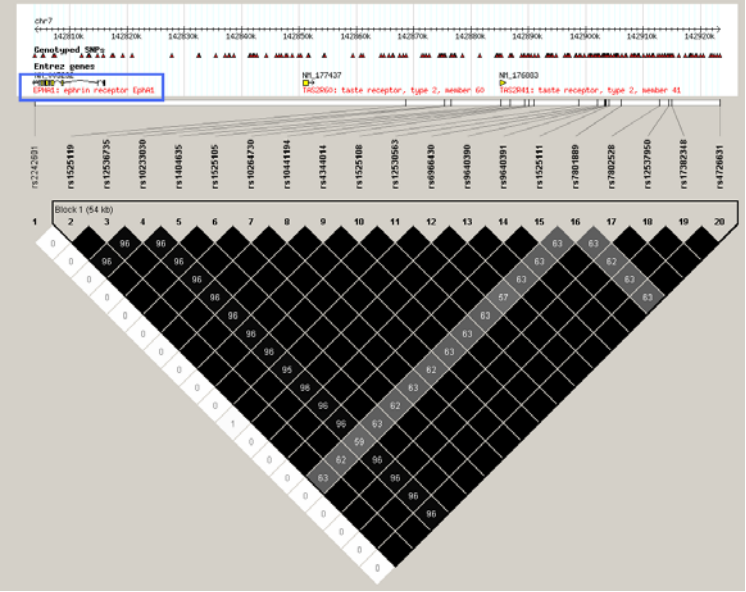

Figure 3.2. HapMap LD plot of selected SNPs from the EPHA1 gene region for phase 2 study. The positions of the gene and SNPs are indicated at the top. The values of r^2 are displayed inside the square (complete black with no number means $r^2=1$).

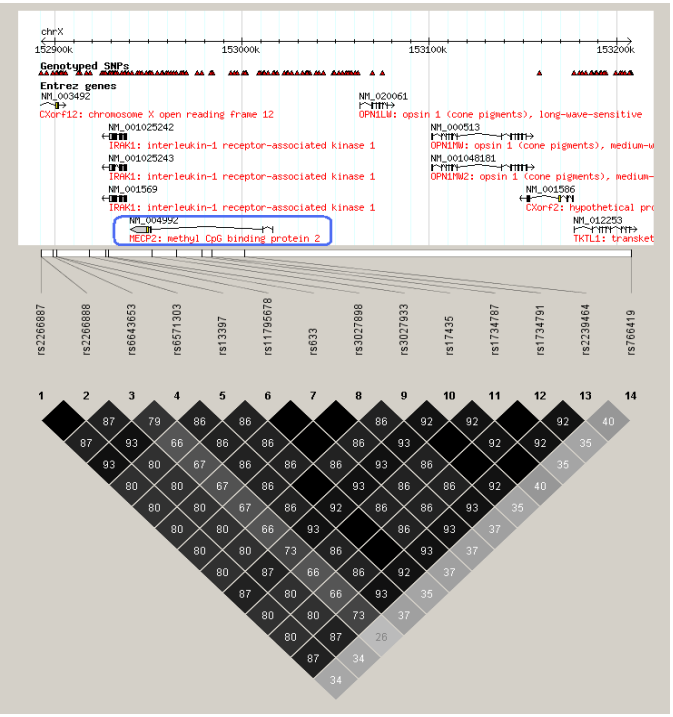

Figure3.3. HapMap LD plot of selected SNPs from the MECP2 gene region for phase 2 study.

3.4 Genotyping

In the Phase 1 study, all selected tagSNP markers were genotyped by collaborators from the Chinese National Human Genome Center, Shanghai, using the Illumina GoldenGate Assay (http://www.illumina.com). The assay products were hybridized to high-density, beadbased microarrays and imaged on the Sherlock scanner (Illumina). Clustering and calling algorithm were applied through the GenCall software (Illumina), resulting in 1507 (98.1%) tagSNPs were successfully genotyped. The assay QC results are listed in Table 3.2.

Sample Call Rate	97.20% (54.40% ~ 98.1%)
Intra-Plate Reproducibility	99.93% (99.63% ~ 100%)
Inter-Plate Reproducibility	99.90% (99.96% ~ 100%)

Table 3.2. Illumina Goldengate Genotyping assay QC data

In the Phase 2 study, all 35 SNP markers were genotyped at the Rutgers University. DNA fragments were amplified using a recently described multiplex PCR approach that minimizes primer complimentary, especially between their 3′-bases (Wang, Luo et al. 2005). Multiplex PCR was performed in 20μl of PCR mix containing 1x PCR buffer (50 mM KCl, 100 mM Tris–HCl, pH 8.3, 1.5 mM $MgCl_2$, and 100 μg/ml gelatin), dNTPs (250 μM each, Invitrogen), primers (5 μM each), 0.5 U AmpliTaq Gold polymerase (Applied Biosystems) and 40 ng of template DNA. The samples were heated to 94 °C for 10 min, followed by 40 PCR cycles of 40 sec at 94 °C, 30 sec at 60 °C, and 5 min of ramping from 60 °C to 70 °C with 0.01 °C/s increase. A final extension step was carried

out at 72 °C for 10 min. PCR amplifications were performed with the PTC-200 Programmable Thermal Controller (MJ Research).

SNPs were genotyped using the Ligase Detection Reaction (LDR) combined with Luminex flow cytometry (Iannone, Taylor et al. 2000; Bortolin, Black et al. 2004). Three primers were designed for each LDR assay: two allele-specific primers incorporating different 5′-FlexMAP™ Tags (Luminex® Corporation) and ending with the variant base, and a single SNP-specific common primer complimentary to the sequence 3′ to the SNP, 5′-phosphorylated, and ending with a 3′-universal tag. LDRs were performed in a 15 µl volume containing 2 µl of multiplex PCR product, 6 U Taq DNA Ligase (New England Biolabs), 0.15 pmol of allele specific and common primers for each SNP, 1.5 µl of 10x Taq DNA Ligase buffer (New England Biolabs), and distilled water. LDR was carried out at 95 °C for 60 s followed by 32 cycles of 95 °C for 15 s and 58 °C for 2 min. The bead hybridization step was performed by adding 50ul volume with 0.8 µl of each Luminex® FlexMap™ bead conjugated to anti-tag probes complementary to the FlexMAP™ Tags on the allele-specific primers, 0.48 pmol of 3′-biotinylated universal oligonucleotide complimentary to the universal tag at the 3′-end of the common SNP-specific primer, and hybridization buffer (3 M tetramethylammonium chloride, 50 mM Tris–HCl, pH 8.0, 3 mM EDTA, pH 8.0, 0.1% SDS). After heating to 95 °C for 1.5 min, the hybridization reaction was carried out at 37 °C for 20 min. Fluorescent labeling was performed by adding 0.18 µl of 1 mg/ml streptavidin-R-phycoerythrin (Molecular Probes) to the hybridization buffer and incubating at 37 °C for 40 min. Detection of allele-specific LDR-bead complexes was performed using a Luminex®100™ Total System.

3.5 Genotype data cleaning

In our study we took the following three steps to identify possible genotyping errors in our dataset, including check for Mendelian inconsistencies, Hardy-Weinberg equilibrium (HWE) and excessive double crossovers.

a. Identify Mendelian inconsistencies

We used the PEDCHECK program (O'Connell and Weeks 1998) to check our data for Mendelian inconsistencies. It gives detailed information of the possible source of those errors and identifies the markers and individuals involved. When an inconsistency was detected, alleles for that marker were set to unknown in the entire family from which the inconsistency arose. PedCheck Level 1 checks for inconsistencies among parents and their offsprings using simple nuclear-family algorithm, while PedCheck Level 2 uses a genotype-elimination algorithm to detect more sophisticated errors. Pedigrees are consistent with Mendelian inheritance after PedCheck Level 2 error cleaning and can therefore be used in further study. In the Phase 1 study, the detected Mendelian error rate of genotype is 0.00027, and in the Phase 2 the rate is 0.00074 .

b. Check for HWE

The program PEDSTATS (Wigginton and Abecasis 2005) was used to check whether genotype frequencies within the sample appear to deviate significantly from HWE. The SNP markers with $P < 0.0001$ were removed from the dataset.

c. Detect excessive double crossovers

Excess crossovers within a short genetic region may be indicative of genotyping errors. MERLIN (Abecasis, Cherny et al. 2002) was used to identify unlikely recombination by comparing genotypes from siblings. That is, if the genotypes from siblings are identical at all markers from certain interval of chromosome except for one locus, then the contradicting information suggest that it is more likely a genotyping error than the occurrence of two recombination events. The detected unlikely genotypes were removed from data set.

Genotypes from 1469 (97.5%) tagSNPs from phase 1 and all 33 SNP markers from phase 2 passed our stringent data cleaning procedure and were suitable for further analysis. Data from two AGRE family samples were excluded due to significantly high error rate detected by Pedcheck, which left 1011 individuals in phase 1 and 1678 (657 from additional family samples) individuals in phase 2 study.

3.6 PPL and PPLD analysis on the Phase 1a dataset

3.6.1 Two-point PPL

We calculated two-point posterior probability of linkage (PPL) using the Kelvin program on our Linux computer cluster. The SNP allele frequencies were estimated by the program MENDEL (Lange K et al. 2001). The SNP marker linkage position was interpolated from its physical position (dbSNP Build 128) through the Rutgers Combined Linkage-Physical Map web tool (Matise, Chen et al. 2007). The trait parameters (see below) were included as a vector of nuisance parameters in the model and integrated out to obtain a marginal posterior density of recombination rate (θ). The posterior marginal

density of θ was computed by calculating two-point LOD scores at each possible combination of parameter values, and then an average value was computed from the resultant set of LOD scores (likelihoods) for each value of θ. The trait parameters include: 1) three penetrances for the AA, Aa, and aa genotypes ranging from 0 to 1, in steps of 0.10; 2) θ ranging from 0 to .5 in steps of 0.01; 3) the admixture parameter (α) ranging from 0 to 1, in steps of 0.05; and 4) the grid for the disease-gene frequency was 0.001, 0.01, 0.1, 0.3, 0.5, and 0.8. The PPL was then computed from the posterior marginal density of θ integrating over $\theta < 0.5$ by numerical approximation.

3.6.2 Multi-point PPL

The multi-point PPL score was calculated on the basis of likelihood result from the Merlin program. Merlin can perform parametric linkage analysis using an approximate multipoint calculation that ignores the unlikely possibility of a large number of recombinants among neighboring markers (Abecasis, Cherny et al. 2002). Thirty pre-set parameter files specifying individual parametric models (the disease allele frequencies and penetrance vectors) were used to compute per-model LOD scores, and these LOD scores were then aggregated into PPL values per position.

3.6.3 PPLD

We also calculated the PPLD score which directly indicates the evidence for (or against) LD conditional on linkage. The trait parameter vectors are the same as in 3.6.1, with an additional LD parameter (D') ranging from -1 to 1 in step of 0.1 to obtain the resultant set of likelihood scores for association test.

3.7 PPL and PPLD analysis on the Phase 2b dataset

The raw genotype data from the Affymetrix 5.0 high-density SNP array that was assayed on 777 CEPH families were released by the Autism Consortium (www.agre.org). We utilized this dataset to carry out analysis on our two candidate gene regions identified from the Phase 1a analysis. We chose to use 240 families from this dataset that overlapped with our samples and extracted the genotypes within +/- 100Kb of the physical coordinates of our suggestive gene regions on Chromosome 7 and the X chromosome. Then this new data were cleaned through the same procedure as in Phase 1a and combined with genotypes from the Phase 1a study. The same two-point, multi-point PPL and PPLD analysis were carried out on this combined Phase 2b dataset as previously described.

3.8 PDT analysis

We carried out the association analyses using the program PDTPHASE (version 2.404) to validate our result from PPLD analysis. The PDTPHASE, which is part of the genetic association analysis package UNPHASED (Dudbridge 2008) is a modification of the pedigree-based transmission/disequilibrium test (PDT) (Martin, Monks et al. 2000). PDTPHASE was designed to allow the use of data from related triads and disease-discordant sibships from extended pedigrees when testing for transmission disequilibrium. It determines the presence of association by testing for unequal transmission of either allele from parents to affected offspring and/or unequal sharing of either allele between discordant sibships. The experiment-wide p values were calculated

from the output of PDTPHASE after determining the effective number of independent test markers by the program SNPSpD. SNPSpD was implemented by Nyholt (2004) as a method to correct for multiple testing of SNPs in LD with each other, through detecting the spectral decomposition (SpD) of matrices of pairwise LD between SNPs.

3.9 TagSNP transferability test

SNPs from the EPHB6-EPHA1gene region at 7q34 (142262 – 142916kb) were used to test tagSNP transferability between the HapMap CEPH population and our AGRE sample genotype data. Within this 753kb region, we found 82 SNPs that are both genotyped in the HapMap project and are on the AGRE Affymetrix 5.0 high-density SNP array. The genotype data of these SNPs were extracted from both sources (HapMap and AGRE). Then we used the program Tagger in Haploview to select a set of tagSNPs using the genotype from the HapMap reference panel, in which each allele satisfied the minor allele frequency minimum threshold of 0.1. Both pairwise and aggressive tagging mode were employed with a threshold of $r^2 >= 0.8$. Then this set of HapMap identified tagSNPs were evaluated in the AGRE Affymetrix SNP array dataset to capture other markers that in high LD ($r^2 >= 0.8$). TagSNP transferability was then evaluated by comparing the number of captured SNPs under the each tagging mode.

Chapter 4. Results

4.1 Two-point PPL and PPLD analysis of phase 1a dataset

Figure 4.1 shows the 2-point PPL and PPLD values for the 1469 tagSNPs analyzed in the Phase 1a study using 263 AGRE families. There were 1139 (77.5%) SNPs that indicated evidence against linkage (2-point PPL ≤ 2%), 24 SNPs with PPL ≥ 5%, and 7 SNPs with PPL ≥ 10% forming three discernable peaks. The highest PPL value of 58.0% came from marker rs7665438 within the SPRY1 gene on chromosome 4, and its neighboring marker rs300564 showed a moderate PPL of 11.3%. The next linkage peak came from marker rs4987691 and rs4987670 within the EPHB6 gene on chromosome 7, with PPL value of 21.6% and 12.6% respectively. The third peak was located within the L3MBTL3 gene on chromosome 6, where three markers from this region reported PPL value of 13.3%, 17.3% and 17.1%. These results revealed possible linkage signals from these three gene regions.

Of all the tagSNPs, 1405 (95.6%) showed evidence against allelic association with autism (PPLD ≤ 2%). Five markers showed PPLD ≥ 5%, including four markers with PPLD ranging from 5.2% to 8.0% from the MECP2 gene region on the X chromosome, and one marker rs2242601 from the EPHA1 gene region on chromosome 7 that just exceeded 10% (PPLD = 10.4%).

4.2 Multi-point PPL analysis of the Phase 1a dataset

Figure 4.2, 4.3 and 4.4 show the multi-point PPL values together with 2-point PPL and PPLD within our suggestive linkage regions from chromosome 4, 6 and 7,

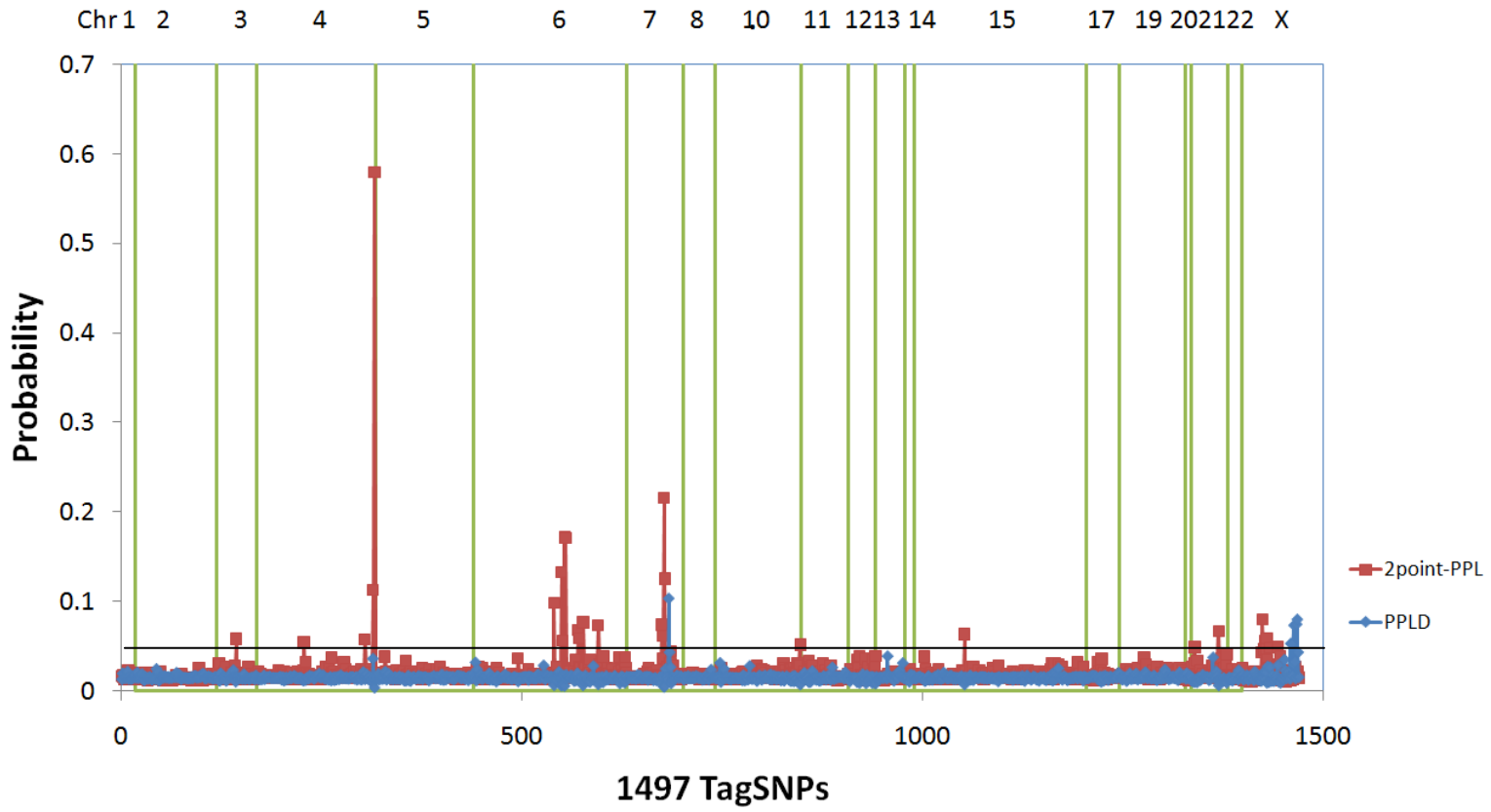

Figure 4.1 Two-point PPL and PPLD of the Phase 1a tagSNPs

respectively. It is shown that multi-point PPL values from the gene regions on chromosome 4 and 6 either do not, or barely, pass the definitive linkage threshold of 2%, despite multiple markers from these regions showing high 2-point PPL values. Since the SNP makers are bi-allelic systems, that is, there are two alleles that an individual may have for any particular marker, the information content per SNP marker is relatively low when compared to other type of marker such as microsatellite markers. Therefore, multi-point methods that combine information from multiple markers are considered more reliable and can be used to avoid possible false positive results. For this reason, we concluded that our findings from 2-point PPL analysis of these two regions may indicate false-positive linkage signals. For the suggestive gene region on chromosome 7, Figure 4.4 shows an overall multi-point PPL value between 5% and 7%. This result is consistent with the 2-point PPL analysis in which three markers from this gene region report probabilities greater than 5%. Therefore we consider the multi-point analysis confirms this linkage region on chromosome 7. The 16 tagSNP markers within this region are from two neighboring candidate genes, 6 markers from the gene EPHB6, and 10 markers, including rs2242601 with PPLD =10.4%, from the gene EPHA1.

4.3 PPL and PPLD analysis of the Phase 1b dataset from suggestive gene regions

Figure 4.5 shows the 2-point PPL, multi-point PPL and PPLD values from the Phase 1 tagSNP dataset plus the AGRE Affymetrix 5.0 SNP array dataset within the EPHB6-EPHA1 gene regions at 7q34-35 (142162 ~ 142916kb). There are a total of 118 SNPs being analyzed within the EPHB6-EPHA1 gene region. Figure 4.5 clearly shows that

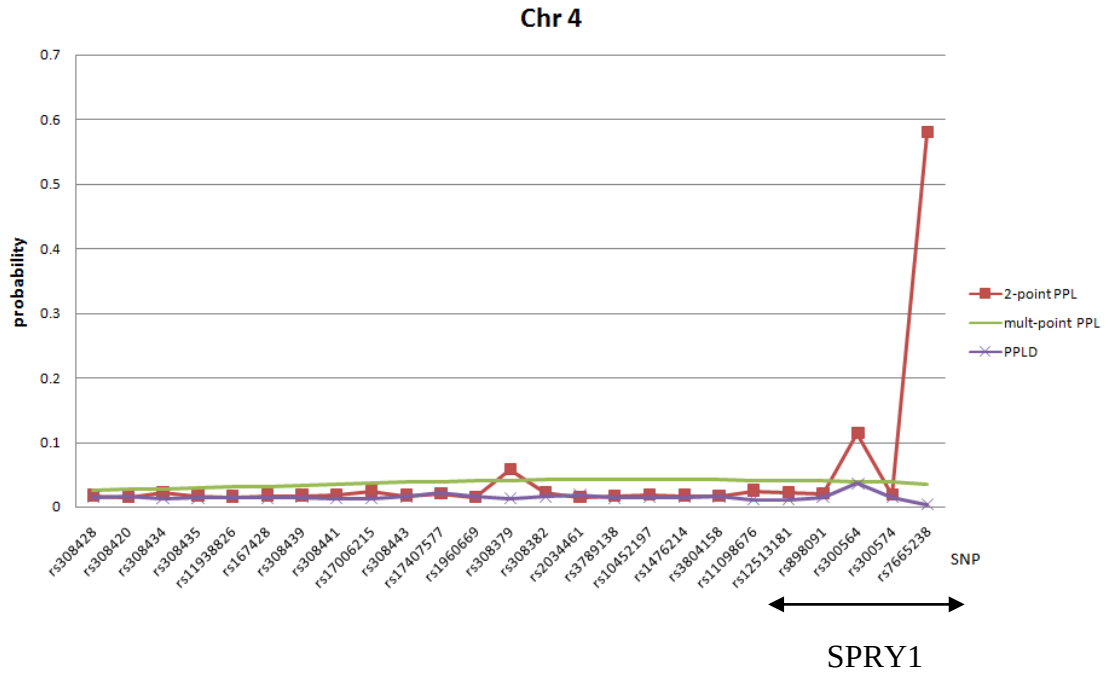

Figure 4.2 PPL and PPLD results of the tagSNPs at gene regions on chromosome 4. Corresponding genes are indicated at the bottom.

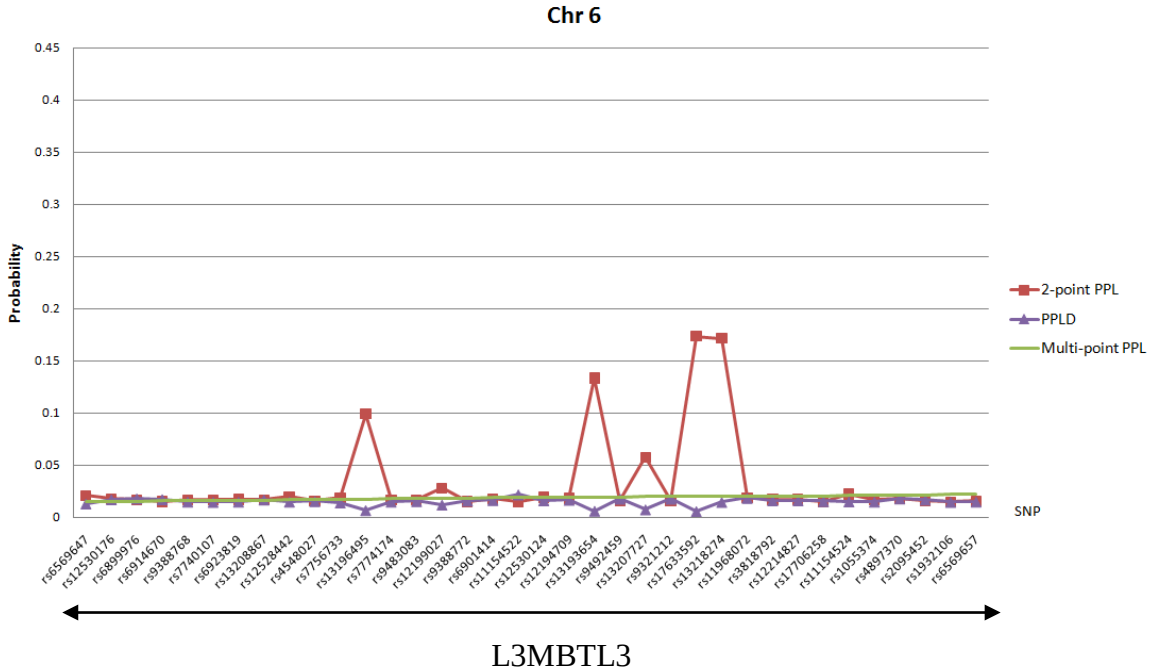

Figure 4.3 PPL and PPLD results of the tagSNPs at gene regions on chromosome 6. Corresponding gene is indicated at the bottom.

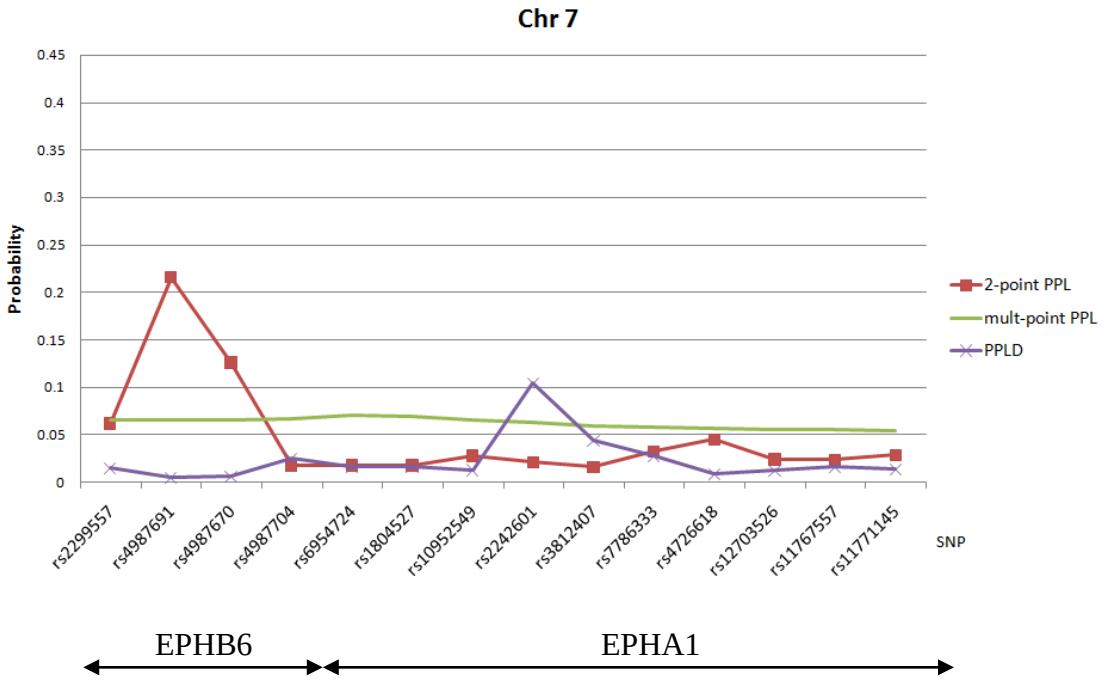

Figure 4.4 PPL and PPLD results of the tagSNPs at gene regions on chromosome 7. Corresponding genes are indicated at the bottom.

the linkage peaks mostly overlap with the EPHB6 gene region and association peaks mostly from the EPHA1 gene region.

From the EPHB6 gene region, a number of markers reported 2-point PPL ≥ 5% and three of them exceed 10% (range from 12.6% to 23.0%). The multi-point PPL values of the EPHB6-EPHA1 gene region remains between 5% and 7%. These results are consistent with previous findings of evidence of linkage from this region.

For markers from the EPHA1 gene region, in addition to the previously identified marker rs2242601, six SNPs at about 90kb downstream of EPHA1 revealed a new association peak with PPLD ranging from 21% to 40%. Figure 4.6 shows the LD plot of markers from the EPHA1 gene region. This plot indicates that all the six markers are correlated with each other ($r^2 > 0.96$), while the SNP rs2242601 has no LD with them.

These results provide direct support for the polymorphisms located within and downstream of EPHA1 as possible candidate loci for autism.

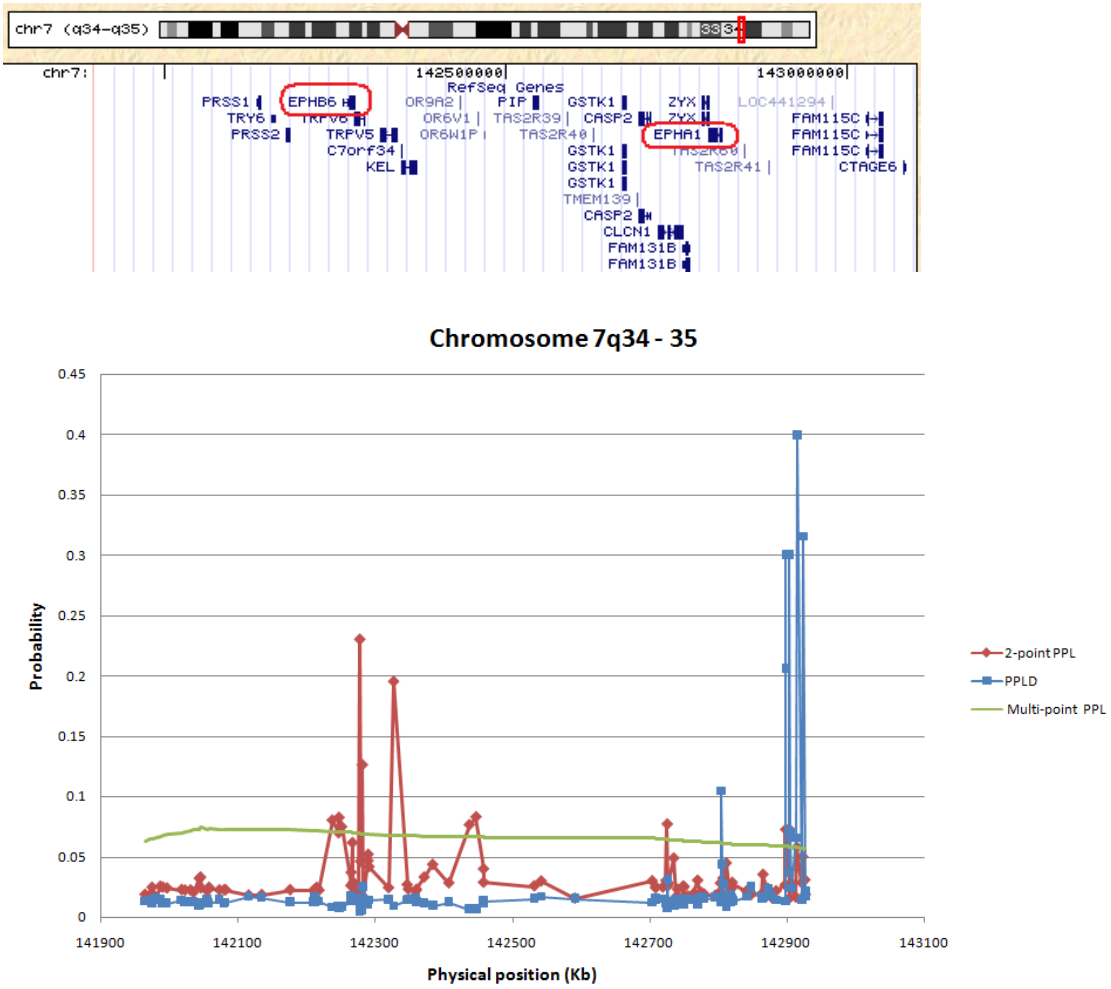

Figure 4.5 PPL and PPLD of markers from combined dataset within the EPHB6-EPHA1 gene region on 7q34-35. The positions of genes are indicated at the top.

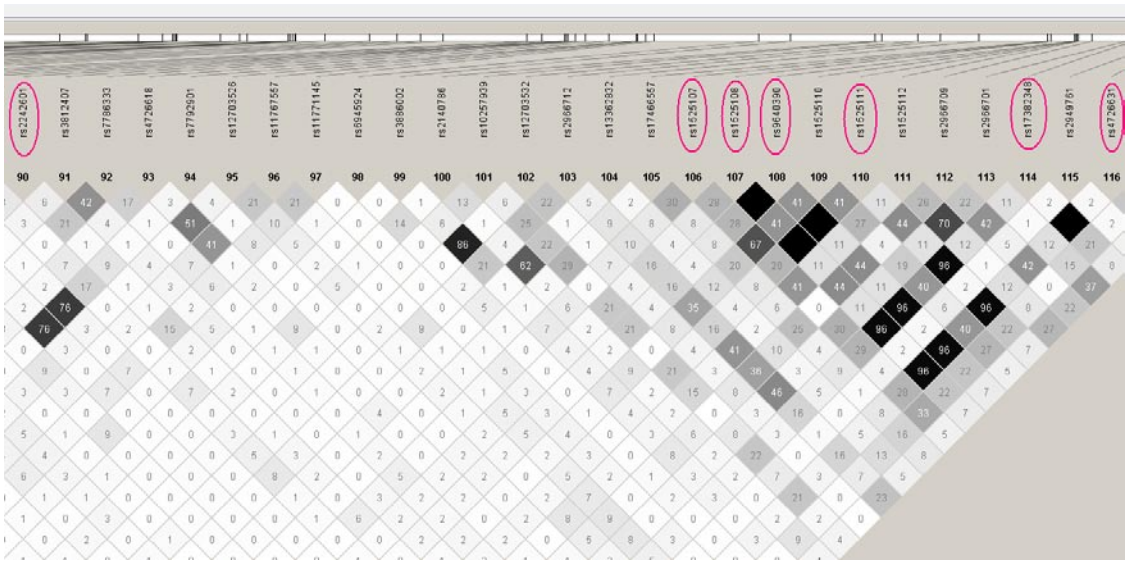

Figure 4.6 LD plot of markers from combined dataset within the EPHA1 gene region, the markers with PPLD > 10% are marked with oval. The numbers within each square indicate percentage r^2 value between each marker pair.

The human gene EPHB6 and EPHA1 both belong to the ephrin receptor subfamily of protein-tyrosine kinase family. The EPHA1 gene contains 18 coding exons. The above identified SNP rs2242601 is an intronic marker between exon7 and exon8, and the associated SNPs downstream of EPHA1 have no overlap with any known gene, although there are a few other genes in this region.

Figure 4.8 shows the 2-point PPL, multi-point PPL and PPLD values from the Phase 1 tagSNP dataset plus the AGRE Affymetrix 5.0 SNP array dataset within the MECP2 gene regions at Xq28 (152179 ~ 153877kb). This figure shows that a number of markers in the MECP2 gene region give PPLD values between 5 and 10 percent. Some of them are located within the gene and the rest are scattered both up- and down-stream of the gene. The inter-marker LD relationships are indicated in Figure 4.9. Very weak

linkage signals (both 2-point and multi-point PPL < 4%) are observed from this region. Therefore there is only limited support for linkage or association of MECP2 with autism.

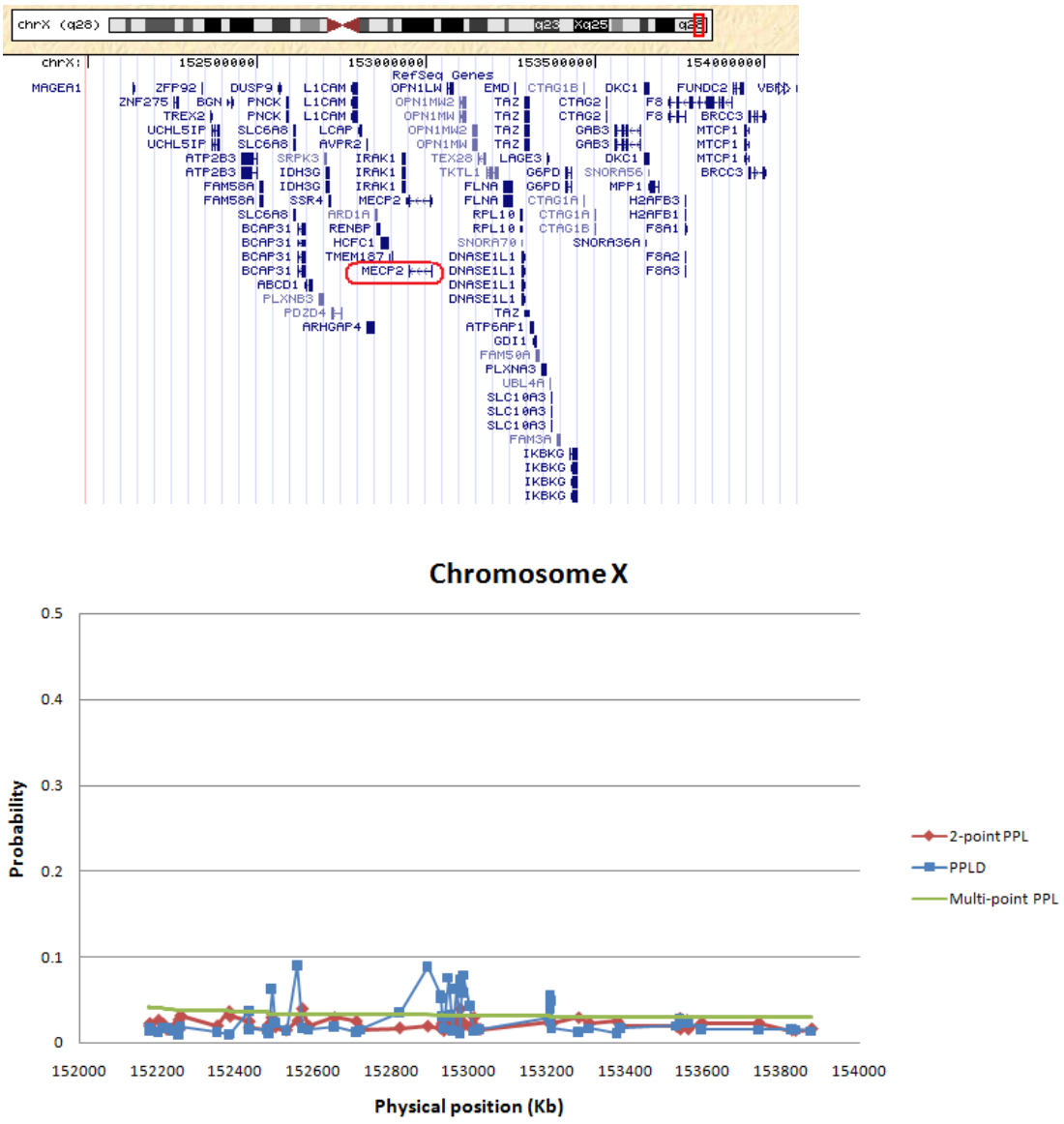

Figure 4.8 PPL and PPLD result of markers from combined dataset within MECP2 gene region on chromosome X. The positions of genes are indicated at the top.

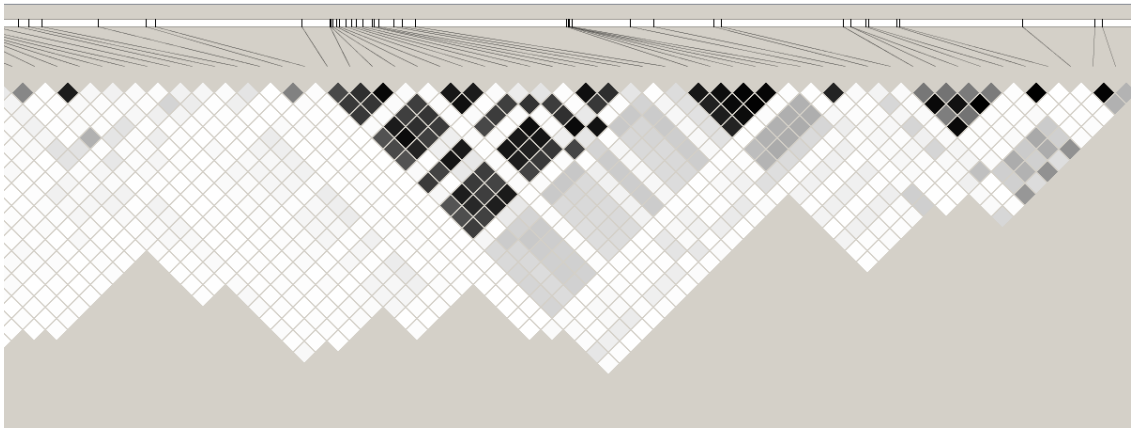

Figure 4.9 LD plot of markers from combined dataset within MECP2 gene region on chromosome X.

4.4 PPLD analysis of the Phase 2 datasets

In Phase 2 of this study, in addition to the 6 SNPs from the EPHA1 gene region that passed the 10% suggestive PPLD threshold in the Phase 1 study, we genotyped 15 other SNPs in both the Phase 1a and Phase 2 AGRE family sets in order to test for association, and hopefully identify the most likely functional risk variant. According to the HapMap database, there are no other markers in LD ($r^2 \geq 0.6$) with the identified intronic SNP rs2242601. The rest of the markers are all from about 90kb downstream of EPHA1 and are in a single LD bin (Figure 4.11). The LD pattern of the markers using the Phase 1a family samples is very similar to that using the Phase 2 family samples. Figure 4.10 shows that when using the Phase 1 a samples all the markers indicate positive evidence of association (PPLDs range from 3.2% to 62.5%). The highest PPLD (62.5%) comes from SNP rs7801889 located at 90.2kb downstream of the gene. The fact that this marker has only moderate LD (r2 ≈ 0.6) with the neighboring markers is consistent with its stronger

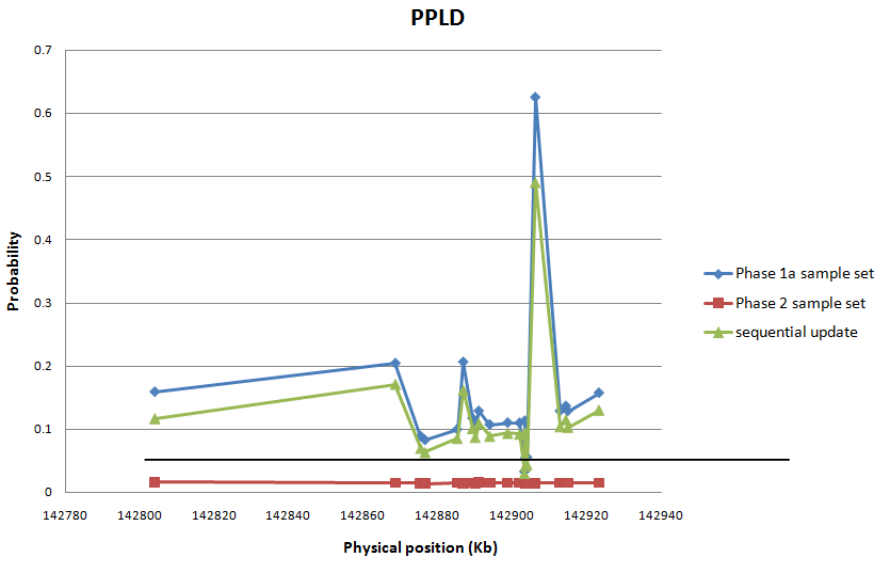

Figure 4.10 PPLD of markers from the Phase 2 study within the EPHA1 gene region

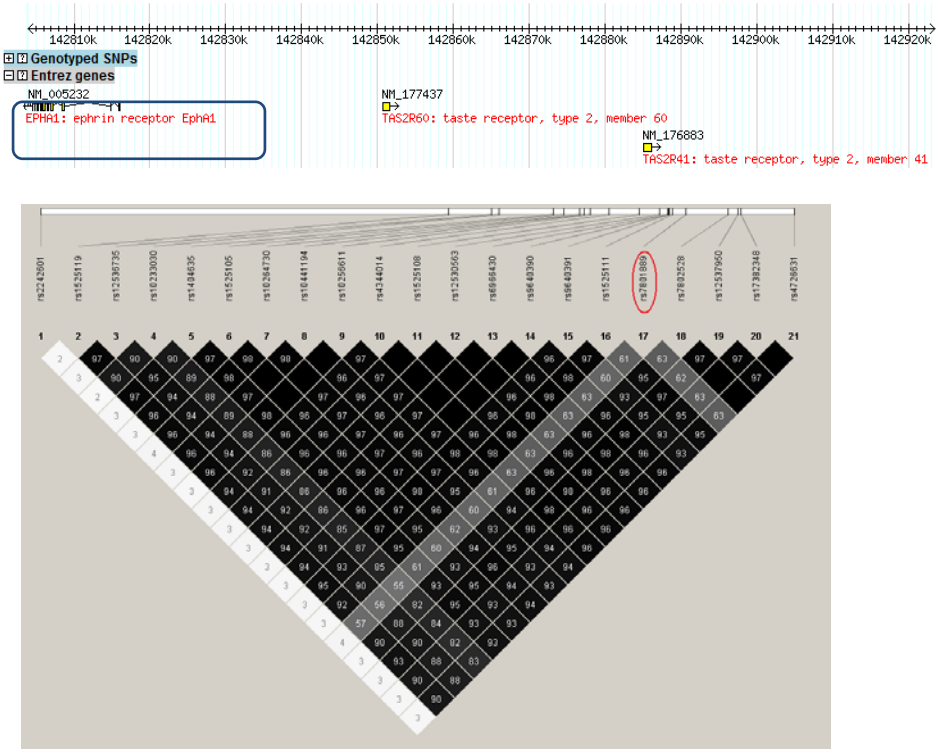

Figure 4.11 LD plot of SNPs from the Phase 2 study within EPHA1 gene region. The positions of the gene and SNPs are indicated at the top. The SNP rs7801889 with highest PPLD is marked with oval.

association signal compared with others. In contrast, none of these markers shows supportive evidence in the Phase 2 additional family set (PPLDs < 2%). Furthermore, considering this sample set may not be fully consistent with Phase 1a samples due to inclusion of female autism patients, we re-analyzed the data without these female patients but still did not find any support for association. Therefore, PPLD values decreased after sequential updating on the two datasets. These results provide mixed support for the intronic SNP 2242601 and the markers downstream of EPHA1 as autism risk variant.

For the MECP2 gene region, 7 SNPs from the phase 1 study and 7 additional markers were genotyped in the original and the additional selected AGRE samples. Figure 4.12 shows PPLD results of the 14 SNPs from the MECP2 gene region using the Phase 1a and Phase 2 family set. In the Phase 1a sample set, very weak support for association (PPLD range from 3% to 7%) was observed from all of the markers. An LD plot of these markers is indicated in Figure 4.13. When the Phase 2 additional sample set was analyzed, no supportive evidence for association (PPLD $\leq$ 2%) was detected. Thus diminished PPLD values were reported after sequential updating on the two datasets. These results, again, illustrate limited evidence for the MECP2 gene as an autism candidate locus.

4.5. Effect of sample selection on PPLD result

In this study, because only a subset (243 out of 265) of pedigrees in the AGRE Affymetrix 5.0 SNP array dataset overlap with our original selected samples, there is a

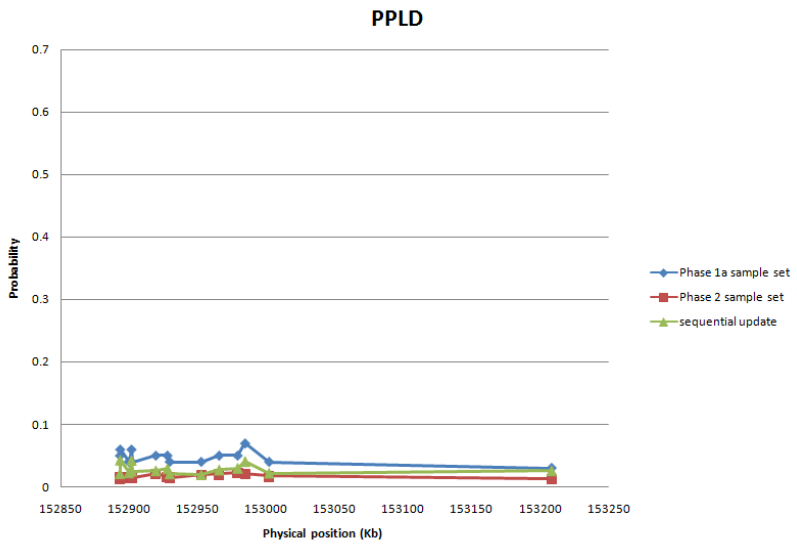

Figure 4.12 PPLD of markers from the Phase 2 study within the MECP2 gene region.

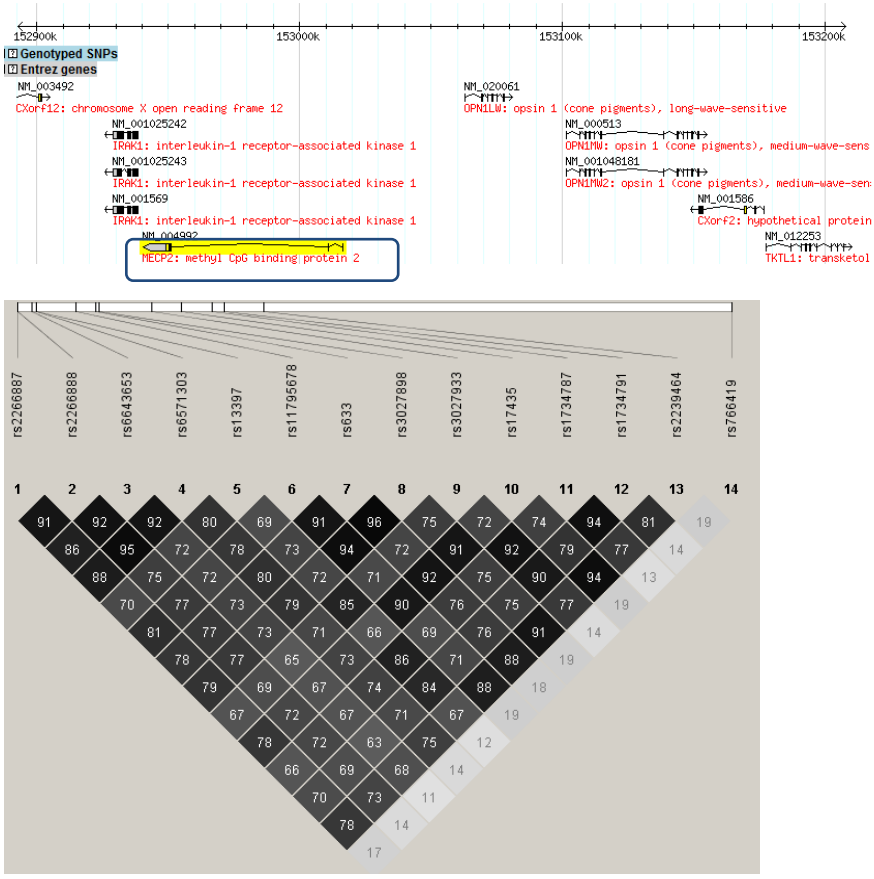

Figure 4.13 LD plot of markers from the Phase 2 study within the MECP2 gene region. The positions of the gene and SNPs are indicated at the top.

discrepancy in the observed PPLD values for the common markers between our phase 1b and phase 2 result. Table 4.1 lists PPLD results of these markers from the EPHA1 gene region in both studies. It shows that when the overlapping subset of AGRE pedigrees were used in the phase 1b analysis, values of PPLD more than doubled for these markers. This result is very interesting considering there is only a relatively small difference in the number of samples. From the phenotype information sheet provided by AGRE, we did not identify any obvious reason for the exclusion of these families in their study, other than that these pedigree samples were not available at the time of their experiment. Nevertheless, this finding implies the significant effect and importance of sample set selection especially in the study of complex diseases, where genetic heterogeneity may play an important role.

Chr	SNP	Physical position (bp)	PPLD	
			Phase 1b dataset	Phase 2 dataset
7	rs1525108	142898876	0.3009	0.1094
7	rs9640390	142903469	0.3009	0.1124
7	rs1525111	142904065	0.3009	0.0545
7	rs17382348	142915034	0.4002	0.1279
7	rs4726631	142923417	0.3159	0.1567

Table 4.1 PPLD difference of some markers form EPHA1 gene region using the Phase 1b and Phase2 sample sets.

4.6 Result of PDT analysis

Table 4.2 shows the p values of PDT analysis on SNPs from the EPHA1 gene region using the Phase 1a family set and the Phase 2 family set. In general this result is consistent with the outcome from the PPLD analysis. In the Phase 1a sample set, two markers passed the highly significant p value threshold of 0.01 after correction for multiple testing. They are SNPs rs2242601 (p = 0.0029) and rs7801889 (p = 0.0003). In the Phase 2 sample set, since none of these markers showed any evidence for allele over-transmission, the correction for multiple testing is not necessary for this sample set. The uncorrected p values from rs2242601 and rs7801889 are 0.103 and 0.332 respectively.

		Phase 1a family set		Phase 2 family set	
SNP	Allele	Frequency	P value (corrected)	Frequency	P value (uncorrected)
rs2242601	A/G	0.74/0.26	0.0029	0.66/0.34	0.109
rs1525119	A/T	0.68/0.32	0.0109	0.72/0.28	0.393
rs12536735	A/G	0.32/0.68	0.0198	0.28/0.72	0.737
rs10233030	C/G	0.34/0.66	0.0705	0.31/0.69	0.513
rs1404635	C/T	0.68/0.32	0.0229	0.72/0.28	0.509
rs1525105	A/G	0.31/0.69	0.0128	0.28/0.72	0.475
rs10264730	A/G	0.32/0.68	0.0151	0.27/0.73	0.519
rs10441194	A/G	0.69/0.31	0.0256	0.72/0.28	0.453
rs4344014	C/G	0.31/0.69	0.0269	0.28/0.72	0.626

rs1525108	A/G	0.69/0.31	0.0109	0.73/0.27	0.446
rs12530563	A/G	0.69/0.31	0.0244	0.73/0.27	0.472
rs6966430	C/T	0.67/0.33	0.0450	0.73/0.27	0.442
rs9640390	A/G	0.69/0.31	0.0315	0.73/0.27	0.509
rs9640391	A/G	0.31/0.69	0.0456	0.73/0.27	0.401
rs1525111	A/G	0.32/0.68	0.1086	0.27/0.73	0.652
rs7801889	C/T	0.43/0.57	0.0003	0.38/0.62	0.332
rs7802528	A/G	0.68/0.32	0.0186	0.72/0.28	0.445
rs12537950	A/G	0.31/0.69	0.0177	0.28/0.72	0.472
rs17382348	A/G	0.68/0.32	0.0186	0.72/0.28	0.549
rs4726631	C/T	0.32/0.68	0.0143	0.28/0.72	0.376

Table 4.2 PDT result of the markers from the EPHA1 gene region in two sample sets.

4.7 Evaluation of tagSNP transferability

We tested the tagSNP transferability (LD structure similarity) between our AGRE sample and the HapMap CEPH reference panel. In phase 1 of our study, the tagSNPs for our analysis were selected using genotype data from HapMap CEPH (Caucasian) samples, but 91 out of 263 of our AGRE sample families are from Hispanic and other ethnic populations. Considering the possible variation of inter-marker association among selected samples from different ethnic populations, we carried out a transferability analysis within our EPHB6-EPHA1 gene region to see whether the tagSNPs can efficiently represent all the variants within our test samples.

The EPHB6-EPHA1 gene region spans about 755kb at the 7q34-35 region. Within this region we identified 82 SNPs in common with both the Hapmap CEPH and

the AGRE Affymetrix 5.0 array data sets. Table 4.2 lists a summary of the SNP minor allele frequency (MAF) from the overlapping families of these two sample sets. This table shows that the distribution of MAF is identical. Figure 4.15 illustrates similar LD structures for these markers within our candidate gene region. Table 4.3 shows the number of markers captured in our sample set by tagSNPs picked from the HapMap CEPH sample set. Under the pairwise tagging mode, 52 selected tagSNPs are able to capture the variation from 73 out of 82 markers in the AGRE sample set; and by the aggressive mode, the same number of markers can be represented by 47 tagSNPs. The markers that cannot be represented by tagSNPs are those with low MAF and can mostly be captured by lowering the threshold of r^2. These results show that our tagging approach can effectively capture the majority (~ 90%) of the genotype information from this gene region, and indicate comparable LD structure among markers from the two data sets.

SNP MAF	AGRE	CEPH
0-0.1	33	33
0.1-0.2	24	24
0.2-0.3	13	13
0.3-0.4	15	15
0.4-0.5	15	15
Total	82	82

Table 4.3. Summary of the SNP minor allele frequency from two data sets

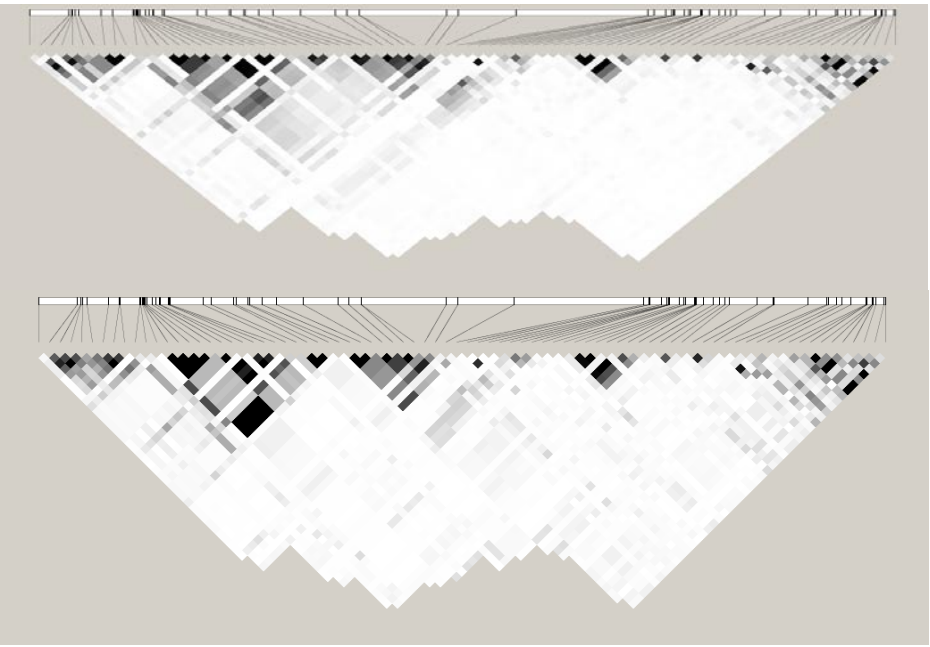

Figure 4.14. LD plot of common SNPs within the EPHB6-EPHA1 gene region. Upper: HapMap CEPH dataset; Lower: AGRE samples set.

Tagging mode	sample	Total SNP (MAF>0.01)	tagSNP	captured SNP (r^2>0.8)	%
Pairwise	CEPH	80*	52	80	100
	AGRE	82	52	73	89
Aggressive	CEPH	80*	47	80	100
(Multi-marker)	AGRE	82	47	73	89

Table 4.4 Number of SNPs captured by two tagging approaches

* Two SNPs were excluded from CEPH dataset due to their MAF =0

4. 8 PPL and PPLD analysis of the phase 1a tagSNPs in ethnic subgroups

In our phase 1 study, the 263 AGRE family samples are composed of 174 Caucasian, 49 Hispanic, and other mixed ethnic groups. To evaluate whether inclusion of multiple populations had an effect on our analysis, we carried out 2-point PPL and PPLD analysis on stratified Caucasian and Hispanic subgroup samples. The Caucasian and Hispanic subgroups include 645 and 182 genotyped subjects, respectively. The observed PPL and PPLD values of 1469 tagSNPs using complete and subgroup datasets are shown in Figure 4.15a and 4.15b.

In the Caucasian subgroup, we detect two markers from chromosome 4 and two markers from chromosome 6 with 2-point PPL just above 10%. While three of these markers were identified previously using the complete sample set, their PPLs are lower in this subgroup. However, the fourth SNP, rs4690150 from chromosome 4, showed increased PPL from 3% to 13%. None of the region shows any interesting result from the multi-point PPL test. Interestingly, the associated intronic SNP rs2242601 from EPHA1 maintained its PPLD value at 10% when analyzed in Caucasians, almost identical to its value when using the complete sample set. Notably, one other marker rs1009848, which is from the EPHB6 gene on chromosome 7, shows an increased in PPLD from 2% to 9% in the Caucasian samples.

In the Hispanic subgroup, 3 markers from chromosome 12, 14 and the X chromosome have 2-point PPL between 10% and 20%, and, again, we did not detect any linkage signal from the multi-point PPL test in this sample subset. In addition, all the markers gave results that are below 10% in the PPLD test.

In summary, although we observed some different results when restricting analysis to ethnic subgroups, none of them showed a very strong signal in the PPL or PPLD analysis. However, the SNP rs1009848 from the EPHB6 gene might be an interesting candidate locus for the follow-up study.

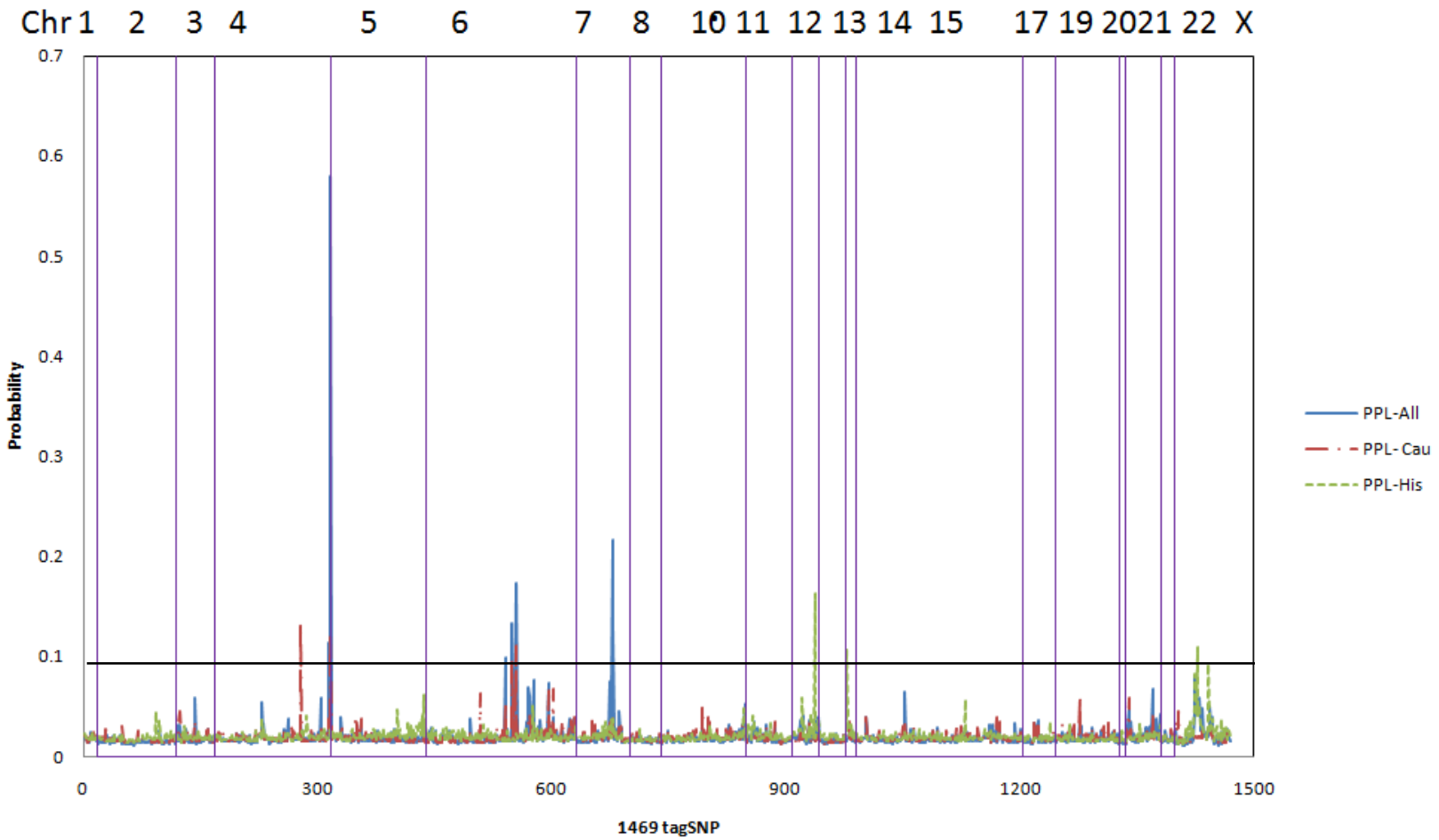

Figure 4.15a. PPL analysis result of 1469 tagSNPs using complete dataset and Caucasian and Hispanic subgroup datasets

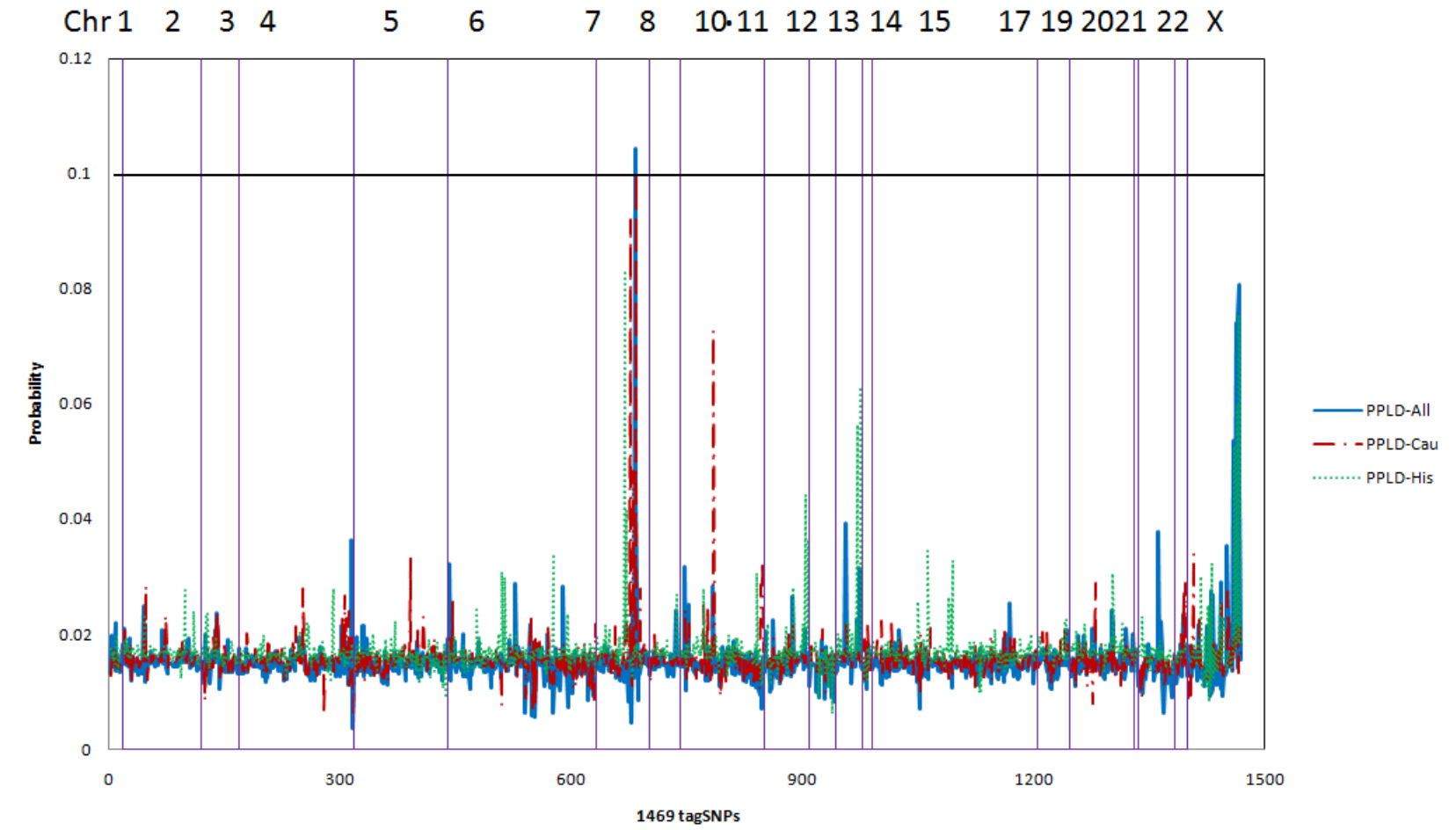

Figure 4.15b. PPLD analysis result of 1469 tagSNPs using complete dataset and Caucasian and Hispanic subgroup datasets

Chapter 5. Discussion

In this study we investigated the possible involvement of 111 candidate genes in autism by studying samples from 386 Autism Genetic Resource Exchange (AGRE) families. These genes were selected based on their functions that relate to the neurotransmission or central neural system. In phase 1 of the study, 1497 tagSNPs were selected based on Linkage Disequilibrium (LD) information from the HapMap CEPH reference panel to efficiently capture the haplotype information of each gene. These markers were genotyped and subsequently subjected to a strict quality control and error checking procedure. The cleaned genotype data were analyzed through the Kelvin program to compute values of Posterior Probability of Linkage (PPL) and Posterior Probability of LD given linkage (PPLD), which directly measure the probability of linkage and/or association. Consistent supportive evidence for linkage was observed for EPHB6-EPHA1 locus at the 7q34 region by 2- and multi-point PPL analysis. Furthermore, some evidence for association was obtained from the intronic SNP rs2242601 of the EPHA1 gene (PPLD = 10.4%), and 5 SNPs from the MECP2 gene at Xq28 (PPLD range from 5~9%). Next, we focused on these two gene regions and tested additional markers for possible association with autism, using a subset of autism genotype data from the newly released Affymetrix 5.0 high-density SNP array by the AGRE. Further evidence for association was obtained for 6 markers located 90kb distal of EPHA1 gene (PPLD range from 21% to 40%).

In phase 2 of this study, in an attempt to conduct fine mapping as well as to replicate our phase 1 results in a set of 123 additional AGRE family samples, we selected 21 SNPs from the EPHA1 gene region and 14 SNPs from the MECP2 gene region for fine-scale genotyping and analysis. Strong support of association with autism was observed for the markers 90Kb downstream of the EPHA1 gene using the

original family samples, with the SNP rs7801889 positioned at 7q35 showing a high PPLD value of 62%. Markers from the MECP2 gene region remained moderately associated with a PPLD value at around 8%. Nonetheless, none of these 35 SNPs showed any evidence of association in the additional family samples. These mixed preliminary results suggested the polymorphisms within and downstream of Ephrin receptor A1 gene as potential novel susceptibility loci for autism. Limited support for the role of MECP2 in autism etiology was also observed.

Within the EPHA1 gene region, we have analyzed a total of 8 SNPs, 2 of which are synonymous coding SNPs and 6 are in the introns. Other than the detected over transmission from the SNP rs2242601, only one other marker, rs3812407, exhibited minimal support of association with autism (PPLD = 4.4%). Since there is no other SNP available from the HapMap database that is in LD ($r^2 > 0.4$) with rs2242601, we were not able to determine whether there is any other unknown risk loci that in LD with this marker. Further experimental analysis, such as detecting the mRNA expression level of the gene under different alleles, is necessary to elucidate possible effects of rs2242601. According to dbSNP (Build 129), a total of 81 polymorphisms have been identified within the EPHA1 gene, but only 18 of them have been genotyped for the HapMap project. In this study we restricted our SNP selection to those already been validated by the HapMap, therefore a significant portion of the polymorphisms annotated for this gene were not available for analysis, which limited our ability to conduct fine mapping of functional loci. To fully examine the possible association of EPHA1 with autism, these markers will also need to be tested.

The most significant PPLD result of this study came from the SNP rs7801889, which is located 90kb downstream of the EPHA1 gene. Considering the distance

between this marker and the EPHA1 gene, it is not clear whether this polymorphism may affect the function of EPHA1 or any other genes. According to the UCSC genome browser (Mar. 2006 Assembly), the genomic position of SNP rs7801889 is within the region of a putative Homo sapiens mRNA AL833583. Interestingly, this mRNA is from the opposite strand of EPHA1 and is overlaps with the gene 5' end portion. Many studies have shown that similar complementary transcription may play a role in the regulation of the gene expression (Kiyosawa, Yamanaka et al. 2003; Beltran, Puig et al. 2008; Li, Zhang et al. 2008). It has been shown that large numbers of natural antisense transcript exist throughout the genome, and they may form linked transcription units with neighboring gene loci (Katayama, Tomaru et al. 2005). This implies a possible regulation mechanism behind the rs7801889 and the EPHA1 gene through AL833583. There are also two other genes located close to rs7801889 (both are Type-2 Taste Receptor genes), but they seem unlikely to be involved in the etiology of autism, hence improbable to be regulated by this SNP. While it is known that regulatory sequences may be located several hundred thousand base pairs away at either upstream or downstream of the genes that they regulate, further investigation will be needed to explore the functional consequence of this variation.

Despite the strong indication of association from multiple loci in the EPHA1 gene region, this result did not extend to the Phase 2 additional AGRE sample set. Many factors may contribute to the lack of replication in the association studies of complex traits. Subjective diagnosis of disease based on behavior criteria, genetic heterogeneity between samples, sample variation due to different background, accumulated effects from multiple disease loci, epigenetic effect, and data over-interpretation have all been suggested as reasons for result discrepancies (Bartlett, Gharani et al. 2005). Therefore, inconsistents result from a second sample

set does not invalidate findings from the original population. Furthermore, the cause of autism is likely due to interactions from multiple genes, effects from any single gene may only play a partial role in the autism etiology. Nevertheless, the discovery of high frequency risk alleles still implies their importance in a subset of autism patients.

The distal long arm of chromosome 7 has been implicated in autism by many studies. Overlaps of linkage peaks suggested susceptibility loci located within the region between 7q32 to 7q36 (IMGSAC 1998; Ashley-Koch, Wolpert et al. 1999; Liu, Nyholt et al. 2001; Alarcon, Cantor et al. 2002; Auranen, Vanhala et al. 2002; Shao, Wolpert et al. 2002; Lamb, Barnby et al. 2005; Ylisaukko-oja, Alarcon et al. 2006). At least four independent studies of genome scans showed evidence for linkage between ASD and 7q34-35, but none of them used markers that overlap with the EPHA1 gene region. In the research carried out by the International Molecular Genetic Study of Autism Consortium (IMGSAC 1998), a significant multipoint maximum lod score (MLS) of 3.55 was found in a set of 56 UK affected sib-pair families near the marker D7S684, which is located about 4.5 Mb upstream of EPHA1. In a follow-up analysis of 99 American multiplex families after a genome screen completed by Shao, Wolpert et al. (2002), the authors reported a suggestive MLS score of 1.66 at marker D7S495 located approximately 5 Mb proximal to EPHA1. In another autism genomic study focused on chromosome 7, multiple markers from the 7q34 region only illustrate weak LOD score ranging from 1 to 1.5, and these markers are located 3Mb or further from EPHA1 (Ashley-Koch, Wolpert et al. 1999). In a recent study, McCauley and co-workers performed a linkage scan in 158 combined autism family samples collected by Tufts, Vanderbilt and AGRE, a suggestive HLOD score of 1.65 was obtained from a marker at a distance less than 1Mb from EPHA1

gene (McCauley, Li et al. 2005). In addition to the researches listed above, our PPL analysis also provided direct support for linkage in this region. Multiple SNP markers from EPHA1 and its neighboring gene EPHB6 showed consistent evidence for linkage in both two-point and multi-point PPL analysis. Therefore, these results provide further support to previous studies that linked this genomic region to autism.

The EPHA1 gene is a member of the ephrin receptor subfamily of the protein-tyrosine kinase family. The ephrin receptors are divided into A (8 members) and B subclasses (6 members) on the basis of sequence similarity and ligand affinity (Yamaguchi and Pasquale 2004). The Eph receptors and ligands function as a guidance system to position cells and modulate cell morphology. Previous studies discovered that Eph receptor families can guide growing neuronal processes during development towards their targets through cell-cell repulsive effects. In recent years mounting studies have unveiled their essential roles in cell morphogenesis, tissue patterning, angiogenesis and neural plasticity, although the exact signaling mechanisms of most Eph system in the adult brain are still largely unknown. Eph proteins have been found to express in high levels in the embryonic nervous system as well as in the adult. A study of gene mRNA expression profiles of 12 different Eph receptors and 8 ligands in 13 different, healthy tissues found that the greatest expression of the EPHA4, EPHA6, EPHA7, EPHB4, and EPHB6 receptors and the ephrin-A5 and ephrin-B2 ligands was in the adult human brain, while most other Eph receptors and ligands were also detected at substantial levels (Hafner, Schmitz et al. 2004). It was also found that Eph expression occurs predominantly in regions where neuronal connections continue to form and undergo remodeling in the adult, such as the olfactory system, hippocampus, cortex, and cerebellum.

There has been some evidence that Eph receptors are possibly involved in behavior and support memory acquisition and retention. Firstly, it was shown that infusion of EphA5 receptor antagonists into the hippocampus impairs performance in two behavioral paradigms that are sensitive to hippocampal function (Gerlai, Shinsky et al. 1999). By contrast, infusion of ephrin-A5 Fc, which activates EphA receptors, can enhance cognitive function in mice with inherent learning impairments and mitigate short-term amnesia (Gerlai and McNamara 2000). In another study, behavioral defects were observed from mice lacking EphB2, including decreased habituation to unfamiliar territory and possibly decreased hippocampus-dependent learning performance (Grunwald, Korte et al. 2001). Secondly, the Eph ligands and receptors have been shown to perform essential functions in the regulation of synapse formation and plasticity, which are similar to some other autism candidate genes like NLGNs, NLXNs and SHANK3 (Klein 2009). Since synapses are specialized intercellular junctions dedicated to the transfer of information from a neuron to its target cell, dysfunction of synaptic cell-adhesion molecules may disrupt neural network and lead to possible developmental disorders. One example is that inhibition of the morphological plasticity of excitatory synapses in the brain occurs during general anesthesia, suggesting the effects of the Eph receptors on learning and memory may be due to their regulation of dendritic spine motility and synaptic plasticity (Kaech, Brinkhaus et al. 1999). Thirdly, the Eph receptor was also involved in the RAS/ERK/CREB signal transduction pathway. Recent discoveries have suggested that the disruptions of RAS and its intracellular targets in this cascade may contribute to the cognitive defects of neurofibromatosis type 1 (NF1) mental retardation syndrome (Takasu, Dalva et al. 2002; Weeber and Sweatt 2002; Fleischmann, Hvalby et al. 2003).

In the review by Murai and Pasquale (2004), the authors noted that a remarkable number of the genes that code for the Eph receptors and ligands are in chromosomal regions that have been associated with susceptibility to various mental disorders in previous linkage analysis. They observed 6 out of 11 potential autism linkage regions overlap with the location of Eph receptor or ephrin genes, especially the 7q region that includes the locations of the EPHB4, EPHB6, and EPHA1 genes. In addition, multiple Eph genes were found in chromosomal regions that have been linked to schizophrenia and bipolar disorder.

While many researchers have studied the role of Eph receptor and ephrin genes in development, other evidence implicates their involvement in tumourigenesis (Surawska, Ma et al. 2004; Campbell and Robbins 2008; Castano, Davalos et al. 2008; Chen, Zhuang et al. 2008; Vaught, Brantley-Sieders et al. 2008). EPHA1 was the first of the Eph family to be identified, and was reported to express widely in epithelial cells (Coulthard, Lickliter et al. 2001). Though there is only limited knowledge of its function, many published studies have related EPHA1 to various aggressive tumors, including breast cancer, ovarian cancer, prostate cancer, colon carcinoma, malignant melanoma, kidney carcinoma, and neuroblastomas(Fox and Kandpal 2004; Hafner, Schmitz et al. 2004; Wimmer-Kleikamp and Lackmann 2005; Holm, de Putte et al. 2008). Lida et al. (2005) suggested that the expression of ephrin A1 induces expression of genes related to tumour cell growth, angiogenesis, invasion, and metastasis. Alford et al. (2007) found that the transglutaminase-cross-linked ephrin binds to A-type Eph receptors, stimulates Eph kinase activity, and promotes invasion and migration of HeLa cells. Interestingly, despite many studies having linked members of Eph receptor gene family with developmental functions, no one has

identified the involvement of the EPHA1 gene with any brain dysfunction or psychiatric disorder.

The MECP2 gene is located on the long arm of the X chromosome at position q28. As a member of methyl-CpG-binding protein family, this gene is capable of binding specifically to methylated DNA and represses transcription of methylated gene promoters. MECP2 is essential for embryonic development. Mutations of this gene have been proved to be the cause of many cases of female Rett syndrome, a progressive neurologic developmental disorder with notably similar clinical features with autism (Moretti and Zoghbi 2006). Whether MECP2 gene is directly related to autism is still under dispute. Despite the fact that most previous reports have not found any evidence that associates MECP2 mutations with autism patients (Beyer, Blasi et al. 2002; Lobo-Menendez, Sossey-Alaoui et al. 2003; Zappella, Meloni et al. 2003), some recent studies did suggest its role in the idiopathic autism (Carney, Wolpert et al. 2003; Li, Yamagata et al. 2005; Loat, Curran et al. 2008). Notably, MECP2 has also been suggested as a key regulator in the formation of synapses between neurons, which results in the establishment of the neural network and forms the cellular basis of learning and memory (Chao, Zoghbi et al. 2007; Palmer, Qayumi et al. 2008).

In summary, our preliminary results from the current study identified the Ephrin receptor A1 gene and the SNP markers downstream as potential novel autism susceptibility loci. Moreover, we provide moderate support for the role of the MECP2 gene in the etiology of autism. Further replication tests on other sample sets and functional studies of RNA or protein expression will be necessary to disclose any effects of EPHA1 on development and/or psychiatric disorders.

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Appendix 1. 2-point PPL and PPLD results of the Phase 1 tagSNPs in complete sample set, Caucasian and Hispanic subset

Chr	SNP	cM	Complete sample set		Caucasian subset		Hispanic subset	
			PPL	PPLD	PPL	PPLD	PPL	PPLD
1	rs6682175	3.7874	0.0178	0.0131	0.0206	0.0128	0.0224	0.0174
1	rs16824627	3.8788	0.0166	0.0198	0.0186	0.0176	0.0192	0.016
1	rs16824628	3.8794	0.0181	0.0191	0.0186	0.0176	0.0201	0.0158
1	rs3128315	3.9324	0.0141	0.0155	0.0133	0.0158	0.0211	0.0172
1	rs7522389	44.5136	0.0157	0.0144	0.0168	0.0156	0.0215	0.0149
1	rs2294630	44.5224	0.018	0.0152	0.0175	0.0144	0.0206	0.0148
1	rs3790756	44.5374	0.014	0.0164	0.0151	0.0168	0.0174	0.0168
1	rs6699866	44.5409	0.0198	0.0219	0.0237	0.0143	0.0173	0.0192
1	rs9659997	44.5439	0.0242	0.0136	0.0188	0.0135	0.0215	0.0196
1	rs9064	44.5508	0.0187	0.0161	0.0239	0.0155	0.0166	0.0163
1	rs3813987	44.558	0.0167	0.0137	0.0156	0.015	0.0254	0.0134
1	rs1883567	44.5632	0.0183	0.0139	0.0234	0.0132	0.0162	0.0163
1	rs4845351	155.204	0.0215	0.0135	0.0177	0.0152	0.0172	0.0171
1	rs585215	155.212	0.0206	0.0147	0.018	0.0152	0.0183	0.0166
1	rs4017737	155.219	0.0199	0.0145	0.0185	0.0151	0.0178	0.0174
1	rs1005436	155.228	0.0158	0.0157	0.0181	0.0153	0.0172	0.0175
2	rs6734859	46.7871	0.018	0.0182	0.0207	0.0183	0.0196	0.0165
2	rs1866146	46.7876	0.0152	0.015	0.018	0.0153	0.0182	0.0177
2	rs6713532	46.7906	0.013	0.015	0.0141	0.0154	0.0174	0.0188
2	rs7565427	46.7912	0.0188	0.0209	0.0207	0.0205	0.0197	0.0165
2	rs7565877	46.7915	0.0172	0.0149	0.0177	0.0149	0.0187	0.0191
2	rs934778	46.7936	0.0142	0.0147	0.015	0.0152	0.0167	0.0162
2	rs3769671	46.7942	0.0173	0.0169	0.0191	0.0176	0.0189	0.0176
2	rs6545976	46.7971	0.0143	0.0162	0.0158	0.0166	0.0189	0.0178
2	rs6705798	84.3507	0.0145	0.0145	0.0159	0.0145	0.0176	0.0159
2	rs2018650	84.3525	0.0161	0.0193	0.0167	0.0186	0.0165	0.017
2	rs6545977	84.3565	0.0146	0.0163	0.0156	0.0166	0.0164	0.0159
2	rs1438852	128.619	0.0188	0.0124	0.0265	0.0109	0.0151	0.0177
2	rs4144782	128.623	0.0211	0.012	0.0218	0.0123	0.0162	0.017
2	rs893574	128.626	0.0157	0.0162	0.0232	0.0162	0.0153	0.0178
2	rs893572	128.626	0.0164	0.0145	0.0193	0.0146	0.0172	0.0166
2	rs6719822	128.628	0.0187	0.014	0.0208	0.0143	0.0176	0.0166
2	rs2579632	129.015	0.0128	0.0152	0.0133	0.0154	0.0151	0.0165
2	rs2587663	129.019	0.0184	0.0137	0.019	0.0141	0.0185	0.0167
2	rs2587692	129.028	0.0136	0.0154	0.0144	0.0157	0.0155	0.0172
2	rs2579643	129.034	0.0162	0.0158	0.017	0.0159	0.0168	0.0182
2	rs2254122	129.036	0.0145	0.0146	0.0158	0.0144	0.0156	0.0168

2	rs1866454	129.037	0.0192	0.013	0.0173	0.0142	0.019	0.0164
2	rs2918939	129.042	0.0209	0.0131	0.0176	0.0147	0.0228	0.0159
2	rs2579640	129.045	0.0144	0.0151	0.0163	0.0153	0.0152	0.0165
2	rs6710114	129.056	0.016	0.0147	0.0154	0.0162	0.0176	0.0165
2	rs10172294	129.056	0.0173	0.0144	0.0171	0.0151	0.0181	0.0168
2	rs2579656	129.06	0.018	0.0132	0.0162	0.0143	0.0188	0.0159
2	rs11687793	129.069	0.0159	0.0249	0.0164	0.0226	0.0196	0.0231
2	rs10200558	129.071	0.0151	0.015	0.0145	0.0156	0.0199	0.0158
2	rs2579616	129.082	0.0179	0.0217	0.0191	0.0282	0.0169	0.0166
2	rs1992248	129.087	0.021	0.0117	0.0175	0.0147	0.0157	0.0158
2	rs7574918	170.427	0.013	0.0153	0.0134	0.0155	0.0159	0.016
2	rs2165208	170.432	0.0221	0.0133	0.0299	0.012	0.0222	0.0163
2	rs6756406	170.439	0.0144	0.0154	0.0162	0.016	0.0175	0.017
2	rs11686777	170.44	0.0133	0.0158	0.0143	0.0156	0.0155	0.0168
2	rs1158135	170.448	0.0141	0.0149	0.016	0.0146	0.0151	0.0179
2	rs1946892	170.456	0.0125	0.0151	0.0142	0.0151	0.0149	0.017
2	rs1439808	170.459	0.0132	0.0171	0.0142	0.0162	0.0155	0.0174
2	rs4667786	170.463	0.0131	0.0154	0.0145	0.0153	0.0148	0.0167
2	rs4667792	170.467	0.0129	0.0152	0.0145	0.0155	0.0148	0.017
2	rs2304710	170.468	0.0129	0.0156	0.0146	0.0161	0.0149	0.0176
2	rs11894144	170.475	0.013	0.0148	0.0146	0.0164	0.0152	0.0176
2	rs6755352	170.477	0.0139	0.0159	0.0142	0.0161	0.0186	0.0177
2	rs2390165	170.487	0.014	0.0145	0.0164	0.0149	0.0164	0.0159
2	rs1978340	177.388	0.0121	0.0153	0.0139	0.0153	0.0163	0.0162
2	rs3791878	177.39	0.012	0.0156	0.0136	0.0155	0.0164	0.0164
2	rs2241165	177.395	0.0137	0.0147	0.0166	0.0145	0.0158	0.0163
2	rs3828275	177.398	0.0117	0.0155	0.0145	0.0153	0.0142	0.0164
2	rs10191129	177.402	0.0133	0.0158	0.015	0.0153	0.0149	0.0169
2	rs7578661	177.422	0.0142	0.0167	0.0171	0.0151	0.0163	0.0166
2	rs16858996	177.425	0.0137	0.0154	0.0157	0.0163	0.0161	0.017
2	rs17701824	177.425	0.0133	0.0159	0.0153	0.0173	0.0147	0.017
2	rs4439928	177.425	0.0191	0.0207	0.0253	0.0161	0.0189	0.017
2	rs788160	178.359	0.0149	0.0156	0.0163	0.0156	0.0169	0.0178
2	rs13390848	178.368	0.0142	0.015	0.0173	0.0151	0.0155	0.0174
2	rs4519482	178.373	0.0136	0.019	0.0153	0.0232	0.0157	0.0165
2	rs10930506	178.389	0.0143	0.0161	0.0177	0.0178	0.0155	0.0171
2	rs2253206	207.295	0.0162	0.0142	0.0167	0.0155	0.017	0.017
2	rs6740584	207.348	0.0183	0.0132	0.018	0.0141	0.0183	0.017
2	rs2551922	207.358	0.02	0.0149	0.0172	0.0164	0.0219	0.0162
2	rs2709387	207.363	0.0145	0.0149	0.0169	0.0148	0.0159	0.0171
2	rs2464978	207.381	0.0145	0.015	0.0169	0.0148	0.0156	0.0173

2	rs2551931	207.398	0.0147	0.0149	0.0169	0.0148	0.0159	0.0171
2	rs2551948	207.408	0.0147	0.0149	0.0169	0.0148	0.0159	0.0171
2	rs13013934	226.759	0.0147	0.0148	0.0149	0.0151	0.0202	0.0153
2	rs3087584	226.765	0.0141	0.0147	0.0143	0.0149	0.0226	0.017
2	rs13433079	226.767	0.0156	0.0143	0.016	0.0149	0.0188	0.0168
2	rs16862636	226.777	0.0156	0.0143	0.0161	0.015	0.0196	0.0166
2	rs10196918	226.781	0.0143	0.0149	0.0148	0.0159	0.0179	0.0162
2	rs2303901	226.783	0.0136	0.0145	0.0143	0.0152	0.0192	0.0159
2	rs3770205	226.792	0.0129	0.0148	0.0136	0.0157	0.0189	0.0172
2	rs4340507	226.795	0.0152	0.0161	0.0157	0.0167	0.0176	0.0172
2	rs3770200	226.799	0.0154	0.0144	0.0153	0.016	0.0191	0.0162
2	rs3770197	226.8	0.0135	0.0151	0.0135	0.0158	0.0213	0.0171
2	rs13416809	226.8	0.0155	0.0171	0.0159	0.0174	0.0178	0.0174
2	rs3770181	226.823	0.0164	0.0162	0.0155	0.0157	0.0456	0.0124
2	rs13385102	226.826	0.0157	0.017	0.0159	0.0186	0.0183	0.0171
2	rs2052942	226.826	0.0137	0.0151	0.0143	0.0157	0.0185	0.0163
2	rs12476016	226.827	0.015	0.0155	0.0149	0.0154	0.0191	0.0173
2	rs3815970	226.832	0.0136	0.0151	0.0142	0.015	0.0195	0.0168
2	rs1430214	226.851	0.0264	0.0155	0.0187	0.0149	0.0361	0.0276
2	rs17379786	226.854	0.0179	0.017	0.0175	0.0165	0.0209	0.0212
2	rs3821025	226.863	0.018	0.0157	0.0193	0.0149	0.0176	0.0165
2	rs3770149	226.87	0.0137	0.0168	0.0155	0.0152	0.0159	0.0169
2	rs16862777	226.891	0.0118	0.0188	0.0131	0.017	0.0146	0.0173
2	rs7573758	226.894	0.0123	0.0194	0.0136	0.0173	0.0148	0.0174
2	rs6436266	226.894	0.0134	0.0189	0.0134	0.0169	0.0221	0.0179
2	rs10498114	226.897	0.0157	0.0147	0.0174	0.0147	0.0208	0.0163
2	rs13408240	226.91	0.0166	0.0141	0.0187	0.014	0.017	0.0159
2	rs6740678	226.919	0.0159	0.0144	0.0162	0.0154	0.0224	0.0149
2	rs11695845	226.93	0.0147	0.0151	0.0156	0.0153	0.0168	0.017
2	rs2710508	226.934	0.0149	0.0159	0.0151	0.0148	0.0168	0.0167
2	rs10932916	226.949	0.0131	0.0167	0.0133	0.0155	0.0178	0.024
2	rs960201	226.975	0.0159	0.0147	0.0157	0.0157	0.019	0.0162
2	rs10191992	226.98	0.0164	0.0158	0.0163	0.0161	0.0253	0.0164
2	rs6716153	226.983	0.0179	0.0152	0.019	0.0155	0.0189	0.0174
2	rs10932919	227.003	0.02	0.0146	0.0185	0.0168	0.0194	0.0162
2	rs11888889	227.016	0.0176	0.0136	0.0157	0.0148	0.0216	0.0145
2	rs3770143	227.021	0.0166	0.0146	0.0167	0.0148	0.0195	0.0163
2	rs7340471	227.023	0.0163	0.0139	0.0158	0.0148	0.0212	0.0157
2	rs2248489	227.035	0.0132	0.016	0.0143	0.0157	0.0223	0.0143
3	rs237902	24.8537	0.0144	0.0144	0.0171	0.0146	0.0153	0.0166
3	rs1728820	29.0592	0.0192	0.0151	0.0205	0.0137	0.017	0.0161

3	rs2601124	29.0701	0.0203	0.0143	0.0187	0.0159	0.0222	0.0176
3	rs2697149	29.0711	0.0148	0.0152	0.0179	0.0144	0.0153	0.0164
3	rs2697146	29.0734	0.0317	0.0121	0.0338	0.0106	0.018	0.016
3	rs1710886	29.0774	0.0309	0.0114	0.0443	0.0083	0.0168	0.016
3	rs1710887	29.078	0.014	0.0201	0.0145	0.0153	0.0176	0.0234
3	rs9990174	29.0789	0.0146	0.0144	0.0204	0.0126	0.0142	0.0165
3	rs2933309	29.0826	0.0201	0.0136	0.0182	0.0148	0.0251	0.015
3	rs11710497	29.0895	0.0154	0.0155	0.0146	0.0176	0.0237	0.0235
3	rs1710892	29.0897	0.0134	0.0164	0.014	0.0162	0.0169	0.0162
3	rs17466478	29.0988	0.023	0.0134	0.0187	0.0152	0.0305	0.0139
3	rs2697144	29.0999	0.0165	0.0149	0.0163	0.0145	0.0183	0.0159
3	rs2930154	29.1045	0.0277	0.0114	0.0215	0.014	0.0245	0.0159
3	rs2933308	29.1089	0.0148	0.0148	0.0161	0.0145	0.0179	0.0173
3	rs1728803	29.1175	0.0177	0.0144	0.0233	0.0142	0.0166	0.017
3	rs11712912	29.1245	0.0155	0.0168	0.0164	0.0193	0.0201	0.0171
3	rs17033829	29.129	0.014	0.0166	0.0153	0.0166	0.023	0.0161
3	rs9879137	29.1301	0.0137	0.0173	0.0153	0.0176	0.0187	0.017
3	rs1728802	29.1304	0.0206	0.0151	0.0174	0.0158	0.0215	0.0195
3	rs10510403	29.1307	0.0164	0.0208	0.016	0.0226	0.0193	0.0163
3	rs9822125	29.1311	0.0147	0.0157	0.0149	0.0164	0.021	0.0153
3	rs11719645	29.1367	0.0178	0.0236	0.0197	0.0242	0.0186	0.0175
3	rs2675163	29.1471	0.0147	0.0162	0.0183	0.0175	0.0166	0.0165
3	rs2697138	29.1509	0.0287	0.0159	0.032	0.0125	0.0206	0.0157
3	rs2697135	29.1529	0.0587	0.0105	0.0364	0.0132	0.0203	0.0157
3	rs2944367	29.1561	0.0131	0.0153	0.0149	0.0153	0.0154	0.0165
3	rs1062246	29.1574	0.0172	0.0156	0.0203	0.013	0.0196	0.0169
3	rs17467186	29.1625	0.0215	0.0136	0.0173	0.0163	0.0282	0.0143
3	rs9311317	65.427	0.0139	0.0149	0.0163	0.0148	0.0164	0.0165
3	rs11129947	65.4279	0.0142	0.0148	0.0154	0.0149	0.0176	0.0159
3	rs8192472	65.4305	0.0163	0.0146	0.0175	0.0179	0.02	0.0146
3	rs11571849	65.4343	0.0134	0.015	0.0143	0.0155	0.019	0.0163
3	rs747455	65.4356	0.0175	0.0135	0.0189	0.0146	0.018	0.0158
3	rs747456	65.4357	0.0148	0.0143	0.0164	0.0143	0.0167	0.0163
3	rs10460960	65.4381	0.0155	0.0191	0.0189	0.0164	0.0171	0.0168
3	rs2279829	155.446	0.0191	0.0135	0.0208	0.0135	0.0197	0.0155
3	rs3852000	155.456	0.0168	0.0135	0.0166	0.015	0.0171	0.0163
3	rs10804719	155.458	0.0196	0.014	0.0184	0.0149	0.0205	0.0161
3	rs954735	155.462	0.0178	0.0152	0.0211	0.0154	0.0184	0.0179
3	rs7614043	155.463	0.0219	0.0143	0.0256	0.0141	0.0201	0.0189
3	rs1394042	155.467	0.0277	0.0136	0.0272	0.0128	0.0198	0.0169
3	rs9833875	155.475	0.0174	0.0135	0.0171	0.0155	0.0175	0.0166

3	rs9289748	155.479	0.0163	0.014	0.0162	0.0164	0.0175	0.0166
3	rs939335	191.758	0.0146	0.0152	0.0139	0.0151	0.0216	0.0147
3	rs12493550	191.771	0.0197	0.015	0.0173	0.0156	0.0195	0.0165
3	rs10937159	191.772	0.0142	0.0145	0.0143	0.0152	0.0176	0.0156
3	rs6792482	191.774	0.0137	0.0154	0.014	0.0152	0.0169	0.0157
3	rs1467257	191.777	0.0159	0.0138	0.0152	0.0146	0.0212	0.0146
3	rs7430671	191.789	0.0172	0.0133	0.0174	0.0138	0.0205	0.0145
4	ATSrs4073083	41.0722	0.0198	0.0176	0.0197	0.0168	0.0169	0.0173
4	ATSrs17143739	41.132	0.0194	0.0154	0.0216	0.0151	0.0212	0.0173
4	rs967413	44.4002	0.0173	0.014	0.0155	0.0149	0.0194	0.0154
4	rs2854030	44.4049	0.0219	0.0131	0.0192	0.0168	0.0232	0.0147
4	rs915889	44.4154	0.0188	0.0148	0.0245	0.0137	0.0188	0.0166
4	rs7665027	44.4172	0.0187	0.0145	0.0246	0.0133	0.0185	0.0167
4	rs2000978	44.42	0.0199	0.0132	0.02	0.0142	0.0178	0.0172
4	rs2725307	44.4226	0.0178	0.0135	0.022	0.0143	0.022	0.0145
4	rs7661204	66.8042	0.016	0.0136	0.0181	0.0142	0.0158	0.016
4	rs1497570	66.8075	0.0159	0.0137	0.018	0.0146	0.0158	0.016
4	rs993677	66.8095	0.0157	0.0176	0.0169	0.0201	0.0171	0.0163
4	rs13140445	66.8096	0.0185	0.0134	0.0229	0.0172	0.017	0.0167
4	rs1391174	66.8133	0.0155	0.0144	0.0178	0.0137	0.0169	0.0157
4	rs17536211	66.8162	0.0152	0.0148	0.0156	0.0154	0.0174	0.0166
4	rs11736752	66.8169	0.0155	0.0155	0.017	0.0141	0.0168	0.0156
4	rs1497577	66.8174	0.0163	0.015	0.0161	0.0143	0.0175	0.0162
4	rs1391166	66.8198	0.0155	0.0149	0.0155	0.0146	0.0162	0.0159
4	rs7654165	66.824	0.0157	0.0164	0.0154	0.0148	0.0168	0.0159
4	rs1603612	66.826	0.0159	0.0155	0.0152	0.0149	0.0182	0.0154
4	rs567926	66.8491	0.0168	0.0144	0.0159	0.0145	0.0184	0.0152
4	rs572227	66.8511	0.0167	0.0144	0.0162	0.0144	0.0183	0.0151
4	rs3822051	66.8522	0.018	0.0146	0.0175	0.0174	0.0182	0.0164
4	rs2119183	66.8558	0.0157	0.0153	0.0165	0.0155	0.021	0.0165
4	rs526752	66.8568	0.0162	0.0144	0.0161	0.0143	0.0173	0.0156
4	rs17537141	66.8636	0.0171	0.0145	0.0165	0.0157	0.0181	0.0176
4	rs279872	66.8643	0.0151	0.0148	0.0157	0.0145	0.0176	0.0155
4	rs279843	66.8696	0.015	0.0147	0.016	0.0144	0.0169	0.0157
4	rs279831	66.8724	0.0159	0.0147	0.0164	0.0145	0.0177	0.0156
4	rs17537359	66.8739	0.0233	0.0142	0.022	0.0153	0.0219	0.0183
4	rs4695148	66.8751	0.0173	0.0153	0.0199	0.0158	0.0182	0.0158
4	rs12647055	66.8781	0.0153	0.0162	0.0158	0.0149	0.018	0.0157
4	rs3849591	66.8819	0.0145	0.0157	0.0156	0.0158	0.0173	0.0198
4	rs9291283	66.8829	0.0218	0.0128	0.0216	0.0132	0.0173	0.0178
4	rs16859354	66.8868	0.0169	0.0137	0.0167	0.0143	0.018	0.0166

4	rs3756007	66.8884	0.0157	0.0157	0.0203	0.0157	0.0167	0.0164
4	rs11503014	66.8884	0.023	0.0117	0.0192	0.0134	0.0188	0.016
4	rs7678338	67.0971	0.0182	0.0144	0.0165	0.0183	0.0243	0.0144
4	rs12506608	67.099	0.0206	0.0125	0.0208	0.0133	0.018	0.0156
4	rs11946433	67.1073	0.0189	0.0154	0.019	0.018	0.0191	0.017
4	rs1160093	67.1085	0.0162	0.0141	0.0163	0.0167	0.0178	0.0155
4	rs1512130	67.1096	0.0173	0.0134	0.0162	0.0148	0.0181	0.0166
4	rs2221855	67.1134	0.0153	0.014	0.0152	0.015	0.0174	0.0154
4	rs17599416	67.1182	0.014	0.0155	0.0159	0.0156	0.0154	0.0164
4	rs3792208	67.1184	0.02	0.0166	0.0239	0.0152	0.0181	0.0163
4	rs2036940	67.1229	0.0211	0.0141	0.0191	0.0166	0.0222	0.0164
4	rs7694035	67.1232	0.0154	0.0151	0.0195	0.0157	0.0152	0.017
4	rs11735333	67.1264	0.0131	0.0162	0.0142	0.0165	0.0161	0.016
4	rs3792211	67.1268	0.0161	0.0159	0.0166	0.0151	0.019	0.0162
4	rs979273	67.1286	0.0147	0.0172	0.0157	0.0169	0.0164	0.0159
4	rs2236781	67.143	0.0144	0.0143	0.0143	0.0151	0.017	0.0159
4	rs4572848	67.1438	0.0171	0.0155	0.018	0.0171	0.0183	0.0166
4	rs13116355	67.1446	0.0135	0.015	0.0143	0.0153	0.0154	0.017
4	rs4315750	67.1493	0.0221	0.0138	0.0253	0.014	0.0266	0.0152
4	rs10015366	67.1518	0.0151	0.0148	0.0163	0.0152	0.0193	0.0158
4	rs6824550	67.1579	0.0135	0.0149	0.0152	0.0151	0.0158	0.0162
4	rs4613538	67.1619	0.0202	0.0136	0.0175	0.0174	0.0222	0.0169
4	rs6854637	67.1674	0.0196	0.0152	0.0224	0.0149	0.0203	0.0161
4	rs1866989	67.1682	0.0192	0.0134	0.016	0.0151	0.0206	0.0167
4	rs2028524	67.1727	0.0219	0.0135	0.0189	0.0138	0.023	0.0159
4	rs1470207	67.1764	0.0239	0.0119	0.0251	0.012	0.0159	0.0176
4	rs1442099	67.1846	0.0547	0.0122	0.0255	0.016	0.0372	0.0123
4	rs1442097	67.1859	0.0197	0.0131	0.0187	0.0143	0.0198	0.0151
4	rs17599816	67.1894	0.0335	0.0122	0.0201	0.0153	0.0294	0.0143
4	rs989808	67.19	0.0169	0.0146	0.0171	0.0153	0.0188	0.016
4	rs10002281	67.1985	0.0197	0.0149	0.0212	0.0148	0.0183	0.0162
4	rs10004181	67.1997	0.0178	0.0138	0.0194	0.0137	0.0214	0.0147
4	rs1372496	67.2007	0.0195	0.0139	0.021	0.0141	0.0194	0.0162
4	rs17539361	67.2037	0.0164	0.0173	0.0167	0.0167	0.0174	0.0177
4	rs12501459	67.2041	0.0179	0.0157	0.0172	0.0162	0.0212	0.0173
4	rs12512314	67.2126	0.0191	0.0156	0.0196	0.0182	0.0197	0.0158
4	rs7672100	67.2126	0.0132	0.0163	0.0134	0.0157	0.0168	0.0163
4	rs10026884	67.2139	0.0134	0.015	0.0142	0.0158	0.0178	0.0159
4	rs12651232	67.2144	0.0172	0.0142	0.0173	0.0175	0.0209	0.0153
4	rs12502993	67.2147	0.0168	0.0137	0.015	0.0172	0.0215	0.0149
4	rs13127214	67.2156	0.0165	0.0162	0.0166	0.0213	0.0198	0.0166

4	rs9999619	67.2161	0.0157	0.0167	0.0174	0.0153	0.0164	0.016
4	rs4695209	67.2167	0.0157	0.016	0.0162	0.0161	0.0188	0.0166
4	rs2078610	67.2176	0.015	0.0166	0.0173	0.0157	0.0162	0.017
4	rs959160	67.2176	0.015	0.0171	0.0161	0.0149	0.018	0.0203
4	rs9683412	67.2208	0.0158	0.0196	0.0166	0.0185	0.016	0.0163
4	rs13102109	67.2209	0.0162	0.0154	0.0174	0.0155	0.0179	0.0174
4	rs4518219	67.2213	0.0142	0.0154	0.0149	0.0148	0.016	0.0179
4	rs6284	67.2253	0.0168	0.0153	0.0192	0.0141	0.0228	0.0158
4	rs3775534	67.2254	0.0221	0.0168	0.0201	0.0278	0.0205	0.0165
4	rs4472116	67.2254	0.0165	0.018	0.0156	0.0172	0.0208	0.0169
4	rs6831556	67.2308	0.0146	0.0158	0.0157	0.016	0.016	0.0168
4	rs728293	67.2327	0.0167	0.0138	0.0191	0.0129	0.0164	0.0202
4	rs6832172	67.233	0.0173	0.0138	0.0177	0.0139	0.0172	0.0223
4	rs7688710	67.2334	0.0274	0.0137	0.0267	0.0133	0.0188	0.0173
4	rs4695224	67.2355	0.0153	0.0141	0.0152	0.0149	0.0177	0.0215
4	rs13107066	67.236	0.0177	0.013	0.0194	0.0129	0.0176	0.0215
4	rs4289418	67.2375	0.0258	0.0128	0.0204	0.0158	0.0232	0.015
4	rs4502656	67.2378	0.0155	0.0147	0.0149	0.0155	0.0185	0.0166
4	rs6813436	67.2379	0.0187	0.016	0.0165	0.0161	0.0225	0.0161
4	rs6817416	67.2395	0.0378	0.0119	0.0207	0.016	0.0236	0.0143
4	rs17600651	67.241	0.0209	0.0143	0.0201	0.0159	0.0218	0.016
4	rs11946601	67.2411	0.0215	0.0135	0.0209	0.0137	0.0184	0.017
4	rs17462190	67.2413	0.0194	0.0154	0.0185	0.0159	0.0207	0.0179
4	rs13106855	67.2414	0.0221	0.0121	0.0283	0.0144	0.0161	0.0158
4	rs17600665	67.2422	0.0162	0.0155	0.0175	0.0162	0.0167	0.0165
4	rs10030377	67.2435	0.0186	0.0133	0.0251	0.0135	0.0162	0.0157
4	rs10028945	67.2445	0.0187	0.013	0.0232	0.0127	0.0171	0.0163
4	rs16998073	93.0061	0.0163	0.016	0.0154	0.0164	0.0193	0.0153
4	rs7658439	93.008	0.0181	0.0163	0.019	0.0162	0.018	0.0176
4	rs3796606	93.0145	0.0166	0.0132	0.0175	0.0145	0.0187	0.017
4	rs7683390	93.0219	0.0165	0.0149	0.0169	0.015	0.0214	0.018
4	rs17004869	93.0243	0.0167	0.0179	0.0179	0.016	0.0242	0.0169
4	rs17004870	93.0254	0.0193	0.0152	0.0173	0.0154	0.0189	0.0186
4	rs3733336	93.027	0.0168	0.0141	0.0169	0.0167	0.0174	0.0171
4	rs6838203	93.028	0.0204	0.0154	0.0237	0.0123	0.0178	0.018
4	rs4690150	93.0303	0.0324	0.0145	0.1334	0.0061	0.0171	0.0159
4	rs6827939	93.6894	0.0157	0.0149	0.0145	0.0159	0.0187	0.017
4	rs11723025	93.7082	0.0252	0.014	0.018	0.0157	0.0256	0.0154
4	rs6821258	93.7161	0.0154	0.0156	0.015	0.0156	0.0183	0.0162
4	rs7688672	93.7607	0.0161	0.0141	0.0168	0.0149	0.0246	0.0136
4	rs11736177	93.7733	0.0165	0.014	0.0172	0.0147	0.0254	0.0133

4	rs17005071	93.7806	0.0182	0.0139	0.0157	0.0156	0.0238	0.0157
4	rs17005082	93.7854	0.0163	0.0142	0.0146	0.0154	0.0233	0.0163
4	rs2028643	93.8088	0.019	0.0159	0.0146	0.0157	0.0403	0.0115
4	rs6857838	93.8141	0.0167	0.0155	0.0155	0.0151	0.0234	0.0142
4	rs17484474	93.8165	0.0194	0.0156	0.0198	0.0167	0.0182	0.0171
4	rs710835	93.8192	0.0148	0.0159	0.0143	0.0156	0.0203	0.0239
4	rs788860	93.8276	0.0156	0.015	0.015	0.0153	0.023	0.0278
4	rs10034345	106.098	0.023	0.0138	0.0264	0.0133	0.0195	0.0169
4	rs308428	129.361	0.0173	0.0149	0.0174	0.0148	0.0198	0.0165
4	rs308420	129.363	0.0154	0.016	0.016	0.016	0.0205	0.0165
4	rs308434	129.365	0.0225	0.0127	0.0184	0.0148	0.0205	0.0165
4	rs308435	129.365	0.0176	0.014	0.0171	0.0149	0.019	0.0165
4	rs11938826	129.366	0.0154	0.0146	0.0164	0.0156	0.018	0.0164
4	rs167428	129.366	0.0174	0.0137	0.0174	0.0148	0.0192	0.0163
4	rs308439	129.366	0.0173	0.0155	0.0182	0.0158	0.0177	0.0173
4	rs308441	129.367	0.0187	0.0133	0.0186	0.0174	0.0207	0.0158
4	rs17006215	129.367	0.0247	0.0127	0.0243	0.0152	0.0219	0.0153
4	rs308443	129.368	0.0171	0.016	0.0225	0.0167	0.0169	0.0175
4	rs17407577	129.37	0.0197	0.0215	0.0194	0.0232	0.0189	0.0173
4	rs1960669	129.372	0.0149	0.0156	0.0147	0.0162	0.0203	0.0173
4	rs308379	129.372	0.058	0.0133	0.0273	0.0266	0.0245	0.0143
4	rs308382	129.372	0.0218	0.0162	0.0189	0.0173	0.0214	0.0158
4	rs2034461	129.373	0.0149	0.0189	0.0166	0.0227	0.0184	0.0169
4	rs3789138	129.373	0.0166	0.0139	0.0162	0.0161	0.0202	0.0154
4	rs10452197	129.389	0.0184	0.0147	0.017	0.0158	0.028	0.0148
4	rs1476214	129.391	0.0177	0.0149	0.015	0.0177	0.0222	0.0145
4	rs3804158	129.392	0.0165	0.0162	0.0153	0.024	0.0199	0.0161
4	rs11098676	129.403	0.0247	0.0112	0.029	0.0111	0.0166	0.017
4	rs12513181	129.405	0.0215	0.0118	0.0233	0.0123	0.0175	0.0159
4	rs898091	129.407	0.0206	0.0149	0.019	0.0166	0.0182	0.0168
4	rs300564	129.656	0.1133	0.0364	0.038	0.0193	0.0223	0.0183
4	rs300574	129.661	0.0179	0.0147	0.019	0.0144	0.0215	0.0152
4	rs7665238	129.664	0.5797	0.0037	0.1234	0.0063	0.0268	0.0143
5	rs12055296	61.3973	0.0217	0.0134	0.0234	0.0138	0.0196	0.0161
5	rs17379771	61.4046	0.0178	0.0144	0.0165	0.0151	0.0281	0.013
5	rs11111	61.4054	0.018	0.0151	0.0191	0.0149	0.0194	0.0156
5	rs7731209	61.4101	0.0205	0.0134	0.0219	0.0134	0.0172	0.0165
5	rs17326972	61.4141	0.018	0.0196	0.0171	0.0171	0.0201	0.018
5	rs884344	61.4225	0.0211	0.013	0.0232	0.0124	0.0184	0.0157
5	rs12521946	61.4235	0.0157	0.0167	0.0166	0.0163	0.0226	0.0149
5	rs2216711	61.4303	0.0181	0.0136	0.0218	0.0132	0.0182	0.0175

5	rs2216710	61.4311	0.0165	0.0157	0.0158	0.0162	0.0224	0.0187
5	rs3096140	61.437	0.0173	0.0136	0.021	0.0168	0.0171	0.0166
5	rs3812047	61.4413	0.0204	0.0144	0.0191	0.0152	0.0189	0.0171
5	rs2975100	61.4509	0.0199	0.014	0.0204	0.0144	0.0186	0.0169
5	rs10455050	137.055	0.0389	0.0214	0.0239	0.0176	0.0254	0.016
5	rs6595800	137.066	0.0212	0.0214	0.0267	0.0176	0.0151	0.017
5	rs1864922	137.075	0.0219	0.0128	0.0283	0.0118	0.0152	0.0166
5	rs3805603	137.106	0.0168	0.0161	0.017	0.0158	0.0182	0.0169
5	rs1993878	137.122	0.0152	0.0142	0.0158	0.0158	0.0167	0.0165
5	rs3805604	137.123	0.0221	0.0193	0.0237	0.0146	0.0164	0.0179
5	rs17607500	137.123	0.0165	0.0138	0.0167	0.0145	0.0168	0.0167
5	rs806100	137.131	0.0163	0.0135	0.0191	0.0142	0.015	0.0165
5	rs10477682	137.159	0.0177	0.0158	0.0161	0.017	0.0203	0.0177
5	rs13175996	137.164	0.0196	0.0151	0.0189	0.016	0.0203	0.0185
5	rs12189448	137.168	0.0219	0.013	0.0202	0.0138	0.0195	0.0167
5	rs251216	137.173	0.0163	0.0138	0.0171	0.0147	0.0184	0.0161
5	rs3805616	137.194	0.0189	0.0155	0.0215	0.0144	0.0157	0.0173
5	rs7721661	154.91	0.0134	0.0154	0.0142	0.0161	0.0216	0.0202
5	rs7733401	154.913	0.0206	0.0132	0.0239	0.0127	0.0239	0.0169
5	rs17639006	154.915	0.0231	0.0147	0.0194	0.0153	0.0279	0.0148
5	rs3995090	154.92	0.0154	0.015	0.0154	0.0154	0.0229	0.0141
5	rs4597955	154.921	0.0169	0.0134	0.0203	0.0132	0.0248	0.0138
5	rs17706683	154.981	0.0159	0.0164	0.0163	0.0168	0.0201	0.0172
5	rs13359903	154.984	0.0198	0.0134	0.0402	0.0134	0.0185	0.0163
5	rs2278392	154.985	0.0184	0.0137	0.0302	0.0129	0.0179	0.0161
5	rs17706743	154.986	0.0196	0.0151	0.0221	0.0159	0.0188	0.0174
5	rs1422636	154.988	0.0145	0.0152	0.0146	0.0153	0.019	0.0174
5	rs4599527	155.005	0.0174	0.0139	0.0275	0.012	0.0183	0.0157
5	rs17777511	155.006	0.0227	0.0118	0.0239	0.0118	0.0227	0.0153
5	rs4343830	155.014	0.0169	0.0134	0.019	0.0132	0.0182	0.016
5	rs4280857	155.022	0.0343	0.0115	0.0379	0.0123	0.0179	0.0174
5	rs7711800	155.03	0.0162	0.0136	0.0171	0.0143	0.0208	0.0161
5	rs7721747	155.044	0.018	0.0126	0.0205	0.0127	0.0189	0.0158
5	rs17706942	155.054	0.018	0.0171	0.0189	0.0164	0.0207	0.0191
5	rs6865654	155.059	0.0195	0.0122	0.022	0.0121	0.0174	0.0154
5	rs17639735	155.064	0.0157	0.0154	0.0176	0.0153	0.017	0.017
5	rs7712170	155.069	0.022	0.0112	0.0247	0.0118	0.0191	0.0148
5	rs1833704	155.073	0.0164	0.0151	0.0192	0.015	0.0172	0.0166
5	rs13161058	155.084	0.0161	0.0142	0.0186	0.0148	0.0187	0.0166
5	rs13177547	169.229	0.0195	0.0155	0.0212	0.0156	0.0211	0.018
5	rs10044322	169.231	0.0154	0.0159	0.0154	0.0164	0.0195	0.0192

5	rs252982	169.234	0.0162	0.0147	0.0172	0.0151	0.0216	0.0162
5	rs679633	169.235	0.0175	0.0141	0.0182	0.0144	0.0226	0.0162
5	rs869648	169.24	0.023	0.0136	0.0256	0.0155	0.0179	0.0174
5	rs252957	169.24	0.0161	0.0147	0.0167	0.0148	0.0216	0.0157
5	rs153296	169.241	0.0186	0.0157	0.0176	0.0147	0.0205	0.0223
5	rs1644522	169.248	0.0151	0.0169	0.0152	0.0158	0.0279	0.0138
5	rs10515827	169.248	0.0194	0.0138	0.0164	0.0158	0.0256	0.0156
5	rs10068979	169.249	0.0154	0.016	0.0158	0.0164	0.0207	0.0171
5	rs187269	169.249	0.0159	0.0146	0.0159	0.0162	0.0217	0.0148
5	rs194072	169.251	0.0137	0.0158	0.0146	0.0165	0.0177	0.0175
5	rs4921190	169.252	0.0261	0.0133	0.0212	0.0153	0.0243	0.0151
5	rs9313880	169.253	0.017	0.0154	0.0179	0.0157	0.0225	0.016
5	rs2617503	169.255	0.0175	0.0151	0.0159	0.0176	0.0239	0.0141
5	rs10515828	169.26	0.0153	0.0157	0.0158	0.0165	0.0194	0.018
5	rs13164252	169.265	0.0198	0.0156	0.0195	0.0162	0.0225	0.0181
5	rs2910295	169.273	0.0155	0.0143	0.0149	0.0159	0.0189	0.0156
5	rs2910289	169.285	0.0177	0.0143	0.0166	0.0167	0.0208	0.0155
5	rs2910287	169.286	0.0156	0.015	0.0156	0.0189	0.018	0.0163
5	rs17521304	169.296	0.0246	0.0119	0.0198	0.014	0.0284	0.0143
5	rs10043074	169.307	0.0166	0.0144	0.017	0.0155	0.0212	0.015
5	rs10077462	169.316	0.0155	0.0145	0.0148	0.0161	0.0205	0.0152
5	rs4403218	169.334	0.015	0.0154	0.0159	0.0168	0.0222	0.0164
5	rs7724146	169.337	0.018	0.0143	0.0184	0.0147	0.019	0.0169
5	rs6891827	169.343	0.0162	0.0154	0.0155	0.0158	0.0223	0.0158
5	rs2962406	169.345	0.017	0.017	0.0176	0.0331	0.0182	0.017
5	rs2964773	169.345	0.0155	0.0154	0.0147	0.018	0.02	0.0157
5	rs12153421	169.349	0.0177	0.0141	0.0157	0.0159	0.0224	0.0145
5	rs13179679	169.352	0.025	0.0145	0.0203	0.0165	0.0225	0.0166
5	rs4426954	169.37	0.0145	0.0159	0.0141	0.017	0.0176	0.0161
5	rs2066949	169.374	0.0176	0.0148	0.0156	0.0156	0.0225	0.0153
5	rs3816596	169.387	0.0149	0.0147	0.015	0.0152	0.0178	0.0161
5	rs11948174	169.483	0.0146	0.0153	0.0143	0.0156	0.0292	0.0135
5	rs13162148	169.487	0.0274	0.0131	0.0263	0.0143	0.0209	0.0169
5	rs13172914	169.494	0.0175	0.0132	0.0164	0.015	0.0213	0.0147
5	rs11959228	169.495	0.017	0.0188	0.0164	0.0206	0.018	0.0169
5	rs11949158	169.495	0.0151	0.0151	0.0146	0.0156	0.0292	0.0135
5	rs6898571	169.496	0.0217	0.0124	0.0187	0.0143	0.0464	0.0112
5	rs13178296	169.498	0.0182	0.0135	0.0154	0.0161	0.0236	0.014
5	rs4263535	169.614	0.0149	0.0163	0.0147	0.0157	0.0226	0.0162
5	rs4428455	169.631	0.0196	0.0128	0.0182	0.015	0.0279	0.0135
5	rs12187575	169.635	0.0155	0.0168	0.015	0.023	0.0182	0.016

5	rs7701394	169.637	0.0163	0.0163	0.016	0.0228	0.0214	0.015
5	rs13156895	169.639	0.0195	0.0151	0.0182	0.0161	0.0219	0.016
5	rs1037715	169.643	0.0162	0.0147	0.016	0.0159	0.0182	0.0161
5	rs1157122	169.646	0.0155	0.0159	0.016	0.0163	0.0219	0.0164
5	rs183294	169.804	0.0167	0.0148	0.018	0.0174	0.0183	0.016
5	rs3797863	169.804	0.0147	0.0154	0.0152	0.0169	0.017	0.0163
5	rs209350	169.811	0.0183	0.0138	0.0206	0.0137	0.021	0.0156
5	rs2268582	169.814	0.0167	0.0161	0.016	0.0156	0.0179	0.019
5	rs209354	169.815	0.0197	0.0131	0.0163	0.0152	0.0329	0.0132
5	rs211037	169.823	0.0183	0.0139	0.0166	0.0157	0.0313	0.0125
5	rs211030	169.825	0.014	0.0149	0.0136	0.0164	0.0212	0.0156
5	rs211029	169.827	0.0146	0.0151	0.0155	0.0175	0.0199	0.0147
5	rs210991	169.828	0.019	0.0171	0.0169	0.0178	0.0339	0.0151
5	rs17060096	169.837	0.0157	0.0165	0.0165	0.016	0.0179	0.0168
5	rs721719	169.855	0.0152	0.0174	0.0155	0.0193	0.0277	0.0134
5	rs2272600	169.862	0.0138	0.016	0.0136	0.0162	0.0226	0.0151
5	rs13173675	169.862	0.0183	0.0146	0.0155	0.0161	0.0279	0.0146
5	rs17060118	169.865	0.0167	0.0166	0.0161	0.0154	0.0207	0.0186
5	rs211013	169.872	0.0191	0.0144	0.0206	0.0158	0.0194	0.0148
5	rs418210	169.873	0.0159	0.0152	0.017	0.0169	0.0239	0.0136
5	rs3806929	187.056	0.0145	0.0163	0.0143	0.0154	0.0304	0.0152
5	rs6887323	187.062	0.0164	0.0148	0.0167	0.0149	0.0276	0.014
5	rs4559013	187.069	0.0195	0.0135	0.0174	0.0167	0.0258	0.0133
5	rs9313543	187.074	0.0154	0.0147	0.0142	0.0157	0.0334	0.0128
5	rs3934591	187.1	0.0158	0.0138	0.0156	0.0146	0.021	0.0147
5	rs12519454	187.104	0.0158	0.0153	0.0151	0.0158	0.0241	0.0158
5	rs10077440	187.104	0.0207	0.0121	0.0191	0.0143	0.0419	0.0106
5	rs11740426	187.115	0.0166	0.0165	0.0159	0.0169	0.0219	0.0183
5	rs4620037	187.116	0.0171	0.0155	0.0151	0.0156	0.0612	0.009
5	rs6891250	187.116	0.0185	0.0149	0.019	0.0154	0.0207	0.0161
5	rs734840	187.135	0.0148	0.014	0.0155	0.0145	0.0206	0.0145
5	rs3112453	187.139	0.0176	0.0151	0.0142	0.0156	0.0314	0.0135
6	rs453658	53.1215	0.0152	0.0194	0.0137	0.017	0.0191	0.0167
6	rs17351888	53.1215	0.0178	0.0158	0.0165	0.0162	0.0194	0.0189
6	rs2534791	53.1216	0.0146	0.0146	0.0139	0.0156	0.0223	0.0149
6	rs995185	53.1217	0.0201	0.0323	0.0185	0.0192	0.0202	0.0161
6	rs362511	53.1218	0.0259	0.0119	0.0163	0.0152	0.0247	0.0167
6	rs1119080	53.1219	0.0175	0.0243	0.0202	0.0257	0.0168	0.017
6	rs1003581	53.122	0.0203	0.0143	0.0206	0.0164	0.0185	0.0168
6	rs362523	53.1222	0.0283	0.0151	0.0198	0.0154	0.0241	0.0146
6	rs926552	53.1223	0.0193	0.0164	0.0162	0.0164	0.0294	0.0196

6	rs1233387	53.1225	0.0154	0.0187	0.0149	0.0163	0.0164	0.0165
6	rs2235698	53.1225	0.0145	0.0148	0.0145	0.0152	0.0202	0.0161
6	rs1233384	53.1226	0.0263	0.0135	0.0193	0.0157	0.0241	0.0145
6	rs3025643	53.1229	0.0172	0.0135	0.0146	0.0153	0.023	0.0146
6	rs10946999	53.123	0.014	0.0153	0.0148	0.0157	0.0174	0.017
6	rs29230	53.1231	0.0132	0.0156	0.0133	0.0158	0.0169	0.0166
6	rs29267	53.1231	0.0151	0.0156	0.0149	0.0156	0.0174	0.0172
6	rs17842396	53.1234	0.0148	0.0157	0.0142	0.0172	0.0167	0.0167
6	rs9257925	53.1239	0.0164	0.0145	0.0149	0.0165	0.0175	0.0169
6	rs29232	53.1241	0.0168	0.0137	0.0142	0.0159	0.023	0.014
6	rs29273	53.1241	0.0171	0.0143	0.0139	0.0156	0.023	0.0144
6	rs29234	53.1245	0.0229	0.02	0.0191	0.0162	0.0224	0.0182
6	rs2535260	53.1246	0.02	0.0127	0.0143	0.0156	0.0272	0.0133
6	rs3130253	53.1247	0.0185	0.0157	0.0173	0.0163	0.0219	0.0168
6	rs2535238	53.125	0.0166	0.014	0.0173	0.017	0.0166	0.0166
6	rs2747430	53.1251	0.0208	0.0126	0.0195	0.0146	0.0193	0.0159
6	rs2747442	53.1252	0.0197	0.0127	0.0137	0.0153	0.0218	0.0143
6	rs3131879	53.1256	0.0179	0.0139	0.014	0.0156	0.0292	0.0135
6	rs3129055	53.1258	0.0194	0.0133	0.0201	0.015	0.0173	0.0172
6	rs3094724	53.1259	0.0212	0.0126	0.0188	0.015	0.0181	0.0171
6	rs4248137	53.1259	0.026	0.0106	0.0166	0.0141	0.0221	0.0148
6	rs7739273	55.6375	0.0185	0.0164	0.0153	0.0155	0.0267	0.0147
6	rs1359781	55.6409	0.014	0.0164	0.0141	0.0165	0.0181	0.0158
6	rs2274459	55.641	0.0211	0.013	0.0185	0.0144	0.0264	0.0138
6	rs2281820	55.6464	0.0167	0.0147	0.0143	0.0154	0.025	0.0146
6	rs4713685	55.6511	0.0158	0.0145	0.0144	0.0153	0.0253	0.0142
6	rs7774407	55.6518	0.0176	0.0144	0.0149	0.0153	0.0242	0.0143
6	rs1547669	55.652	0.014	0.0153	0.0135	0.0161	0.019	0.0166
6	rs6297	93.2533	0.0175	0.0158	0.0171	0.0151	0.0194	0.0242
6	rs4140535	93.2552	0.0155	0.0159	0.0153	0.015	0.0212	0.0162
6	rs9361235	93.2557	0.0133	0.0151	0.014	0.0153	0.024	0.0151
6	rs2226183	93.2561	0.0141	0.0188	0.0144	0.0165	0.019	0.0197
6	rs1213366	93.2563	0.0132	0.015	0.0136	0.0154	0.0279	0.0139
6	rs1796740	99.453	0.0175	0.0152	0.0164	0.0167	0.0194	0.0154
6	rs9353650	99.4533	0.0158	0.0144	0.0155	0.0155	0.0224	0.0184
6	rs9359845	99.4626	0.0135	0.0152	0.0148	0.0163	0.0196	0.0148
6	rs407206	99.4705	0.014	0.0155	0.0151	0.0156	0.0163	0.0174
6	rs9451176	99.4756	0.0161	0.0144	0.019	0.0142	0.0279	0.0139
6	rs676211	99.4875	0.0162	0.0135	0.0156	0.0149	0.0216	0.0149
6	rs2282123	99.4887	0.0177	0.014	0.0158	0.0155	0.0201	0.0174
6	rs3777530	99.4916	0.0193	0.0135	0.0192	0.0143	0.0281	0.0163

6	rs7770056	99.4947	0.0138	0.0153	0.0145	0.0157	0.0176	0.0167
6	rs2297391	99.5006	0.0162	0.0152	0.0154	0.0162	0.0205	0.0168
6	rs9444675	99.503	0.0139	0.0159	0.014	0.0159	0.0184	0.0169
6	rs13196423	99.5037	0.0161	0.0146	0.0164	0.0151	0.0182	0.018
6	rs4707528	99.5054	0.0162	0.0136	0.0167	0.0143	0.0191	0.0153
6	rs13215160	99.5056	0.0165	0.0149	0.0173	0.0155	0.0178	0.0175
6	rs12216134	99.5081	0.0373	0.0108	0.0268	0.0142	0.0225	0.017
6	rs9353653	99.5111	0.0152	0.0144	0.0161	0.0145	0.0176	0.0154
6	rs6902106	99.518	0.0184	0.0131	0.018	0.0142	0.0187	0.0166
6	rs17504587	99.5188	0.0145	0.015	0.0147	0.0154	0.0207	0.0166
6	rs9294425	99.5208	0.0158	0.014	0.0155	0.0146	0.0205	0.0151
6	rs16881632	99.5821	0.0145	0.0148	0.0163	0.0151	0.0176	0.0161
6	rs3734197	99.5833	0.0161	0.0156	0.0175	0.017	0.0193	0.0173
6	rs282128	99.589	0.0165	0.0142	0.0146	0.0154	0.0227	0.0146
6	rs723041	99.5995	0.0157	0.0155	0.0145	0.0161	0.0222	0.0177
6	rs2273507	99.6016	0.0142	0.0162	0.0131	0.0159	0.025	0.02
6	rs6454746	99.6023	0.0159	0.0154	0.0166	0.0155	0.018	0.0176
6	rs9451192	99.6039	0.0138	0.0149	0.0144	0.0154	0.0191	0.0155
6	rs912976	99.6158	0.0148	0.016	0.0151	0.0161	0.0228	0.0163
6	rs9444682	99.6216	0.0246	0.0124	0.0627	0.0076	0.0178	0.0165
6	rs9353660	99.6219	0.0146	0.0166	0.0142	0.0152	0.022	0.0308
6	rs9294430	99.6251	0.0135	0.0154	0.014	0.0157	0.0191	0.0175
6	rs9362632	99.6401	0.0139	0.0159	0.0135	0.0157	0.0322	0.0224
6	rs6454749	99.6406	0.0155	0.0144	0.0155	0.0151	0.0222	0.0152
6	rs3798256	99.6434	0.0139	0.0151	0.014	0.0152	0.0225	0.0298
6	rs17741567	99.6441	0.0201	0.0145	0.0263	0.0134	0.019	0.0188
6	rs964626	99.6491	0.0167	0.0138	0.0163	0.0151	0.0226	0.0146
6	rs9451196	99.6516	0.015	0.0153	0.0153	0.016	0.0226	0.0152
6	rs2148174	99.6622	0.0199	0.0137	0.016	0.0146	0.0272	0.0145
6	rs9344921	99.6632	0.0168	0.0144	0.0165	0.0143	0.0216	0.0145
6	rs9444685	99.6677	0.0137	0.0147	0.016	0.0146	0.0179	0.0159
6	rs13197385	99.6681	0.0176	0.0191	0.016	0.0177	0.0242	0.0199
6	rs1570931	99.6687	0.0162	0.0156	0.0147	0.0163	0.0262	0.015
6	rs1570932	99.6689	0.014	0.0146	0.0165	0.0144	0.0179	0.0159
6	rs6942204	99.6821	0.0133	0.0149	0.0146	0.0157	0.022	0.0144
6	rs6454753	99.6868	0.0143	0.0169	0.0143	0.0166	0.0185	0.0162
6	rs9294432	99.69	0.0147	0.0152	0.014	0.0155	0.0209	0.0147
6	rs3777514	99.6912	0.0138	0.0148	0.0147	0.0153	0.0216	0.0148
6	rs7764875	99.6956	0.0177	0.0288	0.017	0.0185	0.0223	0.02
6	rs2236204	99.7001	0.0133	0.0157	0.0144	0.0157	0.0199	0.0163
6	rs6569647	134.221	0.0207	0.013	0.027	0.0118	0.017	0.0175

6	rs12530176	134.233	0.0172	0.017	0.0173	0.0166	0.0206	0.0157
6	rs6899976	134.242	0.0167	0.0178	0.017	0.0166	0.0171	0.016
6	rs6914670	134.257	0.0148	0.0171	0.0164	0.0167	0.0164	0.016
6	rs9388768	134.258	0.0167	0.0148	0.0193	0.0146	0.0167	0.016
6	rs7740107	134.259	0.0167	0.0145	0.0186	0.0145	0.0161	0.0164
6	rs6923819	134.26	0.017	0.0147	0.0205	0.0141	0.0167	0.016
6	rs13208867	134.269	0.0162	0.0167	0.0174	0.0169	0.0187	0.0177
6	rs12528442	134.28	0.0193	0.0148	0.0287	0.0142	0.0162	0.0169
6	rs4548027	134.283	0.0154	0.0152	0.0176	0.0146	0.0153	0.0165
6	rs7756733	134.283	0.0188	0.0138	0.0188	0.0146	0.0197	0.0148
6	rs13196495	134.289	0.0988	0.0065	0.0554	0.0089	0.0168	0.0173
6	rs7774174	134.291	0.0166	0.0147	0.0191	0.0149	0.0158	0.0163
6	rs9483083	134.302	0.0162	0.0153	0.0182	0.0146	0.0158	0.0166
6	rs12199027	134.304	0.0275	0.0119	0.0214	0.0135	0.0265	0.0155
6	rs9388772	134.314	0.015	0.0157	0.015	0.0188	0.017	0.0156
6	rs6901414	134.326	0.0178	0.0163	0.0171	0.0181	0.018	0.0154
6	rs11154522	134.326	0.0149	0.0217	0.0162	0.0234	0.0153	0.0162
6	rs12530124	134.329	0.0191	0.0161	0.0192	0.017	0.0175	0.0163
6	rs12194709	134.334	0.0179	0.0164	0.0191	0.0177	0.0173	0.0157
6	rs13193654	134.335	0.1331	0.0059	0.1003	0.007	0.0172	0.0172
6	rs9492459	134.337	0.0153	0.0176	0.0161	0.019	0.0159	0.0168
6	rs13207727	134.339	0.0571	0.0073	0.0587	0.0078	0.0189	0.0155
6	rs9321212	134.34	0.0153	0.0176	0.0161	0.019	0.0159	0.0168
6	rs17633592	134.345	0.173	0.0056	0.1115	0.0074	0.0184	0.0171
6	rs13218274	134.346	0.1713	0.0144	0.0385	0.0156	0.0233	0.0171
6	rs11968072	134.346	0.0188	0.0183	0.0199	0.0182	0.0189	0.0176
6	rs3818792	134.348	0.0168	0.0159	0.0193	0.0177	0.0167	0.0175
6	rs12214827	134.349	0.0171	0.016	0.0199	0.0185	0.0167	0.0176
6	rs17706258	134.349	0.015	0.0152	0.0146	0.0153	0.018	0.0157
6	rs11154524	134.349	0.0219	0.0149	0.02	0.0156	0.0211	0.0173
6	rs1055374	134.349	0.0166	0.0146	0.0149	0.016	0.0228	0.0157
6	rs4897370	134.35	0.0174	0.0177	0.0162	0.0148	0.0207	0.0173
6	rs2095452	134.355	0.0157	0.0168	0.0149	0.0155	0.0175	0.0179
6	rs1932106	134.359	0.0146	0.0145	0.0159	0.015	0.0159	0.0168
6	rs6569657	134.363	0.0154	0.0147	0.0145	0.016	0.0186	0.0157
6	rs1932105	134.371	0.0262	0.0111	0.0163	0.0147	0.026	0.0136
6	rs6939344	134.373	0.0159	0.0149	0.0146	0.016	0.0224	0.0149
6	rs1547334	134.374	0.0353	0.012	0.018	0.0151	0.0294	0.0128
6	rs9492471	134.377	0.0194	0.0139	0.0236	0.0144	0.016	0.0169
6	rs9492472	134.377	0.017	0.0201	0.0184	0.0213	0.0163	0.0171
6	rs1475787	134.383	0.0684	0.0121	0.0423	0.0132	0.018	0.0171

6	rs1034263	134.387	0.0594	0.014	0.0423	0.0132	0.018	0.0169
6	rs9402219	134.391	0.0273	0.0116	0.0259	0.0114	0.0176	0.0157
6	rs7749850	134.394	0.027	0.0107	0.0238	0.0119	0.0225	0.0157
6	rs13216555	134.395	0.0185	0.0158	0.0195	0.0148	0.0162	0.016
6	rs9402220	134.396	0.0204	0.0154	0.0171	0.0147	0.0514	0.034
6	rs7760764	134.397	0.0771	0.0064	0.0261	0.0112	0.0226	0.0147
6	rs6900507	134.4	0.0271	0.0117	0.0242	0.0134	0.0179	0.0168
6	rs1932116	134.411	0.0228	0.0144	0.0196	0.013	0.0212	0.017
6	rs7747640	134.416	0.026	0.0176	0.021	0.0155	0.0187	0.0171
6	rs4897377	134.427	0.019	0.0127	0.016	0.015	0.0312	0.0168
6	rs4897378	134.43	0.0156	0.0146	0.018	0.0142	0.0158	0.0166
6	rs9492497	134.434	0.0181	0.0132	0.0163	0.0144	0.0177	0.0156
6	rs4897379	134.437	0.0305	0.0109	0.022	0.0168	0.0204	0.0154
6	rs7762494	134.44	0.0211	0.0143	0.0196	0.0176	0.0187	0.0167
6	rs6915717	134.442	0.036	0.0102	0.0254	0.0136	0.0191	0.0162
6	rs12210856	165.133	0.0165	0.0161	0.0176	0.0166	0.0279	0.0156
6	rs1799971	165.139	0.0171	0.0146	0.0196	0.014	0.0179	0.0173
6	rs511435	165.154	0.0189	0.0147	0.0247	0.0139	0.0165	0.0164
6	rs4870266	165.155	0.0154	0.0282	0.0162	0.0185	0.0181	0.018
6	rs610231	165.174	0.0199	0.0143	0.0206	0.014	0.0166	0.0176
6	rs3778150	165.183	0.0185	0.0145	0.0249	0.0137	0.0163	0.0173
6	rs589046	165.201	0.0201	0.0133	0.0273	0.012	0.0186	0.016
6	rs563649	165.227	0.0198	0.0145	0.0176	0.0161	0.023	0.0155
6	rs9322446	165.229	0.027	0.0127	0.0267	0.0126	0.0228	0.0235
6	rs2075572	165.235	0.0742	0.0074	0.0653	0.0161	0.0262	0.0138
6	rs510587	165.237	0.0181	0.0155	0.018	0.0161	0.0183	0.0176
6	rs3798683	165.246	0.0297	0.0121	0.0259	0.0127	0.0243	0.015
6	rs1323042	165.252	0.029	0.0099	0.0329	0.0141	0.0271	0.0136
6	rs511420	165.256	0.0193	0.0154	0.0214	0.0161	0.021	0.0167
6	rs512053	165.284	0.0196	0.0158	0.02	0.0156	0.0188	0.0158
6	rs538174	165.31	0.0392	0.0099	0.0669	0.0104	0.0164	0.0166
6	rs13193545	165.328	0.0167	0.014	0.018	0.0143	0.0165	0.0173
6	rs9397687	165.328	0.0189	0.0141	0.0206	0.0128	0.0224	0.0152
6	rs518596	165.329	0.0177	0.0134	0.0249	0.0123	0.0169	0.0168
6	rs483481	165.332	0.0215	0.017	0.0311	0.0107	0.0174	0.0183
6	rs569284	165.332	0.0266	0.0128	0.0201	0.016	0.0214	0.016
6	rs12207811	165.334	0.019	0.0138	0.0175	0.0169	0.0172	0.0171
6	rs12200296	165.341	0.0204	0.0133	0.02	0.0178	0.0172	0.0166
6	rs9383692	165.347	0.0171	0.0136	0.0187	0.0138	0.0182	0.0162
6	rs17277929	165.359	0.016	0.0152	0.0189	0.0152	0.0176	0.0167
6	rs2236257	165.36	0.0167	0.0142	0.0169	0.0146	0.0231	0.0149

6	rs1918761	165.367	0.0165	0.0137	0.0189	0.0136	0.0163	0.0161
6	rs9397692	165.377	0.0252	0.0133	0.0359	0.0119	0.0184	0.0173
6	rs2281617	165.377	0.0188	0.014	0.017	0.0154	0.0173	0.0165
6	rs6939625	165.378	0.014	0.0165	0.0147	0.0182	0.018	0.0173
6	rs9479771	165.38	0.0186	0.0169	0.0174	0.0174	0.0219	0.0183
6	rs12198177	165.411	0.0181	0.0141	0.0196	0.0133	0.0176	0.0155
6	rs1998220	165.415	0.018	0.0131	0.0213	0.0128	0.0153	0.0168
6	rs9322451	165.447	0.0188	0.0135	0.0201	0.0139	0.0167	0.0169
6	rs6913456	165.464	0.0159	0.0137	0.0218	0.013	0.0161	0.0163
6	rs790256	165.477	0.0222	0.0126	0.0207	0.0127	0.0213	0.0145
6	rs790263	165.485	0.0385	0.0085	0.0281	0.0109	0.022	0.0144
6	rs2272381	165.488	0.0169	0.0143	0.0181	0.0155	0.0183	0.0165
6	rs17292544	165.492	0.0233	0.0165	0.0245	0.0171	0.0211	0.0184
6	rs2103277	165.5	0.0239	0.0117	0.0359	0.0099	0.0186	0.0152
6	rs17292684	165.512	0.0184	0.0156	0.0271	0.0138	0.0169	0.0177
6	rs9478527	165.532	0.0173	0.0134	0.0246	0.012	0.0178	0.0157
6	rs11155954	165.537	0.0376	0.0093	0.0345	0.0125	0.0199	0.0156
6	rs9383697	165.538	0.027	0.0109	0.045	0.0085	0.0171	0.0166
7	rs11762736	106.786	0.021	0.0151	0.0211	0.0218	0.0301	0.0127
7	rs1005169	106.8	0.0164	0.0164	0.0165	0.017	0.0192	0.0178
7	rs1207730	106.802	0.0173	0.0139	0.0181	0.0153	0.0198	0.0175
7	rs1207735	106.814	0.0147	0.0143	0.0159	0.0154	0.0191	0.0193
7	rs17600014	106.819	0.0148	0.0158	0.0154	0.0162	0.0196	0.0175
7	rs17600042	106.82	0.0148	0.0158	0.0154	0.0162	0.0196	0.0175
7	rs17658419	106.824	0.0138	0.0155	0.0145	0.0155	0.0206	0.0145
7	rs1207716	106.827	0.0176	0.0138	0.0174	0.0157	0.0189	0.0178
7	rs1207719	106.831	0.0136	0.0153	0.0154	0.0165	0.018	0.0175
7	rs191137	110.173	0.0166	0.0162	0.0233	0.0153	0.0168	0.0173
7	rs314346	110.179	0.0139	0.0144	0.015	0.0146	0.0222	0.0167
7	rs3847060	110.181	0.0173	0.0159	0.0246	0.0148	0.0178	0.0172
7	rs144173	110.187	0.0172	0.0134	0.0165	0.0145	0.0209	0.0192
7	rs314312	110.191	0.0147	0.0166	0.0189	0.0151	0.0177	0.0164
7	rs2571607	110.193	0.0138	0.0181	0.0156	0.0172	0.0169	0.0215
7	rs314320	110.195	0.0134	0.0146	0.0141	0.015	0.0194	0.0169
7	rs6706	110.214	0.0146	0.0176	0.0161	0.0165	0.0183	0.017
7	rs12705095	110.221	0.0146	0.0175	0.0161	0.0165	0.0183	0.017
7	rs3087504	110.222	0.0148	0.0142	0.0149	0.0154	0.0192	0.0208
7	rs13241786	110.222	0.016	0.0138	0.0165	0.0144	0.0205	0.0185
7	rs3847063	110.227	0.0148	0.0141	0.0148	0.0153	0.0204	0.0173
7	rs176481	114.886	0.0159	0.0139	0.019	0.0132	0.0168	0.016
7	rs4730134	114.89	0.0192	0.015	0.0396	0.0132	0.0174	0.0171

7	rs176484	114.892	0.0186	0.0163	0.0178	0.017	0.0225	0.0171
7	rs10953491	114.901	0.0184	0.0142	0.0318	0.0139	0.018	0.0171
7	rs6466083	114.914	0.0141	0.015	0.018	0.0151	0.0164	0.0171
7	rs12667386	114.925	0.0142	0.0166	0.0176	0.0212	0.0181	0.0157
7	rs6951125	124.781	0.0228	0.0125	0.0184	0.0136	0.0229	0.0148
7	rs11973869	124.782	0.0266	0.0161	0.0268	0.0151	0.0197	0.0174
7	rs887574	124.783	0.0195	0.0135	0.0227	0.0128	0.0171	0.017
7	rs887575	124.783	0.0217	0.0158	0.0201	0.0136	0.0235	0.0151
7	rs2024233	124.783	0.0217	0.0139	0.0221	0.0126	0.0185	0.0197
7	rs2228946	124.784	0.0176	0.014	0.0177	0.0144	0.0203	0.0161
7	rs733153	124.784	0.0188	0.0135	0.0223	0.015	0.0193	0.0171
7	rs6950765	124.786	0.0215	0.012	0.02	0.0132	0.022	0.0146
7	rs3779547	124.792	0.0171	0.0138	0.0151	0.0151	0.0302	0.0173
7	rs17132543	124.793	0.016	0.015	0.0174	0.0167	0.0199	0.0224
7	rs39306	124.798	0.0188	0.0136	0.0198	0.0146	0.0184	0.0165
7	rs2285544	124.8	0.0236	0.0117	0.019	0.0196	0.0344	0.0832
7	rs1989836	124.802	0.0239	0.0127	0.0257	0.0209	0.0184	0.0191
7	rs2285545	124.803	0.019	0.013	0.0183	0.0236	0.0305	0.0416
7	rs39312	124.807	0.0167	0.0142	0.0168	0.014	0.0247	0.0337
7	rs739517	124.807	0.0155	0.0157	0.0166	0.0158	0.0211	0.0185
7	rs39314	124.81	0.0172	0.0137	0.0165	0.0146	0.0304	0.0153
7	rs1004670	152.369	0.0748	0.0084	0.0337	0.0152	0.0219	0.0149
7	rs1009848	152.387	0.0369	0.017	0.0367	0.092	0.0188	0.0154
7	rs2299557	152.39	0.0619	0.0146	0.022	0.018	0.0383	0.0147
7	rs4987691	152.402	0.2159	0.0046	0.0374	0.011	0.025	0.0144
7	rs4987670	152.406	0.1262	0.0053	0.0237	0.015	0.0381	0.0124
7	rs4987704	152.407	0.0169	0.0248	0.0191	0.0484	0.0182	0.0167
7	rs6954724	153.066	0.0178	0.016	0.0225	0.0142	0.0182	0.0175
7	rs1804527	153.07	0.0177	0.0157	0.0171	0.0171	0.0192	0.0178
7	rs10952549	153.076	0.028	0.0125	0.0193	0.014	0.0238	0.0156
7	rs2242601	153.076	0.0211	0.1043	0.0219	0.1003	0.0177	0.0166
7	rs3812407	153.078	0.0161	0.0437	0.0172	0.019	0.0176	0.0184
7	rs7786333	153.081	0.0321	0.027	0.0286	0.0164	0.0192	0.0161
7	rs4726618	153.086	0.0447	0.0086	0.024	0.0141	0.0199	0.016
7	rs12703526	153.093	0.024	0.0122	0.025	0.0157	0.0205	0.0161
7	rs11767557	153.095	0.0232	0.0155	0.0276	0.0278	0.0189	0.0162
7	rs11771145	153.097	0.0286	0.0131	0.0342	0.0188	0.023	0.014
7	rs2919435	176.947	0.0137	0.015	0.0156	0.0152	0.0149	0.0163
7	rs2581842	176.954	0.0146	0.0148	0.0164	0.0148	0.0156	0.0162
7	rs2873379	176.955	0.0138	0.0151	0.0156	0.015	0.0152	0.0166
7	rs1881691	176.96	0.0147	0.0174	0.0166	0.0174	0.015	0.017

7	rs1800883	176.965	0.015	0.0174	0.0174	0.0186	0.0144	0.0167
7	rs6597455	177.002	0.0154	0.0151	0.0167	0.0168	0.0152	0.0165
7	rs980442	177.022	0.0166	0.0148	0.0171	0.0162	0.0163	0.0167
7	rs1730209	177.024	0.0156	0.0163	0.0173	0.0157	0.0158	0.0168
7	rs1657273	177.037	0.0143	0.0168	0.0153	0.0158	0.0174	0.0162
7	rs893113	177.037	0.0134	0.0154	0.0145	0.0158	0.0148	0.0163
7	rs1861972	178.748	0.0158	0.0143	0.0183	0.0141	0.0166	0.0169
7	rs1861973	178.749	0.0158	0.0143	0.0183	0.0141	0.0166	0.0169
7	rs1233560	180.056	0.0201	0.0129	0.0272	0.0114	0.0151	0.0166
7	rs1233571	180.059	0.0167	0.016	0.018	0.0156	0.0187	0.0168
7	rs1233556	180.083	0.0176	0.0153	0.0213	0.0156	0.0168	0.0172
7	rs872723	180.102	0.0171	0.0149	0.0189	0.0154	0.0174	0.0171
7	rs288746	180.105	0.0187	0.0139	0.0193	0.0148	0.017	0.017
8	rs1721102	30.8582	0.0143	0.0169	0.0151	0.0198	0.0157	0.0168
8	rs7005198	30.8598	0.0171	0.0151	0.024	0.0137	0.0164	0.0173
8	rs7015053	30.8655	0.0159	0.014	0.0162	0.0149	0.0177	0.0163
8	rs12720208	30.8681	0.0164	0.0155	0.0161	0.0162	0.0172	0.0187
8	rs1721100	30.8683	0.0151	0.0144	0.0164	0.0149	0.015	0.0167
8	rs11993811	30.8709	0.0152	0.0143	0.0165	0.0147	0.0155	0.0166
8	rs17488779	30.8716	0.0208	0.0161	0.0187	0.0169	0.0269	0.0158
8	rs11203822	30.8749	0.0164	0.0144	0.0217	0.017	0.0174	0.0159
8	rs10106536	30.8767	0.0146	0.0153	0.0161	0.0159	0.0161	0.0172
8	rs1989754	30.8838	0.0151	0.0148	0.0194	0.0169	0.017	0.0161
8	rs7846685	30.8911	0.0153	0.017	0.0165	0.0167	0.0176	0.0176
8	rs7813392	40.8803	0.0151	0.015	0.0166	0.0161	0.0166	0.0161
8	rs3176260	40.8884	0.0144	0.0161	0.0144	0.0166	0.0188	0.0172
8	rs900781	40.8914	0.018	0.0147	0.0187	0.0149	0.0175	0.0175
8	rs3176292	40.8964	0.0143	0.015	0.0152	0.0159	0.0169	0.0163
8	rs1078363	40.8984	0.0135	0.0149	0.0145	0.0159	0.0174	0.0157
8	rs12541126	40.9142	0.0197	0.0147	0.0167	0.0156	0.0187	0.0188
8	rs8181029	71.0962	0.0138	0.0143	0.0154	0.0145	0.0155	0.0163
8	rs1437277	71.1027	0.0201	0.0126	0.0188	0.0147	0.02	0.0164
8	rs2576577	71.1097	0.0134	0.0145	0.0147	0.0147	0.0161	0.0161
8	rs4737431	71.1103	0.013	0.0152	0.0137	0.0152	0.0155	0.0167
8	rs1476590	99.2987	0.0183	0.0131	0.016	0.0146	0.0181	0.0158
8	rs12549239	99.3018	0.0155	0.0167	0.015	0.0157	0.0192	0.0161
8	rs2091887	99.3067	0.0155	0.0144	0.0145	0.0154	0.0176	0.0161
8	rs1805874	99.3077	0.0165	0.0137	0.016	0.0144	0.0162	0.0161
8	rs2142093	99.3135	0.0167	0.0139	0.0155	0.0151	0.0174	0.016
8	rs3758146	99.3142	0.0188	0.0128	0.0181	0.0144	0.0182	0.0156
8	rs7459577	99.3144	0.0159	0.0161	0.015	0.0155	0.018	0.0174

8	rs7011172	167.555	0.0146	0.0161	0.0155	0.0146	0.0194	0.027
8	rs2272631	167.583	0.0153	0.0241	0.0159	0.0159	0.02	0.0239
8	rs13276942	167.589	0.0198	0.0147	0.0239	0.0147	0.0197	0.0179
8	rs3750214	167.596	0.0134	0.0153	0.0139	0.0155	0.0178	0.0162
8	rs7387960	167.603	0.0137	0.0158	0.014	0.0155	0.0177	0.0168
8	rs4330705	167.631	0.013	0.0154	0.0137	0.0157	0.0189	0.0153
10	rs7075820	76.6851	0.0149	0.0144	0.0161	0.0144	0.0207	0.0175
10	rs7068231	76.6868	0.0153	0.0144	0.017	0.0143	0.0182	0.0157
10	rs10994146	76.6869	0.0199	0.0158	0.021	0.0172	0.0206	0.0162
10	rs10994148	76.6881	0.015	0.0149	0.017	0.0146	0.016	0.017
10	rs1050745	76.6898	0.018	0.0145	0.0216	0.0153	0.0219	0.0161
10	rs7078873	76.6903	0.0142	0.0145	0.0156	0.0149	0.0165	0.0159
10	rs8677	76.6911	0.015	0.0317	0.015	0.0241	0.0192	0.0171
10	rs10994158	76.6967	0.0259	0.0102	0.0233	0.0122	0.0222	0.0142
10	rs16914571	76.6979	0.0212	0.0142	0.0212	0.0159	0.0177	0.0185
10	rs11813307	76.6979	0.0188	0.0146	0.0201	0.014	0.02	0.0159
10	rs7100478	76.7025	0.0195	0.0136	0.0189	0.0149	0.0191	0.018
10	rs2393577	76.7077	0.0149	0.0251	0.0164	0.0216	0.0172	0.0165
10	rs2393582	76.7078	0.0166	0.0156	0.0197	0.0147	0.016	0.0164
10	rs2393581	76.708	0.0172	0.0149	0.0199	0.0146	0.0166	0.0162
10	rs2393576	76.7082	0.0141	0.0148	0.0167	0.0144	0.0164	0.0162
10	rs2393602	76.7093	0.014	0.0163	0.016	0.016	0.0166	0.0163
10	rs9665327	76.7233	0.0164	0.0143	0.0161	0.0154	0.0176	0.0184
10	rs10994171	76.7246	0.0167	0.0139	0.0177	0.0148	0.0158	0.0172
10	rs4359155	76.725	0.0159	0.0135	0.016	0.0147	0.0166	0.0166
10	rs2393609	76.7262	0.0174	0.0156	0.0168	0.0156	0.0218	0.0177
10	rs10994174	76.7276	0.0198	0.0129	0.0247	0.0121	0.0178	0.0171
10	rs10509121	76.729	0.0181	0.0144	0.0196	0.0159	0.0189	0.0194
10	rs17207897	76.7295	0.0175	0.0151	0.0158	0.0154	0.0197	0.0197
10	rs7893313	76.7329	0.0146	0.0145	0.0175	0.0152	0.0151	0.018
10	rs7907721	76.7331	0.016	0.014	0.016	0.0145	0.0181	0.0161
10	rs17208182	76.7359	0.016	0.0148	0.0186	0.0148	0.0161	0.0174
10	rs7902905	76.7406	0.014	0.015	0.0144	0.0153	0.0173	0.0162
10	rs11599164	76.7475	0.0175	0.0148	0.0158	0.0154	0.021	0.0203
10	rs10740006	76.7478	0.0184	0.0137	0.0209	0.0132	0.0173	0.0174
10	rs10994182	76.7567	0.0164	0.0141	0.0181	0.0155	0.0172	0.0216
10	rs2241538	76.7595	0.017	0.0147	0.018	0.0248	0.0175	0.028
10	rs9804190	76.7598	0.0151	0.0146	0.0169	0.0146	0.0163	0.0175
10	rs2393595	76.7639	0.0186	0.0143	0.016	0.0154	0.021	0.0191
10	rs10761451	76.7722	0.0206	0.0129	0.0198	0.0168	0.0197	0.0155
10	rs3793854	76.7812	0.0225	0.012	0.0245	0.0127	0.0189	0.0158

10	rs3793857	76.7884	0.0193	0.0179	0.0229	0.0247	0.0174	0.018
10	rs7077937	76.7923	0.0154	0.015	0.0202	0.0134	0.016	0.0162
10	rs10994200	76.798	0.0224	0.0119	0.0242	0.0126	0.0178	0.016
10	rs11599447	76.8075	0.0187	0.0155	0.0175	0.0173	0.0234	0.0183
10	rs10740008	76.8098	0.0182	0.0137	0.0249	0.0118	0.0157	0.0165
10	rs2393612	76.8286	0.0204	0.0138	0.0199	0.0145	0.0185	0.0154
10	rs10733758	76.8301	0.0186	0.0129	0.0227	0.0128	0.0163	0.0162
10	rs10761460	76.8308	0.0178	0.0171	0.0207	0.0235	0.0163	0.0162
10	rs10821683	76.8343	0.0198	0.0284	0.0263	0.0728	0.0166	0.0174
10	rs10740011	76.8431	0.0153	0.0143	0.0165	0.0154	0.0166	0.0187
10	rs7086260	76.8433	0.0148	0.0146	0.0167	0.0141	0.0158	0.0197
10	rs7100448	76.8435	0.0187	0.0134	0.0185	0.0139	0.0168	0.0187
10	rs10509123	76.847	0.0152	0.0143	0.017	0.0147	0.0183	0.0159
10	rs7072073	76.8501	0.0148	0.0158	0.0169	0.015	0.0169	0.0167
10	rs2893825	76.8658	0.0185	0.0138	0.0186	0.0151	0.0266	0.0131
10	rs12355908	76.9014	0.0178	0.0147	0.0198	0.0137	0.0197	0.0161
10	rs17230650	76.9029	0.0178	0.0146	0.03	0.0114	0.0167	0.0178
10	rs4948255	76.9033	0.0292	0.0111	0.0494	0.009	0.0175	0.0162
10	rs10821694	76.904	0.0155	0.0141	0.0235	0.0122	0.0157	0.0165
10	rs3793861	76.9112	0.0149	0.0145	0.0159	0.0145	0.0212	0.0155
10	rs10994248	76.9229	0.0158	0.0178	0.0162	0.0161	0.0196	0.017
10	rs4948256	76.9257	0.0189	0.0163	0.0242	0.015	0.0169	0.0164
10	rs10994253	76.9349	0.0153	0.0157	0.0177	0.015	0.0159	0.0175
10	rs12411380	76.9356	0.0255	0.0126	0.0393	0.0116	0.0174	0.0163
10	rs17805636	76.9368	0.0178	0.0161	0.0177	0.0168	0.0214	0.0172
10	rs10821704	76.963	0.0237	0.0143	0.0373	0.0127	0.02	0.0149
10	rs1340654	76.974	0.0182	0.0146	0.0174	0.016	0.0314	0.0126
10	rs10821707	76.9741	0.0157	0.0178	0.0177	0.0148	0.0182	0.0198
10	rs16914651	76.9875	0.0213	0.0149	0.0209	0.0176	0.0178	0.0166
10	rs1459731	77.0121	0.0149	0.0155	0.0168	0.0158	0.0222	0.0146
10	rs10821709	77.0285	0.017	0.0143	0.0175	0.0169	0.018	0.0179
10	rs7095717	77.037	0.0159	0.015	0.0159	0.0155	0.0222	0.0159
10	rs17234046	77.0583	0.0176	0.0174	0.0189	0.0174	0.018	0.0182
10	rs12217983	77.0588	0.0174	0.0132	0.0163	0.0147	0.0235	0.0149
10	rs997238	77.0617	0.0182	0.0188	0.0195	0.0174	0.0183	0.016
10	rs1459730	77.0835	0.0227	0.0137	0.0267	0.0146	0.0177	0.0181
10	rs10821729	77.1026	0.0193	0.013	0.0189	0.0136	0.0204	0.0148
10	rs4948410	77.1243	0.0168	0.0147	0.0184	0.0165	0.0204	0.0193
10	rs7895653	77.157	0.0162	0.0173	0.0196	0.0156	0.017	0.0172
10	rs7896287	77.1574	0.018	0.0146	0.0177	0.0149	0.0198	0.0193
10	rs4948412	77.1605	0.0138	0.0162	0.015	0.0164	0.016	0.0181

10	rs10821747	77.1673	0.0176	0.0131	0.0205	0.0132	0.019	0.0157
10	rs10821748	77.1676	0.0136	0.016	0.0148	0.0165	0.0163	0.0173
10	rs1274446	109.967	0.0183	0.0135	0.0185	0.0162	0.0173	0.0161
10	rs3740046	109.969	0.0165	0.0159	0.018	0.0172	0.0164	0.019
10	rs2420203	109.975	0.0153	0.0147	0.0165	0.0156	0.0171	0.0165
10	rs10881829	109.979	0.0164	0.0153	0.0175	0.0162	0.0216	0.016
10	rs4272713	110.018	0.0224	0.0119	0.0265	0.0118	0.0173	0.016
10	rs7916403	110.028	0.0177	0.0134	0.0175	0.0141	0.019	0.0154
10	rs10785973	110.067	0.0187	0.0164	0.0165	0.0158	0.0192	0.0157
10	rs11596991	110.067	0.0311	0.0125	0.0294	0.0134	0.0203	0.017
10	rs2226116	110.069	0.0265	0.0117	0.0249	0.0128	0.0183	0.0161
10	rs12259062	110.079	0.0162	0.0138	0.0166	0.0145	0.0164	0.0159
10	rs12761105	110.083	0.0241	0.0151	0.029	0.0129	0.0175	0.0168
10	rs11186338	110.084	0.0188	0.0168	0.0207	0.0151	0.0188	0.0172
10	rs4917908	120.052	0.0155	0.0146	0.0195	0.0141	0.017	0.0168
10	rs6421335	120.057	0.0189	0.0138	0.024	0.0167	0.0178	0.0174
10	rs4278455	120.057	0.0189	0.0125	0.0207	0.0134	0.0202	0.0168
10	rs4244341	120.058	0.0164	0.015	0.0154	0.0157	0.0254	0.0157
10	rs11190684	120.061	0.0245	0.0113	0.026	0.0116	0.0217	0.0148
10	rs11599825	120.069	0.0245	0.0113	0.026	0.0116	0.0217	0.0148
10	rs3923992	120.077	0.0197	0.016	0.0196	0.0163	0.0194	0.0178
10	rs4600144	120.081	0.0177	0.0166	0.0194	0.016	0.0192	0.0183
10	rs11190708	120.097	0.0269	0.0108	0.0239	0.012	0.0241	0.0142
10	rs10883543	120.1	0.0178	0.017	0.0168	0.0158	0.0214	0.0305
10	rs1006544	120.101	0.021	0.0122	0.0194	0.0135	0.0199	0.0154
10	rs996359	120.135	0.0205	0.013	0.0187	0.0142	0.0197	0.0164
10	rs11816136	120.135	0.0163	0.0144	0.02	0.0141	0.0176	0.0174
10	rs2476964	120.137	0.0319	0.0102	0.0321	0.0102	0.0211	0.0173
10	rs10883688	120.926	0.0318	0.0095	0.0245	0.0286	0.0489	0.0115
10	rs749694	120.932	0.0284	0.0102	0.0245	0.0286	0.0433	0.011
10	rs4919593	120.948	0.0521	0.0072	0.0281	0.0327	0.0323	0.0136
10	rs1008013	120.954	0.0185	0.0157	0.0213	0.0169	0.0166	0.0164
11	rs12280580	1.305	0.0142	0.0161	0.0142	0.0185	0.0298	0.0135
11	rs3842748	6.2242	0.0163	0.0142	0.0173	0.0149	0.0202	0.016
11	rs2070762	6.2388	0.0159	0.0135	0.0157	0.0144	0.0325	0.0139
11	rs6356	6.2525	0.0219	0.0206	0.0193	0.0145	0.0283	0.0173
11	rs10840490	6.261	0.0172	0.0151	0.018	0.0149	0.0297	0.0183
11	rs10840491	6.2621	0.018	0.0154	0.0185	0.0149	0.0279	0.0218
11	rs10743149	6.2627	0.0185	0.0143	0.0209	0.0142	0.0201	0.0162
11	rs7119275	6.264	0.0145	0.0151	0.0169	0.0155	0.0176	0.0159
11	rs2941025	15.3539	0.0295	0.0112	0.0184	0.0156	0.0402	0.011

11	rs2947025	15.3551	0.0349	0.01	0.0166	0.0155	0.0341	0.014
11	rs7943852	15.359	0.0205	0.0124	0.0184	0.0142	0.023	0.0151
11	rs2941029	15.3592	0.0275	0.0104	0.0222	0.0121	0.0225	0.0144
11	rs11040832	15.3644	0.0256	0.0131	0.0187	0.0194	0.0242	0.0153
11	rs12364575	15.3715	0.0292	0.0224	0.0225	0.0166	0.0226	0.0159
11	rs1042048	15.3745	0.0158	0.0142	0.0182	0.0142	0.0158	0.0165
11	rs7951720	15.3777	0.0181	0.0137	0.0201	0.0153	0.0185	0.0162
11	rs10769675	15.3791	0.0159	0.015	0.0184	0.016	0.0178	0.0155
11	rs211102	31.6539	0.0164	0.0147	0.0193	0.0144	0.0175	0.0165
11	rs2056246	31.6603	0.0198	0.0124	0.017	0.0142	0.0268	0.013
11	rs11606304	31.6613	0.016	0.0163	0.017	0.0164	0.0181	0.0173
11	rs17794760	31.6658	0.0171	0.0147	0.0189	0.0144	0.0192	0.0159
11	rs623580	31.6756	0.0207	0.0121	0.0266	0.0114	0.0192	0.0162
11	rs6486403	31.6795	0.0224	0.0114	0.0206	0.0133	0.0196	0.0156
11	rs1519479	48.8186	0.0147	0.015	0.0148	0.0164	0.0184	0.0168
11	rs925946	48.8189	0.0221	0.0123	0.0207	0.0134	0.0235	0.0151
11	rs11030102	48.8321	0.0179	0.0138	0.0162	0.0149	0.0238	0.0146
11	rs2049045	48.844	0.0312	0.0131	0.0302	0.0124	0.022	0.0175
11	rs7103873	48.8494	0.0154	0.0168	0.0145	0.0176	0.0222	0.0159
11	rs7103411	48.8496	0.0179	0.0163	0.0215	0.0147	0.0188	0.0212
11	rs2030323	48.8747	0.0178	0.0159	0.0214	0.0147	0.0188	0.0212
11	rs12273363	48.8892	0.0232	0.0129	0.0171	0.0149	0.033	0.0127
11	rs908867	48.89	0.0191	0.0143	0.0237	0.0147	0.0191	0.0165
11	rs1541315	51.4761	0.014	0.0168	0.0152	0.0204	0.0165	0.0174
11	rs3026398	51.4814	0.0153	0.0158	0.0178	0.0168	0.0173	0.0158
11	rs662702	51.4816	0.0202	0.014	0.0241	0.0138	0.0206	0.0163
11	rs1506	51.4824	0.0162	0.016	0.0183	0.018	0.0171	0.0178
11	rs644242	51.4841	0.029	0.0126	0.0339	0.0121	0.0222	0.0162
11	rs628224	51.4883	0.0143	0.0202	0.0157	0.0215	0.0177	0.0263
11	rs1806180	51.502	0.0147	0.0266	0.0156	0.0196	0.0177	0.0282
11	rs3891484	119.237	0.0153	0.015	0.0157	0.0154	0.0239	0.0156
11	rs10789970	119.24	0.017	0.0134	0.0173	0.0153	0.0184	0.0154
11	rs11214763	119.242	0.0161	0.0152	0.0169	0.015	0.0186	0.0164
11	rs11606194	119.254	0.0165	0.0152	0.0155	0.0159	0.0219	0.0169
11	rs11214769	119.272	0.0139	0.0147	0.0141	0.0152	0.019	0.0161
11	rs1176746	119.295	0.0158	0.0167	0.015	0.0161	0.0194	0.0166
11	rs2276307	119.297	0.0127	0.0151	0.0126	0.0159	0.0229	0.0159
11	rs3782025	119.305	0.0134	0.016	0.0143	0.0154	0.0166	0.0172
11	rs1672717	119.314	0.0157	0.0155	0.0149	0.0157	0.0187	0.0173
11	rs1185027	119.324	0.0162	0.0161	0.0158	0.0157	0.0186	0.0184
11	rs17116164	119.329	0.0152	0.0158	0.0155	0.0163	0.0172	0.0168

11	rs10789980	119.369	0.0135	0.0156	0.0148	0.0152	0.0162	0.0218
11	rs1150226	119.378	0.016	0.017	0.0159	0.0167	0.0176	0.0165
11	rs11604247	119.381	0.0149	0.0149	0.0166	0.0157	0.0173	0.0171
11	rs1985242	119.384	0.0156	0.0139	0.0159	0.015	0.0208	0.0204
11	rs10160548	119.4	0.0161	0.0211	0.0174	0.0151	0.0186	0.0441
11	rs17543605	119.406	0.0167	0.0156	0.0158	0.0162	0.0203	0.0189
11	rs7115470	119.412	0.0169	0.0147	0.0181	0.0148	0.0185	0.0177
11	rs11214800	119.413	0.0159	0.0143	0.0179	0.0143	0.0181	0.0364
11	rs897685	119.415	0.0196	0.0168	0.0187	0.0159	0.022	0.0177
12	rs3782353	65.7458	0.0196	0.0149	0.0168	0.0151	0.0222	0.0146
12	rs833840	65.751	0.0246	0.0109	0.0178	0.0148	0.0248	0.0136
12	rs4760663	65.7528	0.0177	0.0146	0.0168	0.0152	0.0238	0.0136
12	rs11170448	70.4709	0.0182	0.0147	0.0155	0.0178	0.0212	0.0175
12	rs2272306	70.4756	0.0176	0.0146	0.0157	0.0167	0.0214	0.0175
12	rs2293429	70.4902	0.0201	0.0149	0.0182	0.0166	0.0219	0.017
12	rs3814777	70.4914	0.0201	0.0149	0.0182	0.0166	0.0219	0.017
12	rs2272301	70.501	0.0173	0.0148	0.0155	0.0167	0.0214	0.0175
12	rs3825084	70.5051	0.0175	0.0146	0.0159	0.0178	0.0225	0.0186
12	rs1554753	70.5125	0.0165	0.0142	0.015	0.0151	0.0268	0.0144
12	rs3741434	70.5137	0.0358	0.01	0.0237	0.0135	0.0266	0.0174
12	rs1465057	70.5193	0.0167	0.0146	0.0166	0.0155	0.0299	0.0144
12	rs6580936	70.523	0.0264	0.0109	0.0178	0.0145	0.059	0.009
12	rs10082776	70.5259	0.0402	0.0091	0.0256	0.0131	0.0238	0.0142
12	rs7398676	70.5326	0.0188	0.0129	0.0193	0.0136	0.0198	0.0161
12	rs560048	75.4383	0.0153	0.0141	0.0168	0.0153	0.0306	0.013
12	rs2943693	75.4418	0.0169	0.0149	0.0182	0.0148	0.024	0.0161
12	rs3809114	75.4483	0.0127	0.0191	0.0146	0.0207	0.0159	0.0161
12	rs2242578	75.4507	0.0137	0.0152	0.0152	0.0163	0.0168	0.0171
12	rs10783828	75.4549	0.0173	0.0133	0.0165	0.0157	0.0225	0.0153
12	rs7969998	89.0772	0.0208	0.0141	0.0201	0.0147	0.0186	0.0175
12	rs4448731	89.0774	0.0366	0.0087	0.0336	0.0097	0.0298	0.0133
12	rs7954758	89.0813	0.0147	0.0179	0.0145	0.0166	0.0216	0.0173
12	rs2129575	89.0839	0.0147	0.0156	0.0153	0.0155	0.018	0.0161
12	rs7955501	89.0897	0.0278	0.0112	0.0204	0.0136	0.0437	0.0107
12	rs1386493	89.0928	0.0191	0.0137	0.0176	0.0161	0.0249	0.0154
12	rs11179023	89.1014	0.0165	0.0156	0.0159	0.0154	0.0235	0.0142
12	rs1007023	89.1094	0.0176	0.0148	0.0176	0.0151	0.0225	0.0153
12	rs17722134	89.1161	0.0191	0.0163	0.0198	0.0168	0.019	0.0177
12	rs3903502	89.1185	0.0357	0.009	0.0191	0.0134	0.1629	0.0062
12	rs12231356	89.12	0.0155	0.0159	0.0157	0.0171	0.0185	0.0175
12	rs1386483	89.1214	0.0253	0.0112	0.0168	0.014	0.0273	0.0128

12	rs17110747	89.1283	0.0282	0.0118	0.0195	0.017	0.0253	0.0156
12	rs1872824	89.1305	0.0399	0.0083	0.0209	0.0127	0.0362	0.0118
13	rs17759841	34.0092	0.0157	0.0161	0.0147	0.0167	0.0254	0.0164
13	rs9544418	34.0132	0.0177	0.0132	0.0152	0.0149	0.0185	0.0162
13	rs4943303	34.0148	0.0167	0.0135	0.0156	0.0155	0.0181	0.0184
13	rs1461976	34.016	0.0157	0.0137	0.0142	0.016	0.0213	0.015
13	rs3125	51.0082	0.0139	0.0153	0.015	0.0168	0.021	0.0202
13	rs6314	51.0085	0.0168	0.015	0.0167	0.0158	0.0196	0.0162
13	rs1923882	51.0138	0.0128	0.0152	0.0137	0.0162	0.0229	0.0194
13	rs977003	51.0207	0.0133	0.0148	0.0127	0.0154	0.0172	0.0176
13	rs9534493	51.0276	0.0153	0.015	0.0162	0.0155	0.0177	0.0164
13	rs6561333	51.0316	0.0143	0.0146	0.0141	0.0148	0.0179	0.0166
13	rs17069005	51.0395	0.0127	0.0166	0.0149	0.0167	0.0172	0.0167
13	rs2296972	51.0484	0.0141	0.015	0.0139	0.0157	0.0172	0.0167
13	rs9534495	51.05	0.0134	0.015	0.0139	0.0155	0.018	0.0161
13	rs7984966	51.0504	0.0153	0.0144	0.0148	0.0152	0.0163	0.0165
13	rs2274639	51.0521	0.0152	0.0393	0.0134	0.0214	0.0236	0.0161
13	rs17359763	51.0528	0.0201	0.0151	0.0197	0.0161	0.0189	0.0176
13	rs9534496	51.0539	0.0138	0.0174	0.0138	0.0158	0.0205	0.0224
13	rs9526240	51.0546	0.0145	0.0162	0.0147	0.0154	0.0196	0.0207
13	rs2224721	51.056	0.0142	0.015	0.0141	0.0163	0.0229	0.0167
13	rs7323079	51.0576	0.0195	0.0151	0.0193	0.016	0.0197	0.0176
13	rs9316233	51.0585	0.0144	0.0149	0.0147	0.0156	0.0228	0.0159
13	rs6561335	51.0588	0.0145	0.0162	0.0153	0.0152	0.0182	0.02
13	rs1928042	51.0665	0.0229	0.0115	0.0175	0.0141	0.0244	0.0155
13	rs9534502	51.0722	0.0153	0.0165	0.0145	0.0169	0.0198	0.017
13	rs9534501	51.0731	0.0137	0.0165	0.0137	0.0161	0.0178	0.017
13	rs2770296	51.0734	0.0147	0.0155	0.0148	0.0154	0.0173	0.0168
13	rs582854	51.0843	0.0145	0.0165	0.0138	0.0153	0.0189	0.0216
13	rs9534505	51.115	0.0175	0.0145	0.0165	0.0158	0.0195	0.016
13	rs4941573	51.1235	0.0136	0.0214	0.0131	0.0155	0.0194	0.0565
13	rs2296973	51.1275	0.014	0.0228	0.0149	0.0169	0.0169	0.0189
13	rs2070037	51.1281	0.0149	0.0178	0.0151	0.0164	0.0177	0.0171
13	rs6306	51.1379	0.015	0.0164	0.0163	0.0161	0.0168	0.0176
13	rs6312	51.1396	0.021	0.0157	0.0209	0.015	0.0197	0.0173
13	rs17289394	51.1443	0.017	0.0315	0.0155	0.0151	0.0216	0.0629
13	rs11911	76.1424	0.0153	0.0143	0.0141	0.0152	0.0219	0.0147
13	rs497857	76.1487	0.0156	0.014	0.0148	0.0148	0.0225	0.0146
14	rs1483113	54.4246	0.0165	0.0147	0.0142	0.016	0.1074	0.0113
14	rs7154016	54.4494	0.0186	0.015	0.0169	0.019	0.0347	0.0127
14	rs171978	54.4594	0.0252	0.0127	0.0349	0.012	0.022	0.0157

14	rs698015	54.4629	0.0195	0.0134	0.0184	0.0149	0.0215	0.0142
14	rs1123285	54.4747	0.0188	0.0145	0.0172	0.017	0.0224	0.014
14	rs928110	54.4871	0.0251	0.0104	0.0218	0.0119	0.0318	0.0121
14	rs2128673	54.5101	0.0255	0.0182	0.0241	0.022	0.0204	0.0176
14	rs3818239	61.0226	0.0158	0.0152	0.0156	0.0157	0.0274	0.0165
14	rs745686	61.0392	0.0199	0.0182	0.0185	0.0144	0.024	0.0142
14	rs2230491	61.0448	0.0172	0.0142	0.0208	0.0137	0.0163	0.0169
14	rs3742609	61.0463	0.0143	0.0157	0.0148	0.0164	0.0208	0.018
14	rs10131416	61.0551	0.0154	0.0172	0.0176	0.0145	0.017	0.016
15	rs1041931	5.5797	0.0202	0.014	0.0177	0.0151	0.0232	0.0159
15	rs17115479	5.591	0.0182	0.0143	0.0174	0.0154	0.0204	0.0187
15	rs1557872	5.6101	0.017	0.0144	0.017	0.0154	0.0187	0.0182
15	rs12907375	5.6474	0.0148	0.0151	0.0153	0.0151	0.0167	0.0168
15	rs7176973	5.7141	0.0149	0.0155	0.0159	0.0157	0.0168	0.017
15	rs2340625	5.7703	0.0136	0.0153	0.0143	0.0157	0.0165	0.0165
15	rs8179187	5.8165	0.0168	0.0164	0.017	0.0187	0.0201	0.0161
15	rs1041933	5.8251	0.0148	0.0152	0.0153	0.0151	0.0167	0.0168
15	rs12899875	5.8542	0.0185	0.0145	0.0174	0.0153	0.0215	0.0164
15	rs17115585	5.8827	0.0185	0.0145	0.0174	0.0153	0.0215	0.0164
15	rs12901086	5.9072	0.0185	0.0145	0.0174	0.0153	0.0215	0.0164
15	rs11630723	5.9246	0.0179	0.0131	0.0166	0.0147	0.02	0.017
15	rs2928725	9.8231	0.039	0.0116	0.0383	0.0222	0.0205	0.0179
15	rs1963231	9.8459	0.0245	0.0112	0.0215	0.0131	0.0196	0.0178
15	rs10438462	9.9035	0.0196	0.0125	0.0192	0.0137	0.0178	0.0152
15	rs8030011	9.9201	0.0176	0.0148	0.0203	0.0157	0.0173	0.0168
15	rs1426217	9.9273	0.0159	0.0151	0.0176	0.0148	0.0163	0.0165
15	rs17560619	9.9351	0.0159	0.0168	0.0176	0.0156	0.0172	0.0181
15	rs8024564	9.9585	0.0188	0.0125	0.0205	0.014	0.0167	0.0156
15	rs7172993	9.9655	0.019	0.0142	0.0188	0.0163	0.0176	0.0168
15	rs3919613	9.9801	0.0199	0.0141	0.0189	0.0144	0.0198	0.0189
15	rs7178850	9.9861	0.0207	0.0137	0.0197	0.0165	0.0174	0.0165
15	rs754197	10.0765	0.0181	0.0126	0.0202	0.0131	0.0187	0.0171
15	rs1426206	10.0976	0.0133	0.0148	0.0137	0.0158	0.0163	0.0163
15	rs754185	10.0988	0.0145	0.0147	0.0143	0.0152	0.0181	0.0159
15	rs12911879	10.1093	0.018	0.0162	0.0185	0.0222	0.0174	0.0166
15	rs12442543	10.1119	0.0138	0.0163	0.0155	0.016	0.0162	0.0184
15	rs7179514	10.1163	0.0155	0.0138	0.0166	0.0141	0.0166	0.0163
15	rs17738087	10.1407	0.0148	0.0153	0.0169	0.0163	0.0176	0.0166
15	rs2217068	10.1466	0.0249	0.0185	0.0248	0.016	0.0207	0.0163
15	rs2194958	10.1473	0.0185	0.0137	0.0181	0.0144	0.021	0.0153
15	rs11161328	10.154	0.0158	0.0157	0.0179	0.0174	0.0191	0.0173

15	rs7172653	10.1557	0.0174	0.0136	0.0175	0.0141	0.0217	0.0158
15	rs17646800	10.1591	0.0177	0.0136	0.0185	0.0173	0.0181	0.0194
15	rs1863463	10.1595	0.0149	0.0155	0.0164	0.0153	0.0257	0.0158
15	rs890319	10.1618	0.0156	0.014	0.0152	0.0151	0.0204	0.0146
15	rs1863455	10.1728	0.0164	0.0208	0.0181	0.0198	0.02	0.0161
15	rs17561112	10.1826	0.0135	0.0172	0.0145	0.0166	0.0193	0.0167
15	rs890317	10.1828	0.0145	0.0162	0.0172	0.0158	0.0159	0.0164
15	rs7494844	10.1872	0.0149	0.0156	0.0163	0.0162	0.0181	0.0165
15	rs8039336	10.1904	0.0154	0.0141	0.019	0.0138	0.0155	0.0162
15	rs878960	10.1983	0.0151	0.0148	0.0165	0.0158	0.0172	0.016
15	rs11634050	10.199	0.0162	0.0142	0.0167	0.0142	0.0198	0.0162
15	rs17646890	10.1998	0.0133	0.0168	0.0145	0.0171	0.0197	0.0164
15	rs878961	10.2002	0.018	0.0146	0.0202	0.0158	0.0168	0.0181
15	rs7178255	10.205	0.0148	0.0176	0.0162	0.0177	0.0221	0.0162
15	rs12593415	10.2094	0.0131	0.0152	0.015	0.0147	0.0178	0.016
15	rs752414	10.2137	0.0147	0.0149	0.0162	0.015	0.0159	0.0171
15	rs6576594	10.2287	0.0199	0.0134	0.0179	0.0154	0.0191	0.0153
15	rs12905013	10.2479	0.0152	0.0153	0.0165	0.0147	0.0189	0.0152
15	rs1549480	10.2534	0.0172	0.0152	0.0168	0.0156	0.0252	0.0172
15	rs11631421	10.254	0.0198	0.0131	0.0183	0.015	0.0174	0.0161
15	rs11632969	10.2717	0.0137	0.0151	0.0159	0.0154	0.0156	0.0172
15	rs2114217	10.2749	0.015	0.0149	0.017	0.0149	0.0162	0.0168
15	rs11630462	10.2759	0.0176	0.0136	0.0224	0.0129	0.0169	0.0159
15	rs17561473	10.2797	0.0173	0.015	0.02	0.0157	0.0162	0.018
15	rs12592816	10.2898	0.0157	0.015	0.0176	0.0161	0.018	0.0192
15	rs2315903	10.2934	0.019	0.0153	0.0212	0.0179	0.017	0.0165
15	rs737098	10.2943	0.0172	0.0168	0.0178	0.0161	0.0176	0.0189
15	rs11637930	10.3055	0.024	0.0118	0.0298	0.0112	0.02	0.0258
15	rs8043440	10.3087	0.0195	0.0136	0.0247	0.0149	0.0193	0.018
15	rs919075	10.3114	0.0186	0.0151	0.0178	0.0162	0.0183	0.0168
15	rs2162241	10.3183	0.0641	0.0072	0.0354	0.01	0.0246	0.0177
15	rs7179279	10.3314	0.0156	0.0156	0.0159	0.0201	0.0194	0.0169
15	rs7183628	10.3674	0.0218	0.0125	0.0285	0.0119	0.0181	0.0162
15	rs4453447	10.3859	0.0155	0.0149	0.0152	0.0157	0.0214	0.0152
15	rs7178713	10.3874	0.0172	0.0138	0.0202	0.0135	0.0168	0.019
15	rs3212336	10.41	0.0173	0.0147	0.0167	0.0174	0.0236	0.0143
15	rs3212334	10.4141	0.0158	0.0163	0.0152	0.016	0.0237	0.017
15	rs4906902	10.436	0.0156	0.0176	0.0166	0.0166	0.021	0.0163
15	rs7174912	10.4648	0.0272	0.0127	0.0213	0.0155	0.0223	0.0166
15	rs7168574	10.4842	0.0144	0.016	0.0171	0.0146	0.0168	0.0219
15	rs12594043	10.4846	0.0174	0.0137	0.0204	0.0132	0.0253	0.0344

15	rs7170111	10.4898	0.0276	0.0122	0.03	0.0159	0.0216	0.0178
15	rs12913992	10.6815	0.0167	0.0153	0.0196	0.0176	0.0187	0.0166
15	rs7403139	10.6829	0.0199	0.015	0.019	0.0211	0.0198	0.0149
15	rs7173687	10.7547	0.016	0.0157	0.0188	0.0156	0.017	0.0158
15	rs4887529	11.0846	0.0154	0.0154	0.0153	0.0155	0.0209	0.0157
15	rs17647384	11.0869	0.0151	0.0145	0.0162	0.0151	0.0197	0.0151
15	rs10519587	11.0923	0.0155	0.0146	0.0165	0.015	0.0197	0.0151
15	rs140683	11.0999	0.0232	0.0148	0.0181	0.0156	0.0282	0.0177
15	rs140685	11.1004	0.0147	0.0151	0.0157	0.0152	0.019	0.0157
15	rs4887530	11.1064	0.0146	0.0161	0.018	0.0155	0.0189	0.017
15	rs17647448	11.1115	0.015	0.0147	0.0164	0.0148	0.019	0.0153
15	rs17561800	11.1163	0.0193	0.0161	0.017	0.0179	0.0203	0.0172
15	rs7402018	11.1214	0.0137	0.0158	0.017	0.0156	0.0172	0.017
15	rs11263717	11.1328	0.0212	0.0137	0.0182	0.0147	0.0247	0.0169
15	rs6606903	11.163	0.0141	0.0158	0.0174	0.0156	0.0176	0.017
15	rs140670	11.215	0.0145	0.0154	0.0161	0.0151	0.0181	0.018
15	rs7178872	11.2183	0.0196	0.0148	0.0197	0.0134	0.0201	0.0152
15	rs9920534	11.2415	0.0168	0.0135	0.0188	0.0132	0.0172	0.0162
15	rs11637860	11.2554	0.0167	0.0145	0.0168	0.0165	0.0181	0.0155
15	rs12440254	11.2904	0.0175	0.0154	0.0191	0.0165	0.0191	0.0177
15	rs8023397	11.3042	0.0149	0.0143	0.0143	0.0156	0.0227	0.0141
15	rs7172672	11.3498	0.016	0.0141	0.0196	0.0133	0.0166	0.0164
15	rs6606855	11.3714	0.0152	0.0147	0.0192	0.0135	0.0157	0.0166
15	rs891791	11.3744	0.0164	0.0153	0.0185	0.0146	0.0173	0.0179
15	rs17738834	11.3783	0.0262	0.0137	0.02	0.016	0.0193	0.0168
15	rs6606856	11.3862	0.0223	0.0141	0.0252	0.0121	0.0182	0.0264
15	rs6606859	11.4206	0.0167	0.0136	0.0177	0.0156	0.017	0.0178
15	rs4468579	11.4213	0.0156	0.0144	0.0148	0.0155	0.0209	0.0153
15	rs7403483	11.4219	0.0167	0.0136	0.0164	0.0142	0.0187	0.0151
15	rs17562125	11.4263	0.0162	0.0145	0.019	0.0151	0.018	0.0253
15	rs7171954	11.4355	0.0167	0.0151	0.02	0.0138	0.0167	0.0168
15	rs12903002	11.4361	0.0292	0.0108	0.0277	0.0121	0.0241	0.0327
15	rs12439085	11.441	0.0154	0.016	0.0179	0.0146	0.0168	0.017
15	rs17738971	11.4442	0.0168	0.0147	0.0171	0.0153	0.02	0.0166
15	rs2376483	11.4462	0.0145	0.0144	0.0162	0.0147	0.0161	0.0167
15	rs17671508	11.4473	0.0161	0.0146	0.0151	0.0166	0.0205	0.0157
15	rs11636450	11.451	0.0164	0.0146	0.0159	0.0156	0.0226	0.0181
15	rs2376478	11.4636	0.0152	0.0142	0.0167	0.0153	0.0159	0.0168
15	rs2376479	11.466	0.0152	0.0152	0.0177	0.014	0.0161	0.0171
15	rs11638213	11.4701	0.0144	0.0151	0.0152	0.0159	0.0182	0.0155
15	rs12910388	11.473	0.0155	0.0155	0.0159	0.0147	0.0192	0.0165

15	rs1011455	11.477	0.0152	0.0148	0.0178	0.015	0.0173	0.0161
15	rs12439106	11.4791	0.0198	0.0143	0.0261	0.0133	0.0202	0.0166
15	rs12592156	11.4822	0.0164	0.0154	0.0158	0.0164	0.0205	0.0162
15	rs4078843	11.4828	0.0156	0.0142	0.0168	0.016	0.0168	0.0162
15	rs17647933	11.4838	0.017	0.0137	0.0177	0.0141	0.0185	0.0175
15	rs7494955	11.5012	0.0161	0.0149	0.0164	0.0169	0.0172	0.0166
15	rs13380359	11.509	0.0164	0.0154	0.0168	0.0166	0.0186	0.017
15	rs7403557	11.512	0.0138	0.0151	0.015	0.0152	0.0174	0.0171
15	rs6606866	11.5213	0.0218	0.0125	0.0229	0.0139	0.0167	0.0162
15	rs4340300	11.5291	0.0166	0.0161	0.0174	0.0168	0.0175	0.0172
15	rs878921	11.534	0.0189	0.0135	0.0189	0.0147	0.0173	0.016
15	rs12050742	11.536	0.0172	0.0156	0.0167	0.0151	0.0176	0.0155
15	rs17648036	11.5399	0.0145	0.0154	0.0175	0.0151	0.0153	0.0175
15	rs12595253	11.5439	0.0179	0.0151	0.0163	0.0164	0.0191	0.0186
15	rs9330237	11.5621	0.0217	0.0133	0.0279	0.0119	0.0193	0.0156
15	rs6606870	11.5667	0.0141	0.0156	0.0186	0.0146	0.0151	0.0182
15	rs7179575	11.5813	0.0164	0.0144	0.0194	0.0149	0.0177	0.0161
15	rs4354903	11.6387	0.0177	0.0155	0.0236	0.013	0.0157	0.0173
15	rs4887531	11.6564	0.0197	0.0131	0.0166	0.0152	0.022	0.0187
15	rs6606873	11.6757	0.0207	0.0129	0.0301	0.0107	0.0155	0.0162
15	rs2110209	11.7339	0.0175	0.0169	0.0167	0.0177	0.0244	0.0162
15	rs6606876	11.7553	0.0198	0.0136	0.0181	0.015	0.0203	0.0151
15	rs1029935	11.7666	0.0171	0.0147	0.0227	0.0145	0.0165	0.0166
15	rs1029938	11.7677	0.0238	0.0113	0.0205	0.013	0.0199	0.0167
15	rs208176	11.7931	0.0168	0.0141	0.0158	0.0155	0.0203	0.0176
15	rs6606877	11.8249	0.0195	0.0143	0.0173	0.0155	0.0568	0.0098
15	rs741124	11.8927	0.0149	0.0176	0.0161	0.0156	0.0156	0.0186
15	rs12910678	11.9117	0.0238	0.0161	0.0223	0.0163	0.02	0.01
15	rs4887565	11.912	0.0163	0.0151	0.0163	0.0159	0.0173	0.0185
15	rs17671946	11.9697	0.0166	0.014	0.0163	0.0147	0.0177	0.0165
15	rs208129	11.9701	0.0162	0.0139	0.0172	0.0138	0.0167	0.0176
15	rs208128	11.971	0.0189	0.0126	0.0243	0.0116	0.0189	0.0158
15	rs7402139	12.0546	0.0176	0.0139	0.0178	0.0138	0.0194	0.0153
15	rs208152	12.0756	0.0169	0.0141	0.0191	0.014	0.0169	0.017
15	rs1378094	12.0889	0.016	0.0164	0.0197	0.0156	0.0174	0.0178
15	rs17672063	12.1	0.016	0.0153	0.0197	0.0153	0.0163	0.0165
15	rs2045151	12.1171	0.0206	0.0156	0.0189	0.0169	0.0187	0.0167
15	rs6606888	12.1177	0.0182	0.0136	0.018	0.016	0.0205	0.0152
15	rs8036270	12.1186	0.0196	0.0127	0.0195	0.0142	0.0181	0.0179
15	rs17648549	12.1218	0.016	0.0141	0.0155	0.0151	0.0179	0.0159
15	rs897174	12.1388	0.0194	0.0137	0.0238	0.0194	0.0179	0.018

15	rs1454665	12.1399	0.022	0.0115	0.0281	0.0118	0.0167	0.0159
15	rs897176	12.1413	0.0173	0.0149	0.02	0.0189	0.0179	0.0187
15	rs17648585	12.1426	0.0153	0.016	0.0165	0.0159	0.0187	0.0183
15	rs17672216	12.2133	0.0162	0.0143	0.0164	0.0167	0.0175	0.0162
15	rs7180136	12.239	0.016	0.0148	0.0169	0.0147	0.0165	0.0208
15	rs11630979	12.2423	0.0169	0.0138	0.018	0.0155	0.0185	0.016
15	rs17563374	12.2493	0.0169	0.0161	0.0226	0.0142	0.0166	0.0168
15	rs7402129	12.2805	0.0192	0.0129	0.0194	0.0136	0.0197	0.0162
15	rs8043244	12.2873	0.0193	0.0126	0.0181	0.014	0.0205	0.0149
15	rs7497522	12.3211	0.021	0.0122	0.0181	0.0135	0.0276	0.0138
15	rs6606897	12.4034	0.0179	0.0149	0.0182	0.0164	0.0218	0.0154
15	rs12914497	12.409	0.0196	0.0156	0.0171	0.017	0.0219	0.0175
15	rs4600441	12.4242	0.0178	0.0137	0.0167	0.0144	0.0228	0.0156
15	rs11632705	12.4745	0.0205	0.014	0.0219	0.0167	0.0228	0.015
15	rs8041046	13.1366	0.0186	0.0129	0.0174	0.0138	0.0192	0.0167
15	rs8028000	13.1544	0.0252	0.0133	0.019	0.0143	0.0208	0.0163
15	rs4778159	13.1626	0.0321	0.0192	0.0246	0.0204	0.0229	0.0155
15	rs7166417	13.1721	0.0222	0.0117	0.0172	0.0145	0.0256	0.0136
15	rs12591921	13.2026	0.014	0.019	0.0141	0.0175	0.0177	0.0168
15	rs8030466	13.243	0.0317	0.0133	0.02	0.0151	0.022	0.0159
15	rs11853763	13.248	0.0197	0.0136	0.0199	0.0145	0.018	0.0165
15	rs11631444	13.2697	0.0158	0.02	0.0176	0.0172	0.0228	0.0144
15	rs3922613	13.3297	0.0153	0.0145	0.0166	0.0154	0.0194	0.0161
15	rs8042276	13.3758	0.0182	0.0173	0.0211	0.015	0.0204	0.0159
15	rs8037353	13.4067	0.0297	0.0255	0.0388	0.02	0.0189	0.0166
15	rs4595752	13.4076	0.0144	0.0152	0.0138	0.016	0.0216	0.015
15	rs8037055	13.408	0.0177	0.0144	0.0154	0.0156	0.0229	0.0145
15	rs7174138	13.4154	0.019	0.0142	0.0196	0.0185	0.018	0.0162
15	rs12906172	13.4289	0.0279	0.0154	0.0341	0.0156	0.0183	0.0173
15	rs7167756	13.4393	0.0205	0.0126	0.0184	0.0158	0.0231	0.0147
15	rs12913576	13.4752	0.019	0.0153	0.0173	0.0198	0.0192	0.0158
15	rs8024595	13.5073	0.0192	0.0169	0.0195	0.0167	0.0205	0.0166
15	rs4533233	13.5284	0.0144	0.0149	0.0151	0.0163	0.0191	0.0151
15	rs8035979	13.5477	0.0153	0.0148	0.0168	0.0147	0.0188	0.0167
15	rs12592749	13.5711	0.0175	0.015	0.0218	0.0148	0.0184	0.017
15	rs11074284	13.5898	0.0206	0.0122	0.0168	0.0142	0.0216	0.0147
15	rs4778146	13.6066	0.0205	0.0126	0.0176	0.014	0.0185	0.0155
15	rs4288951	13.608	0.0187	0.014	0.0176	0.0159	0.0201	0.019
15	rs4778147	13.6128	0.016	0.0142	0.0149	0.015	0.0204	0.0162
15	rs11074291	13.6566	0.0144	0.0141	0.0154	0.0151	0.0169	0.0166
15	rs4778154	13.7979	0.0154	0.014	0.0174	0.014	0.019	0.0158

15	rs4778156	13.8058	0.0142	0.015	0.0152	0.0153	0.0184	0.0162
15	rs6495639	29.4418	0.0161	0.0155	0.0155	0.0161	0.0187	0.0172
15	rs4779660	29.4435	0.0182	0.0141	0.0181	0.0149	0.0198	0.0154
15	rs16958878	29.4655	0.0167	0.0154	0.016	0.016	0.0181	0.0171
15	rs17236791	29.4833	0.0144	0.016	0.0149	0.0168	0.0181	0.0173
15	rs2290940	29.4875	0.0147	0.0163	0.0142	0.0162	0.0172	0.0167
15	rs2705343	29.4908	0.016	0.0149	0.0143	0.0157	0.0188	0.0166
15	rs2615358	29.492	0.0327	0.0138	0.0206	0.0141	0.0227	0.0184
15	rs440025	29.5501	0.0146	0.0159	0.015	0.016	0.0165	0.0176
15	rs12591967	29.5552	0.0155	0.0153	0.0152	0.0161	0.0177	0.0169
15	rs7165973	29.5585	0.0201	0.0163	0.0202	0.0162	0.0196	0.0201
15	rs12594569	29.5631	0.0141	0.0161	0.015	0.016	0.0165	0.0176
15	rs16958995	29.6424	0.0155	0.0156	0.015	0.0161	0.0173	0.0166
15	rs8028600	29.6436	0.0157	0.0142	0.0145	0.0154	0.0171	0.0164
15	rs11638692	29.6529	0.028	0.0116	0.024	0.0131	0.0232	0.0151
15	rs872670	29.6646	0.0164	0.0165	0.0167	0.017	0.0208	0.0161
15	rs11631094	29.669	0.0159	0.0144	0.016	0.015	0.0175	0.0165
15	rs17817854	29.6749	0.0155	0.0157	0.0153	0.0163	0.0197	0.0173
17	rs2074222	20.5526	0.015	0.0142	0.0163	0.0142	0.0166	0.0175
17	rs222852	20.5808	0.0143	0.0148	0.0167	0.0142	0.016	0.0167
17	rs17710	20.5898	0.017	0.0143	0.0171	0.015	0.0196	0.0162
17	rs222843	20.595	0.015	0.0152	0.016	0.0146	0.0163	0.0195
17	rs4151125	21.0851	0.0145	0.0151	0.0179	0.0152	0.0159	0.0167
17	rs3853818	21.089	0.0153	0.0161	0.016	0.016	0.0176	0.0169
17	rs7215056	21.0971	0.0159	0.0167	0.0166	0.0167	0.021	0.0176
17	rs17732878	21.1191	0.0141	0.0172	0.0153	0.0203	0.0195	0.0165
17	rs4239111	21.7625	0.0187	0.0157	0.0179	0.0161	0.0203	0.0158
17	rs9891006	21.775	0.0129	0.0176	0.014	0.0157	0.0165	0.0163
17	rs4239115	21.7859	0.0127	0.0163	0.0141	0.015	0.0164	0.0171
17	rs4791987	21.7894	0.0125	0.0165	0.0135	0.0153	0.0171	0.0163
17	rs7211792	21.8008	0.0126	0.0164	0.0138	0.0151	0.0167	0.0166
17	rs7224199	54.3342	0.0202	0.0146	0.018	0.0209	0.0157	0.0162
17	rs11657536	54.3351	0.0333	0.0134	0.0355	0.0132	0.0189	0.0181
17	rs140700	54.3375	0.0209	0.0138	0.019	0.0148	0.019	0.0169
17	rs2020942	54.3381	0.022	0.012	0.0225	0.0142	0.0189	0.0172
17	rs4251417	54.3388	0.018	0.0163	0.0195	0.0151	0.018	0.0183
17	rs12150214	54.3389	0.0306	0.0107	0.0307	0.0112	0.0187	0.0161
17	rs16965628	54.3395	0.0363	0.0106	0.0293	0.0157	0.0198	0.0168
17	rs12946680	68.6088	0.0144	0.0165	0.0167	0.0151	0.0165	0.0169
17	rs2715554	68.6152	0.0197	0.0139	0.0179	0.016	0.0194	0.0168
17	rs2715553	68.6207	0.0207	0.0119	0.0209	0.0131	0.0213	0.014

17	rs9303285	68.6244	0.0143	0.0173	0.0167	0.0153	0.0162	0.017
17	rs4890109	68.6303	0.0167	0.0164	0.0173	0.0165	0.0194	0.0176
17	rs603769	74.7978	0.0163	0.0156	0.0168	0.015	0.0169	0.0171
17	rs9908234	74.8101	0.0134	0.0157	0.0149	0.0162	0.0162	0.0168
17	rs565042	74.8109	0.0195	0.0123	0.0189	0.0155	0.0186	0.0172
17	rs534561	74.8252	0.0171	0.0133	0.0167	0.0144	0.0179	0.0156
17	rs2072445	74.8279	0.0145	0.0156	0.0153	0.0158	0.021	0.0165
17	rs7224806	74.8349	0.0153	0.0164	0.0173	0.0192	0.0202	0.0163
17	rs741072	74.8353	0.0149	0.0153	0.0192	0.0166	0.0157	0.0163
17	rs741073	74.8356	0.0158	0.0147	0.0163	0.0144	0.0188	0.0195
17	rs11466177	74.8389	0.0191	0.0146	0.0187	0.0157	0.0197	0.0163
17	rs985626	75.8879	0.0187	0.0146	0.0158	0.0167	0.0351	0.0158
17	rs919089	75.9046	0.0146	0.0154	0.0155	0.0177	0.0167	0.0172
17	rs1058564	75.9147	0.0151	0.0154	0.016	0.0213	0.017	0.0225
17	rs8066341	75.9155	0.0153	0.0152	0.0163	0.0207	0.017	0.0225
17	rs9897343	75.9415	0.0172	0.0146	0.0157	0.0174	0.022	0.0152
17	rs16948563	75.9451	0.019	0.0178	0.024	0.018	0.0186	0.0171
17	rs3891034	75.9568	0.0151	0.0207	0.0156	0.0171	0.0211	0.0158
17	rs11656951	75.9628	0.0146	0.0195	0.0155	0.0164	0.02	0.0162
19	rs3814892	0	0.0178	0.0147	0.0171	0.0158	0.0193	0.0159
19	rs7260011	0	0.017	0.0139	0.0214	0.0144	0.016	0.0167
19	rs2074460	0	0.018	0.0142	0.0181	0.0151	0.0173	0.0178
19	rs3787004	0	0.0199	0.0127	0.0213	0.0135	0.018	0.0172
19	rs3787011	0	0.0196	0.016	0.0189	0.0156	0.0189	0.0183
19	rs2419233	33.5559	0.0163	0.0145	0.0201	0.0135	0.0151	0.0169
19	rs11085835	33.5718	0.017	0.0141	0.0171	0.0152	0.0197	0.0171
19	rs1865033	33.5727	0.016	0.0151	0.0174	0.0156	0.0173	0.0175
19	rs3816027	33.5785	0.025	0.0111	0.0315	0.0105	0.0154	0.0181
19	rs4926240	33.6101	0.0199	0.013	0.0194	0.0139	0.0194	0.0206
19	rs12462609	33.6128	0.0151	0.0158	0.0175	0.0158	0.0168	0.017
19	rs11085838	33.6143	0.0175	0.014	0.0186	0.0149	0.0164	0.0186
19	rs16035	33.6191	0.0181	0.0198	0.0176	0.0186	0.0222	0.0149
19	rs8112821	33.6298	0.0146	0.0143	0.0169	0.0148	0.016	0.0169
19	rs4926242	33.6424	0.0226	0.0132	0.0197	0.0149	0.0208	0.0185
19	rs8101524	33.6441	0.0154	0.0143	0.0175	0.0144	0.0155	0.0165
19	rs2074880	33.6514	0.0165	0.0139	0.0245	0.0133	0.0141	0.0166
19	rs7250783	33.659	0.0158	0.0166	0.0138	0.0159	0.0325	0.0157
19	rs7249323	33.6616	0.0186	0.0163	0.0188	0.0174	0.0192	0.0171
19	rs11085840	33.6676	0.0172	0.0141	0.0227	0.0135	0.0175	0.0171
19	rs7251409	33.6697	0.0158	0.0197	0.0197	0.0143	0.016	0.0218
19	rs4926250	33.6725	0.0233	0.0167	0.0269	0.0193	0.0195	0.0179

19	rs11673216	33.6735	0.0261	0.0129	0.0309	0.0109	0.0162	0.0167
19	rs4926252	33.6745	0.0155	0.0148	0.0174	0.014	0.0156	0.0171
19	rs16030	33.6837	0.0151	0.015	0.0183	0.0145	0.0161	0.0168
19	rs12608501	33.7182	0.0171	0.0151	0.0184	0.0155	0.0176	0.0175
19	rs4926261	33.7305	0.0176	0.0142	0.0201	0.0132	0.0174	0.0158
19	rs16018	33.7412	0.015	0.0149	0.0167	0.0154	0.0156	0.0164
19	rs16016	33.7487	0.0182	0.0151	0.0205	0.0152	0.0213	0.0159
19	rs11878230	33.7546	0.0177	0.0174	0.0231	0.0159	0.0161	0.0164
19	rs16015	33.7588	0.0377	0.0148	0.061	0.0078	0.0175	0.0189
19	rs8182590	33.7657	0.0172	0.021	0.0232	0.0144	0.0158	0.0164
19	rs2292033	33.7803	0.0302	0.0207	0.0257	0.0186	0.0181	0.0176
19	rs2419248	33.7899	0.0171	0.0195	0.0214	0.0288	0.0152	0.0165
19	rs10409541	33.7939	0.0173	0.0142	0.0219	0.0135	0.0163	0.0165
19	rs8101955	33.8085	0.0142	0.0151	0.0141	0.0157	0.0181	0.0165
19	rs10408012	33.8334	0.0142	0.0157	0.0159	0.0157	0.0157	0.0167
19	rs10424440	33.8442	0.0151	0.0149	0.0164	0.0157	0.0163	0.0168
19	rs4926155	33.8522	0.0198	0.0152	0.0221	0.0154	0.0183	0.0163
19	rs1742	33.8547	0.0199	0.0138	0.0213	0.0154	0.0175	0.0164
19	rs4926278	33.862	0.0163	0.0142	0.0204	0.0127	0.0151	0.0165
19	rs12985786	33.8662	0.0234	0.0143	0.0216	0.015	0.0197	0.0183
19	rs16007	33.873	0.0148	0.0176	0.0149	0.0184	0.0178	0.0166
19	rs4926281	33.8969	0.0145	0.0166	0.0168	0.0176	0.016	0.017
19	rs11670018	33.901	0.0181	0.0137	0.0175	0.0142	0.0207	0.0157
19	rs4461194	33.9189	0.0181	0.0128	0.0155	0.0146	0.0247	0.0135
19	rs2900918	33.9458	0.0283	0.0123	0.0289	0.0133	0.0184	0.0182
19	rs8109003	33.9737	0.0169	0.0134	0.0155	0.0146	0.0199	0.0153
19	rs8113506	33.9768	0.0178	0.0147	0.0163	0.0158	0.0191	0.0163
19	rs4926285	34.0016	0.0142	0.0147	0.015	0.0152	0.0167	0.0162
19	rs4926286	34.0072	0.0146	0.017	0.0163	0.0169	0.0159	0.017
19	rs4926287	34.0146	0.0209	0.0135	0.0221	0.0143	0.0172	0.0175
19	rs1422259	34.0186	0.0167	0.0139	0.0201	0.015	0.016	0.0171
19	rs8109635	34.0464	0.0151	0.0184	0.0178	0.0172	0.0162	0.0194
19	rs2900964	34.0466	0.0205	0.0174	0.0202	0.0166	0.0175	0.0174
19	rs10419374	34.0595	0.0167	0.0144	0.0227	0.0133	0.0157	0.0198
19	rs11879358	34.0663	0.0155	0.0241	0.0181	0.0178	0.0162	0.0305
19	rs3764615	34.0703	0.0164	0.0217	0.0179	0.0167	0.0181	0.0221
19	rs10408880	34.0823	0.0261	0.0155	0.0279	0.0147	0.0186	0.0169
19	rs4926289	34.0831	0.0184	0.0142	0.0252	0.0128	0.0173	0.0182
19	rs7257149	34.0838	0.0215	0.0158	0.0293	0.0126	0.0163	0.0197
19	rs1363345	34.0918	0.0178	0.0132	0.0158	0.0154	0.0193	0.0177
19	rs4926290	34.0961	0.0168	0.0145	0.0213	0.0138	0.0153	0.0165

19	rs11879128	34.1071	0.0175	0.014	0.0207	0.0136	0.0155	0.0167
19	rs12985705	34.1099	0.0171	0.0152	0.0174	0.0151	0.0165	0.0178
19	rs8107958	34.117	0.017	0.0149	0.0184	0.0151	0.0176	0.0172
19	rs10411263	34.121	0.0207	0.0167	0.035	0.0111	0.0176	0.0189
19	rs12609735	34.1222	0.0162	0.0147	0.0211	0.0146	0.0168	0.0166
19	rs2112461	34.1261	0.0163	0.0142	0.0161	0.015	0.0193	0.0217
19	rs2112460	34.1262	0.0205	0.0145	0.0225	0.0131	0.0183	0.018
19	rs1120559	34.1456	0.0211	0.014	0.0221	0.019	0.0212	0.0152
19	rs7250452	34.1544	0.0218	0.0149	0.0189	0.0155	0.0169	0.0175
19	rs5021327	34.1683	0.024	0.0122	0.0221	0.0129	0.0195	0.016
19	rs1477293	34.1854	0.0179	0.0138	0.0166	0.0145	0.0178	0.0166
19	rs2217342	67.6962	0.0266	0.021	0.0254	0.0178	0.0225	0.0177
19	rs4803520	67.7032	0.0152	0.0164	0.0173	0.0154	0.016	0.0171
19	rs454150	67.7054	0.0146	0.0161	0.0169	0.0156	0.0157	0.017
19	rs443239	67.7063	0.0152	0.0164	0.0173	0.0154	0.016	0.0171
19	rs10408650	67.7201	0.0231	0.015	0.018	0.0166	0.0203	0.0173
19	rs899661	67.7263	0.0148	0.0164	0.0177	0.0153	0.0157	0.017
19	rs4803523	67.7266	0.0132	0.0167	0.0138	0.0166	0.0165	0.0165
19	rs10407506	67.7303	0.0141	0.0155	0.0156	0.0165	0.0162	0.017
19	rs10414815	67.746	0.0214	0.0138	0.0222	0.0137	0.0228	0.0154
20	rs11697250	9.9715	0.0151	0.02	0.0157	0.0162	0.0177	0.0199
20	rs4813625	9.9731	0.0161	0.0147	0.0147	0.0152	0.0264	0.0136
20	rs2740210	9.9778	0.0127	0.0152	0.012	0.0163	0.0217	0.0149
20	rs4813627	9.9808	0.0142	0.0166	0.0142	0.0158	0.0167	0.0178
20	rs1410713	9.9872	0.0143	0.0174	0.0147	0.0171	0.0158	0.0163
20	rs2770381	9.9894	0.0133	0.0152	0.0133	0.0156	0.0161	0.0157
20	rs6084265	10.0013	0.0126	0.0153	0.0131	0.0158	0.0149	0.0173
21	rs415573	51.0587	0.0274	0.0109	0.0264	0.0134	0.0186	0.0179
21	rs381716	51.0618	0.0202	0.0122	0.0222	0.0131	0.0181	0.0164
21	rs374162	51.0622	0.0319	0.0107	0.032	0.0114	0.0193	0.0162
21	rs2299742	51.0743	0.0495	0.01	0.0592	0.0088	0.0196	0.0171
21	rs2837263	51.0965	0.0203	0.0127	0.0189	0.0143	0.0207	0.0231
21	rs2065317	51.1099	0.0185	0.0132	0.0169	0.0146	0.0172	0.0164
21	rs741792	51.1142	0.0348	0.0098	0.0269	0.0118	0.0215	0.0159
21	rs2837268	51.1296	0.0155	0.0143	0.0162	0.0151	0.0164	0.0167
21	rs17753847	51.1306	0.0157	0.0151	0.0152	0.0159	0.0174	0.0183
21	rs2250341	51.1313	0.0156	0.0144	0.0153	0.0156	0.0187	0.0159
21	rs2837269	51.1315	0.0236	0.0123	0.0193	0.0149	0.0177	0.0157
21	rs2299754	51.1344	0.0147	0.0153	0.0143	0.016	0.0227	0.0147
21	rs1006891	51.1452	0.0153	0.0138	0.0166	0.0141	0.0193	0.0158
21	rs8130100	51.154	0.0198	0.0183	0.0174	0.0157	0.0204	0.0161

21	rs2837272	51.1584	0.0145	0.015	0.0147	0.0154	0.0237	0.0136
21	rs2837275	51.163	0.015	0.016	0.0163	0.0157	0.0163	0.0179
21	rs3787930	51.1645	0.0158	0.0162	0.0188	0.0159	0.0165	0.0179
21	rs2837284	51.1762	0.0173	0.016	0.0146	0.0155	0.0341	0.015
21	rs2837285	51.1777	0.0154	0.0156	0.0166	0.0155	0.0163	0.0177
21	rs2837286	51.1789	0.0152	0.0156	0.0166	0.0154	0.0163	0.0177
21	rs2244084	51.1804	0.0157	0.015	0.0186	0.0144	0.0154	0.0176
21	rs6517577	51.1812	0.0232	0.0121	0.0194	0.013	0.0207	0.0162
21	rs2244189	51.185	0.021	0.0138	0.0198	0.0144	0.0189	0.0172
21	rs2299766	51.1861	0.0189	0.0135	0.0191	0.0142	0.0164	0.0164
21	rs2244297	51.1869	0.0206	0.0167	0.0209	0.0141	0.0184	0.0176
21	rs968582	51.1874	0.0288	0.0172	0.0279	0.0135	0.0231	0.0153
21	rs2299771	51.1912	0.0292	0.0379	0.0241	0.0159	0.0204	0.0165
21	rs2299776	51.1945	0.0155	0.0149	0.0156	0.0155	0.0193	0.0158
21	rs16998883	51.1989	0.019	0.0166	0.0189	0.0144	0.0178	0.0188
21	rs928294	51.201	0.024	0.0141	0.0173	0.0155	0.0223	0.0154
21	rs2299782	51.2015	0.0207	0.0221	0.0208	0.0152	0.0191	0.0174
21	rs2299783	51.2019	0.0308	0.0172	0.0189	0.0162	0.0235	0.0162
21	rs994810	51.2028	0.0288	0.0121	0.0183	0.0147	0.0205	0.0171
21	rs9808736	51.2039	0.0674	0.0063	0.0445	0.0104	0.0178	0.0154
21	rs2837290	51.2071	0.025	0.0122	0.0213	0.0136	0.0218	0.0158
21	rs2837291	51.2082	0.0225	0.0141	0.0154	0.0159	0.026	0.0139
21	rs2299788	51.2232	0.0211	0.0135	0.0183	0.0145	0.0198	0.0162
21	rs2299787	51.224	0.0371	0.0116	0.024	0.0137	0.0235	0.0152
21	rs2837293	51.2281	0.0221	0.0128	0.0201	0.0138	0.0201	0.0161
21	rs2251453	51.233	0.0163	0.0148	0.0169	0.0154	0.0171	0.017
21	rs2837295	51.2358	0.0265	0.0123	0.0232	0.0124	0.0171	0.0171
21	rs2252048	51.2466	0.0185	0.0132	0.0204	0.0135	0.0171	0.0168
21	rs17827195	51.2575	0.0304	0.0118	0.0207	0.0145	0.0227	0.0157
21	rs2837297	51.26	0.0418	0.0091	0.0198	0.0142	0.0325	0.0127
21	rs2837302	51.2621	0.0175	0.0131	0.0155	0.0146	0.0192	0.0149
21	rs2837305	51.2696	0.0185	0.0132	0.0166	0.0146	0.0203	0.0157
22	rs933271	11.9522	0.0133	0.0153	0.0151	0.0163	0.0154	0.0169
22	rs5993882	11.9638	0.0186	0.0139	0.0176	0.0154	0.0202	0.0155
22	rs2239393	11.9882	0.0173	0.0138	0.0189	0.014	0.0171	0.0161
22	rs4680	11.9899	0.016	0.0141	0.0189	0.0146	0.0154	0.0166
22	rs4646316	11.9916	0.0255	0.0115	0.0247	0.0124	0.0218	0.0148
22	rs165774	11.9924	0.0181	0.0132	0.0195	0.0134	0.0176	0.0161
22	rs174696	11.9936	0.0174	0.0136	0.019	0.0143	0.0182	0.0157
22	rs174699	11.9961	0.0136	0.0169	0.0159	0.0168	0.0157	0.0173
22	rs9332377	11.9985	0.0151	0.0154	0.015	0.017	0.0172	0.0165

22	rs165849	12.0043	0.0165	0.0184	0.0199	0.0199	0.0169	0.016
22	rs165815	12.0059	0.0155	0.0182	0.02	0.0159	0.0163	0.0175
22	rs5993891	12.0064	0.0254	0.0127	0.0263	0.0133	0.018	0.0172
22	rs2518823	12.0073	0.0184	0.0234	0.021	0.0278	0.0172	0.0167
22	rs9778000	62.1611	0.0203	0.0146	0.0182	0.016	0.0201	0.0166
22	rs28625707	62.2115	0.0158	0.0158	0.0176	0.0287	0.0161	0.0185
22	rs28439308	62.2117	0.014	0.0151	0.0174	0.0148	0.0147	0.0184
22	rs10448585	62.2665	0.0134	0.0157	0.0164	0.0151	0.0149	0.0169
23	rs3810680	85.8003	0.0267	0.0181	0.0266	0.0128	0.0198	0.017
23	rs5906754	85.8144	0.0141	0.0128	0.0358	0.0087	0.013	0.0158
23	rs2071316	85.8221	0.0129	0.0152	0.0266	0.0116	0.0137	0.0158
23	rs2075866	85.8243	0.0128	0.0142	0.0278	0.0111	0.013	0.0157
23	rs926175	85.8266	0.0138	0.014	0.0447	0.0083	0.0136	0.0158
23	rs4844284	95.7843	0.0136	0.0179	0.0138	0.018	0.018	0.0153
23	rs4844285	95.7962	0.0138	0.0169	0.0141	0.0177	0.0178	0.0154
23	rs10127395	95.803	0.0177	0.0126	0.0173	0.0132	0.015	0.016
23	rs2503132	95.8032	0.0148	0.0164	0.0164	0.0339	0.0164	0.0184
23	rs6624537	95.8182	0.0115	0.0142	0.0139	0.0145	0.0126	0.0163
23	rs5981084	95.8222	0.0143	0.0156	0.0143	0.0151	0.0188	0.0155
23	rs6625760	95.8268	0.0113	0.0156	0.0133	0.0145	0.0143	0.0153
23	rs12013169	178.441	0.0148	0.0145	0.0134	0.0157	0.0262	0.0144
23	rs10521868	178.453	0.0143	0.0173	0.0157	0.0159	0.0307	0.0183
23	rs28900	178.456	0.0223	0.0121	0.0172	0.0147	0.0202	0.0172
23	rs25726	178.467	0.0122	0.0218	0.0138	0.0225	0.0158	0.0158
23	rs29277	178.474	0.0149	0.0147	0.0138	0.0158	0.023	0.0154
23	rs29282	178.478	0.0143	0.0174	0.0157	0.0164	0.0307	0.0183
23	rs5904817	178.509	0.0157	0.0147	0.0134	0.014	0.0202	0.0301
23	rs2269416	188.505	0.0186	0.0124	0.0157	0.0139	0.0356	0.0108
23	rs2239684	188.524	0.0148	0.0134	0.0158	0.0141	0.0274	0.0121
23	rs2256756	188.526	0.0145	0.0137	0.0153	0.0145	0.0274	0.0121
23	rs2266858	188.558	0.0171	0.0118	0.0172	0.0133	0.019	0.0136
23	rs5925082	188.606	0.0196	0.0111	0.02	0.0118	0.0293	0.0199
23	rs17254377	189.127	0.0438	0.0151	0.0184	0.0128	0.0519	0.0114
23	rs3848926	189.137	0.0808	0.014	0.0198	0.0123	0.0822	0.0108
23	rs1388515	189.153	0.0468	0.0214	0.0198	0.0123	0.0404	0.025
23	rs4828688	189.169	0.0468	0.0214	0.0198	0.0123	0.0404	0.025
23	rs7890488	189.173	0.0568	0.0133	0.0175	0.0134	0.1098	0.0081
23	rs17320283	189.174	0.0468	0.0214	0.0198	0.0123	0.0404	0.025
23	rs6653441	189.262	0.0591	0.0093	0.02	0.0121	0.0497	0.0102
23	rs1907600	189.305	0.035	0.0276	0.0191	0.0126	0.0289	0.0323
23	rs5925139	189.33	0.0264	0.0098	0.0187	0.0131	0.0289	0.0126

23	rs7062484	189.333	0.0262	0.0106	0.0183	0.0133	0.0297	0.0121
23	rs17280085	189.359	0.0488	0.0268	0.0256	0.0182	0.0304	0.0176
23	rs994423	189.376	0.0207	0.0116	0.0162	0.0147	0.0242	0.014
23	rs5970232	189.437	0.0213	0.0112	0.0164	0.0149	0.022	0.0136
23	rs1961170	189.462	0.0199	0.018	0.0177	0.0169	0.0207	0.0171
23	rs12833553	189.494	0.0242	0.0116	0.0183	0.0137	0.0207	0.0153
23	rs5970242	189.508	0.0217	0.0112	0.0165	0.0153	0.022	0.0136
23	rs17221020	189.513	0.0177	0.0156	0.0184	0.0172	0.0173	0.0167
23	rs5970247	189.561	0.0205	0.0134	0.0183	0.0138	0.0319	0.0207
23	rs11796898	189.64	0.0255	0.0172	0.0205	0.013	0.0936	0.0254
23	rs1492302	189.691	0.0277	0.0134	0.0217	0.0127	0.0376	0.0214
23	rs750841	189.729	0.0497	0.0291	0.0307	0.0252	0.0256	0.0154
23	rs1565610	189.831	0.0298	0.0104	0.0224	0.0131	0.0319	0.0207
23	rs6526099	189.872	0.0298	0.0123	0.0209	0.0127	0.0319	0.0207
23	rs5970281	189.923	0.0394	0.0093	0.022	0.0144	0.0274	0.0229
23	rs1009387	189.953	0.0216	0.0132	0.0192	0.0135	0.0376	0.0214
23	rs389292	190.03	0.0122	0.014	0.0132	0.0141	0.016	0.0156
23	rs6526104	190.115	0.0149	0.0129	0.0141	0.014	0.0232	0.0138
23	rs5970304	190.233	0.0145	0.0136	0.0134	0.0144	0.0226	0.0143
23	rs5970307	190.258	0.0209	0.0353	0.0172	0.0274	0.0309	0.0158
23	rs10218139	190.306	0.0158	0.0232	0.0153	0.0215	0.0238	0.0171
23	rs6526116	190.399	0.011	0.0159	0.0134	0.0144	0.0149	0.0171
23	rs4562491	191.041	0.0179	0.0143	0.0153	0.0163	0.0217	0.016
23	rs5925191	191.058	0.0191	0.02	0.0177	0.017	0.0219	0.0143
23	rs5925192	191.06	0.0185	0.0217	0.0171	0.0192	0.0219	0.0142
23	rs5924752	191.092	0.0237	0.016	0.0205	0.0135	0.0372	0.0152
23	rs5924754	191.139	0.0122	0.0137	0.0167	0.0131	0.0144	0.0155
23	rs4898375	194.775	0.017	0.0536	0.0141	0.02	0.0225	0.0481
23	rs633	194.777	0.0178	0.0526	0.0146	0.0185	0.0289	0.0528
23	rs11465839	194.789	0.0139	0.0174	0.0139	0.0182	0.019	0.0174
23	rs1059702	194.797	0.0185	0.0305	0.0141	0.0176	0.0289	0.0339
23	rs2734647	194.813	0.0178	0.074	0.0141	0.0232	0.0257	0.0596
23	rs3027933	194.826	0.0212	0.033	0.0149	0.0184	0.0289	0.0339
23	rs3027935	194.838	0.0281	0.0142	0.0288	0.0131	0.0164	0.0183
23	rs1734787	194.88	0.0214	0.0752	0.0149	0.0184	0.0257	0.0753
23	rs1734791	194.891	0.023	0.0807	0.0154	0.021	0.0257	0.0617
23	rs2239464	194.926	0.018	0.0437	0.0143	0.0175	0.0257	0.045
23	rs5945397	194.977	0.0155	0.0156	0.0157	0.0153	0.0207	0.0181

Appendix 3. 2-point PPL and PPLD results of the Phase 2 analysis using original family samples, additional family samples and the result after sequential update

Chr	SNP	bp	Original families		Additional families		Additional families - fem removed		Seq update		Seq update-fem removed	
			PPL	PPLD	PPL	PPLD	PPL	PPLD	PPL	PPLD	PPL	PPLD
7	rs2242601	142803946	0.02	0.16	0.01	0.02	0.01	0.02	0.01	0.12	0.02	0.12
7	rs1525119	142868672	0.19	0.20	0.02	0.01	0.02	0.01	0.17	0.18	0.16	0.17
7	rs12536735	142875457	0.19	0.09	0.02	0.01	0.02	0.01	0.17	0.07	0.16	0.07
7	rs10233030	142876623	0.36	0.08	0.02	0.01	0.02	0.01	0.34	0.07	0.35	0.06
7	rs1404635	142885276	0.22	0.10	0.02	0.01	0.02	0.01	0.20	0.09	0.19	0.09
7	rs1525105	142886920	0.18	0.21	0.02	0.01	0.02	0.01	0.18	0.16	0.17	0.16
7	rs10264730	142889384	0.26	0.12	0.02	0.01	0.02	0.01	0.24	0.10	0.23	0.10
7	rs10441194	142890129	0.15	0.11	0.02	0.01	0.02	0.01	0.15	0.09	0.15	0.09
7	rs4344014	142891075	0.12	0.13	0.02	0.01	0.02	0.02	0.10	0.11	0.10	0.11
7	rs10256611	142894037	0.13	0.11	0.02	0.01	0.02	0.01	0.11	0.09	0.11	0.08
7	rs1525108	142898876	0.18	0.11	0.02	0.01	0.02	0.01	0.17	0.09	0.16	0.09
7	rs12530563	142902065	0.12	0.11	0.02	0.01	0.02	0.01	0.11	0.09	0.10	0.09
7	rs6966430	142903359	0.77	0.03	0.02	0.01	0.02	0.01	0.75	0.03	0.74	0.03
7	rs9640390	142903469	0.12	0.11	0.02	0.01	0.02	0.01	0.11	0.09	0.10	0.09
7	rs9640391	142903637	0.13	0.05	0.02	0.01	0.02	0.01	0.12	0.04	0.12	0.04
7	rs1525111	142904065	0.09	0.05	0.02	0.01	0.02	0.01	0.07	0.05	0.07	0.04
7	rs7801889	142906295	0.16	0.62	0.02	0.01	0.02	0.01	0.18	0.45	0.15	0.49
7	rs7802528	142912953	0.14	0.13	0.02	0.01	0.02	0.01	0.13	0.10	0.12	0.10
7	rs12537950	142914520	0.20	0.14	0.02	0.01	0.02	0.01	0.18	0.11	0.17	0.12
7	rs17382348	142915034	0.14	0.13	0.02	0.01	0.02	0.01	0.12	0.10	0.12	0.10
7	rs4726631	142923417	0.15	0.16	0.02	0.01	0.02	0.01	0.14	0.13	0.13	0.13

Fem removed: re-analysis result after removing the female patients.

Chr	SNP	bp	Original families		Additional families		Additional families - fem removed		Seq update		Seq update- fem removed	
			PPL	PPLD	PPL	PPLD	PPL	PPLD	PPL	PPLD	PPL	PPLD
X	rs4328010	152531191	0.02	0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.02	0.01
X	rs4898429	152539449	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01
X	rs3761536	152559486	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.03	0.01
X	rs2266887	152892781	0.02	0.05	0.03	0.01	0.03	0.01	0.03	0.02	0.03	0.02
X	rs2266888	152892914	0.02	0.06	0.02	0.02	0.02	0.02	0.02	0.04	0.02	0.04
X	rs6643653	152899212	0.02	0.04	0.02	0.01	0.02	0.02	0.02	0.02	0.02	0.02
X	rs6571303	152901148	0.02	0.06	0.02	0.01	0.02	0.01	0.03	0.04	0.02	0.04
X	rs13397	152901442	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.03
X	rs11795678	152918922	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03
X	rs633	152927422	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03
X	rs3027898	152929084	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
X	rs3027933	152952068	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.02
X	rs17435	152965174	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03
X	rs1734787	152978640	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.03
X	rs1734791	152984114	0.02	0.07	0.02	0.02	0.02	0.02	0.02	0.04	0.02	0.04
X	rs2239464	153001625	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
X	rs766419	153207855	0.03	0.03	0.03	0.01	0.04	0.01	0.06	0.03	0.07	0.03

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PUBLICATIONS

1. Tara Matise, **Fang Chen**, et al. A Second-Generation Combined Linkage-Physical Map of the Human Genome. Genome Res. 2007 Dec;17(12):1783-6.

2. **Fang Chen**, Yiguang Wang. The protease produced by Streptomyces strain. World Notes on Antibiotics (in Chinese). 2002(2) 23.