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GENETICS OF SCHIZOPHRENIA: CANDIDATE GENES AND POSITIONAL  
CLONING ANALYSIS

by

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Linda M. Brzustowicz, MD

and approved by

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ABSTRACT OF THE DISSERTATION

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Schizophrenia (SZ) is a multifactorial phenotype. Candidate gene approach and positional cloning are the primary methods for elucidating its etiology.

We genotyped two TNF gene SNPs (-G308A, -G238A) and analyzed the haplotype structure in 24 Canadian families. Our results demonstrate that there is evidence for association ( $P=0.026$ ) of a specific haplotype with SZ with a Trimhap test. Stratifying the 22 families with genome scan data by TNF promoter haplotypes followed by reanalysis of linkage to SZ, we identified few loci that exhibit a considerable increase in LOD/HLOD scores. A locus on chromosome 1q44 demonstrated a significant increase in LOD from 0.15 to 3.01.

The synapsin 2 (Syn2) gene is implicated in synaptogenesis, neurotransmitter release, and the localization of nitric oxide synthase. 37 pedigrees of Northern European ancestry from the NIMH HGI collection were used in this study. Four microsatellites and twenty SNPs were genotyped. Linkage (FASTLINK) and association (TRANSMIT,

PDTPHASE) were evaluated. A maximum HLOD of 1.93 was observed at D3S3434. Significant results were obtained for association with SZ using TRANSMIT ( $p=0.0000005$ ) and PDTPHASE ( $p=0.014$ ) using single marker analyses. Haplotype analysis provided a single haplotype that is significantly associated with SZ using TRANSMIT ( $p<0.00000001$ ) and PDTPHASE ( $p=0.02$ ).

The results of a linkage scan for SZ in the NIMH HGI Chinese family collection were reported by Faraone et al. with the largest NPL z score of 2.88 for D10S2327. We have reanalyzed the genome using the posterior probability of linkage (PPL). We split the sample into two subsets: those without any family members with affective diagnoses (SZ subgroup); and those with SZ, schizoaffective disorder, and bipolar disorder (HET subgroup). Genotypes were cleaned using PEDCHECK and SIMWALK. Sample specific genetic maps were constructed. SZ and HET groups were analyzed by four-point PPL analysis, and the results from each group were combined via pooling and sequential updating. The results confirmed the linkage peak on 10q22 with a PPL of 32.1% after updating. In addition we observed a peak of 30.5% over D3S1311 on 3q29 coming primarily from the HET group. Our results confirmed previous and yielded novel linkage findings in this family sample.

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## DEDICATION

To my parents, my sister, Vladimir Pershin, and Efstathios Papachristos

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## **List of Abbreviations**

BPD	Bipolar disorder
cM	Centimorgan
DALY	Disability Adjusted Life Years
DSM-III-R	Diagnostic and statistical manual of mental disorders, third edition, revised
DSM-IV	Diagnostic and statistical manual of mental disorders, fourth edition
FBTA	Family-based test of association
HLOD	Heterogeneity logarithm of the odds
LD	Linkage disequilibrium
LOD	Logarithm of the odds
MHC	Major histocompatibility complex
NIMH	National Institute of Mental Health
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NPL	Nonparametric linkage analysis
OMIM	Online Mendelian Inheritance in Men database
PCR	Polymerase chain reaction
PPL	Posterior probability of linkage
SAD	Schizoaffective disorder
SADB	Schizoaffective disorder, bipolar type
SADD	Schizoaffective disorder, depressive type
SNP	Single nucleotide polymorphism

Syn2	Synapsin 2
SZ	Schizophrenia
TDT	Transmission disequilibrium test
TNF	Tumor necrosis factor

## **Chapter 1. General introduction**

Schizophrenia (SZ) is a group of complex heritable debilitating disorders characterized by psychotic features expressed as hallucinations, delusions, and thought disorder, as well as by flattened affect, impaired social functioning, avolition and anhedonia. The original name for this illness, “dementia praecox,” was proposed by a German psychiatrist Emil Kraepelin in the late nineteenth and early twentieth century, whose description of the illness remains a guiding force for modern investigators. Back in the nineteenth century, theories of autointoxication and focal infections dominated medicine in general and psychiatry in particular. Emil Kraepelin speculated that dementia praecox was caused by a poisoning of the brain from toxins produced in the sex glands, the intestines, the mouth and other parts of the body. Treatments for dementia praecox that followed logically from this etiological theory included colonic irrigations and major abdominal surgeries such as appendicostomies, colectomies and the removal of presumably infected ovaries, testes and other organs associated with reproduction. Autointoxication and focal infection theories disappeared from psychiatry by the mid-1930s (Noll 2004).

Currently, the groups of illnesses defined as SZ (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, DSM-IV, entries 295.1-295.3, 295.90) (DSM-IV 2000) is considered to be a common disorder with a lifetime prevalence of about 1%. The specified diagnostic criteria for SZ in DSM-IV are offered as guidelines for making diagnoses, because it has been demonstrated that the use of such criteria enhances agreement among clinicians and investigators. The proper use of these criteria requires

specialized clinical training that provides both a body of knowledge and clinical skills.

Table 1 below summarizes the current diagnostic criteria for SZ according to DSM-IV.

Table 1. Major DSM-IV Diagnostic Criteria for Schizophrenia.

<p><b>A. Characteristic symptoms:</b> Two (or more) of the following: (1) delusions (2) hallucinations (3) disorganized speech (4) grossly disorganized or catatonic behavior (5) negative symptoms, i.e., affective flattening, alogia, or avolition</p> <p><b>B. Social/occupational dysfunction:</b> For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset.</p> <p><b>C. Duration:</b> Continuous signs of the disturbance persist for at least 6 months.</p> <p><b>D. Schizoaffective, Mood Disorder, Substance/general medical conditions are excluded.</b></p>
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Overall sex ratio of SZ is approximately equal, though males tend to manifest the onset of illness earlier than females. Average age of onset in males is around early twenties and for females is around late twenties. Overall, incidence peaks at ages 20-40 years, though the disease may manifest in childhood or be delayed until the sixties. Among other sex differences in SZ are more frequent occurrence of brain abnormalities in men, and better premorbid functioning and higher frequency of a remitting course in women (Jablensky 2000).

Before an actual onset of the disease, a prodrome period is recognized in the majority of cases. Prodrome symptoms include introversion and peculiar interests. Relatives describe the prodrome as a “change in the patient’s personality”. Prior interests and habits tend to be abandoned and replaced by irritation, seclusion, and sometimes superstition. SZ symptoms manifest acutely or insidiously. Clinically, SZ is characterized by delusions, or persistent false beliefs, that are defined as contradictory to the evidence of reality and are not shared in the particular subculture. Hallucinations most frequently appear as false auditory perceptions without an appropriate sensory stimulus. Disorganized speech and behavior are classic symptoms of SZ. In certain cases, grossly disorganized behavior manifests as catatonia, a syndrome characterized by stupor with rigidity or “waxy flexibility” of musculature. Probably the most devastating and the least pharmacologically controllable features of the disease are described as negative symptoms. Those include flattening of affect or decrease in emotional expressivity, alogia or poverty of speech, and avolition or lack of purposeful action. Work performance, social function, and self-care tend to decrease dramatically and contribute enormously to the severity of the illness. Though violence is one of the features of the disease that receives exaggerated attention, studies demonstrate that the proportion of violent acts in the United States committed by people with SZ is minimal, and is much less than that due to alcohol and physical abuse (Nestor 2002).

The rates of suicide attempts and successes in people with schizophrenia are high. The risk of suicide is greatest early in the course of schizophrenic illness but remains high throughout life. Several risk factors for suicide have been identified. Among them are

psychosis, depression and substance abuse. Antisuicidal interventions such as treating positive symptoms and depression, reducing substance abuse, avoiding akathisia (uncontrollable motor restlessness), addressing demoralization and instilling hope are important approaches in therapy. The newer generation of antipsychotics (clozapine) and cognitive behavioral therapy seem to be useful in reducing suicide rates (Tandon 2005) and currently are the mainstream of the therapy in modern psychiatry. Recent research demonstrated that the lack of societal acceptance and stigmatization of SZ subjects is extremely common. Labeling as “schizophrenic” increased the likelihood that someone suffering from the disease would be considered as being unpredictable and dangerous. This, in turn, led to an increased preference for social distance (Angermeyer and Matschinger 2005).

The societal burden of SZ is enormous. In general, according to the report of the National Institute of Mental Health (NIMH), the mental illnesses, including SZ, account for over 15% of the burden of disease in established market economies. This is more than the disease burden attributed to all cancers. According to the Disability Adjusted Life Years (DALY) index that measures lost years of healthy life due to premature death or disability, active SZ psychosis is equivalent to the disability produced by quadriplegia. Particularly for females, SZ is among the top ten causes of DALY. Among all psychiatric disorders, SZ was the second illness after unipolar major depression with an impressive 2.3 million of healthy years lost in the developed world in 1990 (Murray and Lopez 1996).



While DSM-IV and other classification manuals provide strict criteria for diagnosis of SZ, diagnosis per se is of little use for genetic research. The term diagnosis refers to the description of the observed illness in an individual based on the presented clinical signs and symptoms. Diagnosis is used to determine the most appropriate treatment and further prophylactics of complications, provides guidance for prognosis, and is often affected by external factors like insurance policies, disease prevalence in a particular population, the duration of the presented symptoms, and personal skills of the physicians. Instead, for genetic research a “phenotypic description” of the illness is a more suitable entity. A phenotype is defined as the observable characteristics of an organism that result from the interaction of its genotype and environment. For mental disorders like SZ, without clearly defined morphological or biochemical features, a phenotype is defined prior to the diagnostic interview as a generalized (to a certain degree) description of the particular condition. An investigation of a patient by several experienced psychiatrists is required to minimize the chance of diagnostic error that would lead to a phenocopy (a condition that develops under unusual environmental conditions and resembles another condition that is usually developed due to a particular genotype; for example, lysergic acid intoxication is characterized by psychosis and may appear as SZ to an inexperienced clinician) which may drastically diminish the power of genetic studies. Afterwards, a consensus is reached on whether the particular subject does or does not have the defined phenotype. Therefore, a phenotype is a description of a patient’s condition which does not reflect its severity (categorical; quantitative phenotypes may reflect the severity), cannot be used for identifying treatment strategies or prognosis, is not affected by particular insurance policies or other external factors, and has a minimal chance of an error. In the light of

current research of SZ genetics, a group of “SZ spectrum disorders” was established to facilitate the determination of the exact phenotype. Spectrum disorders are defined as a group of diseases with similar clinical presentations and an increased rate of occurrences among biological relatives of subjects with SZ implying the sharing of etiological factors. Schizoaffective disorder (SAD) is the second (after SZ) nosological entity in the narrow phenotype definition of SZ used for the studies presented in this dissertation (nosology is a branch of medical science that deals with classification of diseases). Both illnesses are characterized by chronic psychosis (hallucinations, delusions), with SAD having a full and sustained affective episode (depressive, manic, or mixed). During the affective episode of SAD an exacerbation of the pre-existing psychotic symptoms is usually observed. Early family, twin, and adoption studies supported a separate classification of broadly defined schizoaffective psychoses as possibly being phenotypical variations or expressions of genetic interforms between SZ and affective psychoses (Bertelsen and Gottesman 1995).

Recently, the classic Kraepelinian dichotomy that separates SZ and bipolar disorder (BPD) has been questioned on the basis of current scientific understanding of these illnesses, and a concept of continuum between SZ and BPD has been proposed (Crow 2008). Currently, DSM-IV places BPD under the Mood Disorders section, defining BPD as a clinical course that is characterized by the occurrence of one or more manic or mixed episodes. Major depressive episodes are common as well. Psychotic symptoms often develop on the background of manic or mixed episodes, and once they occur, tend to reappear during the consequent exacerbations (DSM-IV, 2000). Studies suggest that as

much as 50% of individuals with BPD experience psychosis during their lifetime, while a significant proportion of SZ patients may experience mood symptoms (Coryell et al. 2001; Keck et al. 2003; Lin and Mitchell 2008). Outcomes of the modern pharmaceutical management of patients with SZ and BPD provide further evidence of the continuum. Recently, psychiatrists started to utilize the atypical antipsychotics, which block dopamine and serotonin receptors, in the treatment of BPD and the positive outcomes of such management suggest common pathogenetic pathways in both diseases (Bowden 2005). However, the outcomes of genetic studies provide the most compelling support for shared etiology of SZ and BPD. Family studies repeatedly demonstrated that the risk of developing SZ, SAD, and schizotypal personality disorder is considerably increased in relatives of SZ probands. On the other hand, the risk of BPD, SAD, and unipolar depression is significantly elevated for the relatives of the BPD probands (Owen et al. 2007). However, the majority of family studies, of which twin studies are the main tool to investigate the shared genetic and non-genetic risk factors, focus on phenotypic definitions based on a single main lifetime diagnosis. For example, if an individual manifests a clear manic episode during the premier of the illness, but consequently the clinical picture becomes typical of SZ, the lifetime diagnosis is assigned as SZ, and the manic episode in the debut presentation is disregarded as non-specific (Cardno et al. 2002). However, relaxing the diagnostic hierarchy to syndromal definitions of mania and psychosis (or schizophrenic syndrome) demonstrates a significant comorbidity within probands. Twin pair correlations are significantly higher in monozygotic than in dizygotic twins, revealing a genetic contribution to the comorbidity (Cardno et al. 2002). Linkage and candidate genes studies further demonstrate an intimate relationship between

the disorders, as multiple chromosomal regions and genes appear to contribute to both, SZ and BPD (Owen et al. 2007).

The results of twin studies also clearly demonstrate a shared familial liability of SAD with SZ and BPD, when either hierarchical or non-hierarchical phenotypic definitions are applied (Nurnberger et al. 1988; Maier et al. 1993; Cardno et al. 2002). The reliability of SAD diagnosis is probably one of the lowest among psychiatric nosologies: the disagreement in diagnosis can be seen among different psychiatrists evaluating the same individual, as well as diagnosticians actively changing the established SAD diagnosis to either SZ or BPD over the clinical time course (Lake and Hurwitz 2007). SAD is also widely used in genetic studies as part of the SZ or BPD phenotypes, further highlighting the uncertainty of its hierarchical place in the modern understanding of mental pathology. The concept of SAD promoted a merge between SZ and BPD, possibly predicting the end of the traditional Kraepelinian dichotomy and uniting all of the functional psychotic states into a single nosological unit (Lake and Hurwitz 2007).

For the broader phenotype definition in genetic studies, a few personality disorders that tend to accumulate in SZ families have been used. Personality refers to a distinctive set of traits, behavior styles, and patterns that make up a person's character or individuality. How we perceive the world, our attitudes, thoughts, and feelings are all part of our personality. A healthy personality usually refers to set of described characteristics that allow an individual to cope with normal stresses and have no trouble forming relationships with family, friends, and co-workers. A personality disorder is defined as

pervasive, persistent maladaptive patterns of behavior that are deeply ingrained, not attributed to Axis I (defined psychiatric syndromes), Axis III (physical disorders or conditions), or cultural role difficulties. Maladaptive traits are behavioral, emotional, cognitive, perceptual, or psychodynamic (Kaplan and Sadock 1990). In this dissertation, Cluster A personality disorder (“odd / eccentric”: paranoid, schizotypal, and schizoid personalities) were used most frequently as components of the broad SZ phenotype. Paranoid personality disorder is characterized by a distrust of others and a constant suspicion that people around the subject have sinister motives. People with this disorder tend to have excessive trust in their own knowledge and abilities, and usually avoid close relationships. They search for hidden meanings in everything and suspect hostile intentions in actions of others. They are quick to challenge the loyalties of friends and loved ones and often appear cold and distant. Paranoid personality disorder is a chronic, lifelong condition, more common in men than in women, occurs in 0.9% of the population, and manifests in early adolescence. It is over-represented in the first-degree relatives of SZ subjects (1.7%) and it is suspected that the personality disorder exists as a “forme fruste” (an incomplete, unusual, or abortive form of a disease) of paranoid SZ (Maier et al. 1994; Moore and Jefferson 2004). Schizotypal personality is primarily characterized by peculiarities of thinking, odd beliefs, and eccentricities of appearance, behavior, interpersonal style, and thought. Persons with this disorder may have peculiar ideas, like believe in psychic phenomena or have magical thinking. Persons with schizotypal personality disorder are distant and aloof, and others often view them as odd or eccentric. Schizotypal personality disorder is present in up to 0.3% of the general population and up to 2.1% of nonpsychotic relatives of SZ probands. It appears to be

more common in males than females (Maier et al. 1994; Moore and Jefferson 2004). Schizotypal traits may become evident in early adolescence or, at times, in childhood. Items that describe the “negative” symptomatology of this disorder are the main source of familial aggregation (Maier et al. 1994). People with schizoid personality disorder avoid relationships and do not show much emotion. Schizoid personality disorder patients genuinely prefer to be alone and do not secretly wish for popularity. They tend to seek jobs that require little social contact. Their social skills are often weak and they do not show a need for attention or acceptance. They are perceived by others as humorless and distant and often are termed "loners." Though likely to be under-reported, this is probably an uncommon disorder, and may be slightly more common in males. Schizoid traits are chronic and typically appear in adolescence or late childhood (Moore and Jefferson 2004). In a survey of SZ premorbid conditions, 85% of SZ subjects were diagnosed with a personality disorder before the onset of illness. In 27.5% of those patients schizoid personality disorder was recognized as a premorbid state (Rodriguez Solano and Gonzalez De Chavez 2000). Delusional disorder is considered to be a part of broader phenotypic definition of SZ and is characterized by the presence of a non-bizarre delusion without other features of SZ. Erotomantic, grandiose, jealous, persecutory, and somatic delusions are seen most frequently in this disorder manifestation (DSM-IV, 2000).

Family history and environmental factors like place and season of birth are well established risk factors for SZ. According to Mortensen et al. (1999) a relative risk for SZ for a person whose mother, father or sibling has the illness is about 9.31, 7.2, and 6.99

respectively as compared with persons without a family history. The authors showed that the risk of SZ was associated with the degree of urbanization of the place of birth (relative risk for the capital vs. rural areas, 2.40). In addition, the risk was significantly associated with the season of birth: it was highest for births in February and March and lowest for births in August and September. The population attributable risk was 5.5% for a history of SZ in a parent or sibling, 34.6% for urban place of birth, and 10.5% for the season of birth (Mortensen et al. 1999).

The risk of developing SZ is significantly higher among biological relatives of SZ subjects than in the general population. Data pooled in 1967 showed that the risk for children of one SZ parent was nearly 15 times higher than in the general population; for siblings and parents about 10 times higher; and for uncles and aunts, nephews and nieces, grandchildren, and half-siblings, roughly three times higher than the population rate (Zerbin-Rudin 1967). Twin, family and adoption studies are the principal methods that have been used to elucidate the genetic contribution to SZ (McGuffin et al. 1994). Concordance rates for SZ were found to be higher in monozygotic (MZ) twin pairs, which have the same genetic constitution, than in dizygotic twin (DZ) pairs, which have the same genetic relationship as that of ordinary siblings. There were at least 11 twin studies published before 1972 that demonstrated a concordance rate in MZ twins ranging from 35% to 69%, whereas DZ twins exhibited only 0-26% concordance (Hamilton 1976). Overall, the mean concordance rate was about four times higher in MZ (55.5%) than in DZ (13%) twin pairs. It is known that environmental factors shared within a family may contribute to the “genetization” of certain phenotypes (infection

predisposition, eating patterns, etc.). Adoption studies were employed to further investigate the genetic contribution to SZ. As reviewed in Ban et al., significantly more adopted children of SZ subjects in families without history of psychotic illness develop SZ and SZ spectrum disorders. Prevalence of SZ is also much higher in biological relatives of adopted SZ subjects than among the foster relatives (Ban 2004). In addition, a significantly higher prevalence of SZ spectrum disorder was found among children of SZ-affected parents raised by normal adoptive parents, than among children of normal parents raised by SZ-affected adoptive parents (Ban 2004).

Despite of strong evidence of genetic contribution to SZ, the mode of inheritance remains unknown. SZ appears to be a disorder with a complex inheritance caused by interaction of multiple genes with various deleterious dosage. The number of susceptibility loci, the recurrence risk ratio conferred by each locus, and the degree of inter-locus interactions all remain unknown. Considering the high concordance rate of SZ in MZ twins, and the very much lower relative risks for SZ in more distant relatives, an oligogenic hypothesis of SZ inheritance has been proposed (Gershon and Badner 2001) with 10 or less interacting genes at multiple locations contributing to the phenotype development.

Several strategies are being used to identify genes for SZ with positional cloning and candidate gene analysis being the two major approaches. Positional cloning is a technique used to identify genes that are usually associated with diseases, based on their location in the genome. The overall strategy of positional cloning is to map the location of a human disease or trait gene by linkage analysis and to then use the mapped location on the



chromosome to clone the gene of interest. Positional cloning is a relatively new approach to finding genes suitable for complex phenotypes. Traditionally, researchers began with a known gene product and used the protein's amino acid sequence to isolate the gene.

Linkage analysis proposed by Morgan (1911) refers to the ordering of the genetic markers on a chromosome with estimation of genetic distances between them (Ott 1999).

Two essential requirements for mapping disease genes are: 1) sufficient numbers of families to establish linkage; and 2) adequately informative DNA markers. The second requirement can be met relatively easily now, because the Human Genome Project has identified thousands of useful DNA markers throughout the human genome. Finding suitable extended families, however, can be a challenge for researchers, particularly for rare disorders or for disorders in which the affected person has a decreased fecundity or dies at a young age. Extended families are more suitable for linkage analysis since fewer families are required to reach the power to detect linkage at statistically significant level. In addition, affected members of the same pedigree are more likely to have the same genetic defect that causes the phenotype and therefore it decreases the effect of genetic heterogeneity. The alternative approach taken by researchers is to collect a large number of somewhat smaller families. This is easier to do for relatively common diseases, such as cystic fibrosis, but this approach carries the risk that not all families may have the genetically identical disorder, especially when complex phenotypes are being studied.

A particular DNA marker is said to be "linked" to the phenotype if family members with certain alleles at the marker always have the phenotype and family members with other alleles at the marker do not have the phenotype. The smaller the genetic distance between

the disease gene and the marker, the smaller the likelihood of recombination events. Additional features of complex genetic disorders like SZ, diabetes, asthma, bipolar disorder make linkage analysis more challenging than diseases with classic Mendelian inheritance. Among them is incomplete, age- and sex-dependent penetrance, uncertain mode of inheritance, involvement of multiple genetic and non-genetic factors.

Classically, dominant and recessive models are tested in parametric linkage analysis, or model-free analysis may be employed. Results of linkage analysis are reported as LOD scores – logarithm (base 10) of odds. LOD score measures the plausibility of the observed data on a log scale. In calculating the LOD score a number of recombination fractions ( $\theta$ ) between the marker and phenotype loci are tested and the likelihood is calculated for each of them. Largest observed LOD score specifies a  $\theta$  value, which is considered to be the best estimate of  $\theta$  between the two loci. If there is linkage, the maximum LOD score increases with an increase in informativeness of the marker locus and number of families. A LOD score of 3 generally implies that linkage is observed between the two loci at a statistically significant level. LOD score of 2 is considered to be suggestive. LOD scores at a specific value of  $\theta$  from multiple studies can be added if the same genetic model and phenotype definition are used (Lander and Kruglyak 1995; Ott 1999). In the 4<sup>th</sup> chapter of this dissertation, we will demonstrate a novel Bayesian-based approach to linkage analysis called a posterior probability of linkage (PPL), which appears to be superior to traditional linkage analysis in detecting and evaluating of linkage data.

SZ is a genetically heterogeneous phenotype. A phenotype is considered heterogeneous when different individuals express the same phenotype derived from different genetic etiologies. Familial breast cancer is another example of genetic heterogeneity in humans. Mutations in several different genes manifest as familial breast cancer at a younger age with frequent bilateral involvement and frequent occurrence in men. Two unlinked genes, BRCA1 and BRCA2 were identified as major risk factors for breast cancer. In addition, several genetic cancer syndromes are described in which breast cancer is one of the presentations, including Li-Fraumeni syndrome due to the germline mutations in p53, Cowden syndrome due to mutations in the PTEN gene, and Peutz-Jegher syndrome due to mutations in the STK11 gene. There also appears to be an increased risk of breast and ovarian cancer in ataxia-telangiectasia, and there is some evidence that heterozygotes for the ATM gene have an increased risk of breast cancer (see OMIM 114480). In terms of linkage analysis, two types of heterogeneity are distinguished. Allelic heterogeneity refers to the presence of multiple mutations in the same gene that manifest as identical phenotype or pattern of traits. Nonallelic or locus heterogeneity refers to the presence of multiple loci in the human genome that manifest phenotypically similarly. Since the presence of heterogeneity in a sample of families can considerably decrease the ability to find linkage, a number of approaches exist to address this issue. Separation of families into groups based on a reliable independent criterion may be utilized. An example of this criterion would be a distinct phenotypic presentations, family ethnicity, population or phenotype-associated genetic marker. Another method involves the calculation of the LOD score in a whole sample with a model allowing for admixture. The most commonly used linkage method allowing for heterogeneity is HOMOG, which denotes a linked

proportion of a sample as  $\alpha$  (Ott 1986). The results of the statistics are reported as the heterogeneity LOD (HLOD) score,  $\alpha$ , and  $\theta$ . The statistically significant and suggestive cut-off values for HLOD scores are higher than those for LOD scores (Lander and Kruglyak 1995). Frequently, simulation studies are used to estimate the significance of the results when multiple genetic models and phenotype definitions are used to evaluate the significance of the LOD and HLOD values.

Since SZ is a complex trait that appears to be highly heterogeneous with locus and allelic heterogeneity, linkage studies have revealed much about the disease but none of its essential etiological secrets. Multiple genome searches for SZ were performed in recent years, however, only a few of them reached the established statistical significance criteria (Lander and Kruglyak 1995). By 2005, three regions of human genome demonstrated significant linkage to SZ at least once followed by multiple replications with suggestive findings. A gene rich chromosome 6p is one of the likeliest sites for SZ susceptibility gene(s). In an Irish Study of High Density SZ Families Straub et al. have identified a heterogeneity LOD score (HLOD) of 2.13 ( $p=0.005$ ) and non-parametric LOD score (NPL) of 3.57 ( $p=0.0005$ ) in the area of 6p25-24, and HLOD of 2.42 ( $p=0.001$ ) and NPL of 3.07 ( $p=0.001$ ) on 6p23 (Straub et al. 1995; Straub et al. 2002). Moises et al. reported results from a multistage genome scan for SZ with suggestive linkage to chromosome 6p in large Icelandic pedigrees. Additional suggestive linkage results were also observed in families from Austria, Canada, Germany, Italy, Scotland, Sweden, Taiwan and the United States. In addition, a sample from China showed suggestive linkage and evidence of linkage disequilibrium to the area. The results of a meta-analysis from these three studies

reached statistically significant values (Moises et al. 1995). Maziade et al. obtained a HLOD of 3.47 at 6p22-p24 with 66% of SZ and BPD families linked, though the results proved to be only suggestive ( $p=0.08$ ) (Maziade et al. 2001). A genome scan of a 3,400-member pedigree with SZ with DNA samples from 210 individuals demonstrated that chromosome 6q25.2 is linked to the SZ phenotype ( $LOD=6.6$ ) with a 6 cM haplotype being shared among the majority of affected individuals over 12 generations (Lindholm et al. 2001). Chromosomes 1q21-22 and 13q32 are the other examples of the regions with multiple reports of significant and suggestive linkage in various populations as summarized in the meta-analysis study of (Lewis et al. 2003).

The term genetic association study refers to a type of genetic analysis when the allele or genotype frequencies at the DNA markers are determined in affected individuals and compared with those of controls. Two major types of the association studies exist. Population based studies compare the unrelated individuals with a disease with unrelated controls from the same population. This type of studies usually compares the allele or genotype frequencies in affecteds versus nonaffecteds at the candidate genes in a particular population. For general populations, ideal designs are those amenable to recruitment of large samples with sufficient power and to seamless modeling of both environmental and genetic factors, thereby capturing as many of the sources of variability as possible. Human populations, however, often exhibit substructure due to non-random mating, such as that based on proximity or culture. This substructure, or stratification, creates concern about the validity of association tests (Devlin et al. 2001). It is known that population association studies can often produce association between the unlinked

loci (Ewens and Spielman 1995). This can cause an increase in the false positive rate of the confounding effect since most human populations are stratified to some degree. It means that as sample size or the number of loci tested for association increases the false positive rate also tend to increase. Moreover, once the association of a marker and a disease are found, it is virtually impossible to locate the causative allele precisely on the chromosome, since information on the haplotype structure and recombination events in populations of various ethnicities is still limited. Other factors, like the complexity and genetic heterogeneity of the phenotype, population allele frequencies, and control for genotyping errors put the case-control association studies at a disadvantage in evaluating candidate genes for complex diseases (Devlin et al. 2001).

The second type of association study is the family-based test of association (FBTA). FBTA is usually based on the observation of transmission of alleles to the affected subjects (Newton-Cheh and Hirschhorn 2005). These methods are usually blind to the population substructure since related unaffected individuals are used as controls. Among other advantages of FBTA are better methods to detect genotyping errors, facilitation of the determination of recombination events and haplotype structure, and decrease in genetic heterogeneity since affected family members are likely to have the same genetic defect. Several methods of FBTA were developed in recent years. The statistical approaches vary among those methods. While the specific sections of this dissertation describe the statistical methods used for the data analysis, a description of the classical FBTA is provided here. The transmission disequilibrium test (TDT) tests if the transmission of the alleles from heterozygous parents to affected probands deviates from

the expected equilibrium of 50% (Spielman et al. 1993). There are few common disadvantages of the TDT. If parental genotypes are unknown, the obvious methods of inferring them may introduce a significant bias. Careful adjustment for the effects of linkage in the area must be taken if multiple affecteds from a single family are used. Fortunately, extensions of the TDT were developed that avoid these difficulties (Martin et al. 2000).

Association studies have become increasingly popular in recent years as a means to identify complex diseases genes. However, the lack of reproducibility of the results remains a major obstacle in the way of the researchers in the field of SZ and other multifactorial complex genetic diseases. Hirschhorn et al. (2002) reviewed the studies performed on 268 genes that contain polymorphisms reported to be associated with one of 133 common diseases or dichotomous traits. Overall, these 268 genes accounted for 603 different gene-disease associations. Many of those genes have been associated with several different diseases; for example, polymorphisms in the tumor necrosis factor gene (TNF) have been associated with 20 different diseases or traits, and variants in ACE (encoding angiotensin converting enzyme), VDR (encoding the vitamin D receptor), and MTHFR (encoding methylene tetrahydrofolate reductase) have each been associated with over a dozen of different diseases or traits. Out of 166 initial studies that reached statistical significance, only six associations were reproduced at a level of consistency of 75%. The most reproducible was the association of the ApoE4 gene and Alzheimer's disease, for which dozens of reports reach statistical significance (Hirschhorn et al. 2002). The traditional 5% significance level usually used in the field of human genetics

does not fully explain the lack of reproducibility of the majority of association studies. Underpowered studies also contribute to the low reproducibility level (false-negative results). Genetic heterogeneity predicts that the true positive results in one population are not to be expected in other populations since the genetic etiology may be influenced by different genes in various populations. In addition, using identical study design, even in the presence of a true association of a DNA marker in two different populations, the difference in allelic frequencies may produce significant results in one but not the other sample (Hirschhorn et al. 2002). Due to the complexity of the FBTA, unknown performance of particular methods in pedigrees of various structures, and the need to correct for multiple testing (for example, multiple phenotypes defined in a single sample), simulations are frequently used to identify the true statistical significance of the results.

Results of linkage and family based association studies for TNF (Saviouk et al. 2004) and Synapsin 2 (Syn2) genes (Saviouk et al. 2007) and SZ are presented in this dissertation.



## **Chapter 2. Tumor necrosis factor promoter haplotype associated with schizophrenia reveals a linked locus on 1q44**

### **2.1 Introduction**

One of the problems with linkage analysis studies of SZ is that they rarely satisfy strict criteria for statistical significance (Lander and Kruglyak 1995). Markers from only two regions in the human genome have produced highly significant evidence for linkage when multiple pedigrees were used for the analysis: D1S1679 on chromosome 1q21-q22 and D13S779 and D13S174 on chromosome 13 (Blouin et al. 1998; Brzustowicz et al. 2000). The difficulties in identifying susceptibility loci for SZ may be explained by the intrinsic complex etiology of the disease. The phenotypes associated with SZ may be caused by the simultaneous presence of multiple interacting genes with various morbid dose-effects in a population. Environmental and other heritable and non-heritable influences may also contribute to the etiology of SZ (Bassett et al. 2001) and may be different for each subject, making genetic research more difficult due to incomplete penetrance in subjects with favorable environmental, epigenetic and genetic backgrounds. The presence of undetected genetic heterogeneity can greatly reduce the power to obtain a significant LOD score in a data set of multiple families if a true negative result at one locus in one family overrides a true positive result at the same locus in another family.

One approach to reduce the impact of heterogeneity is to make the data set more genetically homogenous. Traditionally, this has been attempted by limiting sample collection to subjects of a single ancestry, environment, or diagnostic subclass. Another

approach is to divide an existing sample into hopefully more genetically homogeneous subsets based on an independent, reasonable criterion.

A good candidate for such a criterion might be the Major Histocompatibility Complex (MHC) or a polymorphic marker that resides within the complex. It is well known that genes in HLA I, II, and III are involved into the pathogenesis variety of diseases where an infectious or autoimmune component is involved. There are lots of established associations of HLA polymorphisms with the common diseases like diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, obesity, sepsis, septic shock, acute graft rejection. The MHC is known for high degree of linkage disequilibrium and is located on 6p chromosome. HLA complexes in SZ were studied extensively for a long time and associations of HLA I A9, A28, A10 and HLA II Dr1/DRB1\*01, DQB1\*0602, DRB1\*04 and DRw6 with the disease were reported more than once in various population groups with the use of immunological as well as genotyping techniques (Wright et al. 2001). Linkage studies also suggest there may be one or more loci on chromosome 6p that affect susceptibility to SZ (Moises et al. 1995; Schwab et al. 1995; Straub et al. 1995; Maziade et al. 1997; Riley and Williamson 1997). In addition, there is some evidence that genetic loci on chromosome 6p may influence the manifestation of the endophenotype of eye-tracking dysfunction (Arolt et al. 1996) and modify the severity of positive symptoms in affected subjects (Brzustowicz et al. 1997). An example of the utility of stratifying linkage data set on the basis of HLA genotypes (DR3 and DR4) was demonstrated in the successful identification of a causative locus for Type I diabetes mellitus on chromosome 11q (Hashimoto et al. 1994), a finding that was

confirmed by other linkage (Davies et al. 1994; Luo et al. 1996) and linkage disequilibrium studies (Nakagawa et al. 1998; Eckenrode et al. 2000).

The tumor necrosis factor alpha (TNF) gene (OMIM 191160) is located on chromosome 6p21.3, and polymorphisms within this gene have been shown to be in linkage disequilibrium with other genes in HLA I, II, and III (Hajeer and Hutchinson 2001; Selvaraj et al. 2001). Recently, at least two studies have provided positive results for association of the TNF promoter -G308A polymorphism with SZ in Caucasian populations (Boin et al. 2001; Schwab et al. 2003). It is well known that TNF plays an important role in initiation and regulation of inflammatory process. The changes of its expression may trigger the anomalous response to infection which can lead to a certain degree of brain damage at critical stages during the development and result in an onset of SZ later in life. Immunopathological findings are common in SZ, with individuals sometimes showing signs of infectious factors and non-specific inflammatory reactions that would be consistent with a possible role of TNF dysfunction in the disease etiology (Rothermundt et al. 2001).

Several polymorphisms have been identified in the TNF gene, a number of which reside within the promoter region of the gene. We have analyzed the haplotype structure of two TNF single nucleotide polymorphisms (-G308A, -G238A) in 24 Canadian families of primarily Celtic origin. Our results demonstrate that after correction for multiple testing based on simulations of 10,000 replicates of unlinked/unassociated data there is evidence for association ( $p=0.026$ ) of a specific haplotype (-308A, -238G) with SZ and SZ

spectrum disorders. Furthermore, our results show that upon stratification of these families by TNF promoter haplotypes, several loci throughout the genome exhibit considerable increases in LOD/HLOD scores. Among these is a locus on chromosome 1q44 (D1S1609), which demonstrates a significant increase ( $p=0.025$ ) in LOD score from 0.15 to 3.01 with a broad definition of the SZ phenotype and a dominant mode of inheritance. This result replicates a previously reported positive result of linkage of SZ spectrum disorders to this area of the genome (Ekelund et al. 2001).

## **2.2 Material and Methods**

### **2.2.1 Subjects**

The family sample used for this study is an extension (Brzustowicz et al. 2004) of a set of Canadian families that was used for a genome scan for SZ susceptibility loci (Brzustowicz et al. 2000). Briefly, this is a sample of 24 families of Celtic ( $n=23$ ) and German ( $n=1$ ) origin, with 330 subjects with comprehensive phenotypic assessments and 332 subjects with DNA samples available for study. Written informed consent was obtained from all subjects after an explanation of possible consequences. Protocols were approved by the institutional review boards of Rutgers University, University of Toronto, and by the Centre for Addiction and Mental Health. Direct interviews were conducted using the Structured Clinical Interview for DSM-III-R (SCID-I) for major disorders and SCID-II for personality disorders. The interviews, collateral information, and medical records were used to make consensus diagnoses for 319 subjects based on DSM-III-R criteria. For 11 additional subjects – 2 alive, but unavailable for full phenotypic

assessment, and 9 deceased – only medical records and collateral information were reviewed, through the consensus diagnosis procedure. Details of the diagnostic and ascertainment procedures have been described in literature (Bassett et al. 1993; Bassett and Honer 1994). 85 subjects were considered affected under a narrow diagnostic classification (SZ and SAD) and 125 subjects under a broad diagnostic classification that also includes non-affective psychotic disorders, schizotypal personality disorder, and paranoid personality disorder. Twenty-two of these families were used for the original genome scan (Blouin et al. 1998; Brzustowicz et al. 2000). In addition to two new families (17 participating subjects), additional members of the previously studied families (n=25) were also included. Another 65 subjects without DNA samples or phenotype data were included for statistical analysis as pedigree founders and connecting individuals.

### **2.2.2 Genotyping**

To assure the quality of the genotype data, two methods of DNA analysis were used. The first genotyping method used PCR amplification and restriction fragment length polymorphism detection by NcoI for the –G308A polymorphism and AvaII for the –G238A polymorphism. Primers and PCR conditions for –G308A were taken from a previously published study (Boin et al. 2001), with SNP detection by overnight incubation with NcoI (New England BioLabs Inc.). The primers for identification of –G238A were designed using Primer3 (Whitehead Institute) using 6p chromosome sequence available from build 34 of the human genome assembly (UCSC). A 127-bp fragment of the TNF promoter was amplified by PCR using primers 5'-AAAAGAAATGGAGGCAATAGGT-3' and 5'-CACTCCCCATCCTCCCTGGTC-3'.

This second primer contained a single base mismatch with the genomic sequence, which introduced an *Ava*II site into the PCR product when the –238G allele was present. PCR reactions contained 40 ng of template DNA, 0.5 U AmpliTaq Gold polymerase (Applied Biosystems), 0.01  $\mu$ M of each primer, 0.1 mM dNTP, 1.0 mM  $MgCl_2$ , and 1  $\mu$ l of GeneAmp 10x buffer II (Applied Biosystems), in a 10  $\mu$ l volume. After 3 min at 95°C, 30 cycles were done at 94°C for 15 s, at 62°C for 15 s, at 72°C for 15 s, followed by a final extension step at 72°C for 3 min. The SNP was detected using overnight incubation with *Ava*II (New England BioLabs Inc.). Both alleles of –G238A had one permanent site for *Ava*II, which served as an internal control for the enzymatic reaction. The digest products were resolved by Higher Resolution Microplate Array Diagonal Gel Electrophoresis (Day and Humphries 1994), using a 7.5% polyacrylamide gel run at 120 V for 45 minutes.

The second genotyping method was Pyrosequencing<sup>TM</sup>, performed as simplex assays on the automated PSQ HS96A platform (Ronaghi et al. 1998; Ahmadian et al. 2000). PCR primers were designed using Primer3 (Whitehead Institute) and the sequencing primer used for the Pyrosequencing assay was designed using the Pyrosequencing SNP Primer Design Software v1.0 (Pyrosequencing). For both polymorphisms the following PCR primers were used: 5'-CTGTCTGGAAGTTAGAAGGAAACAG-3' (left), 5'-GGACACACAAGCATCAAGGATAC-3' (right). PCR reactions contained 40 ng of template DNA, 0.5 U AmpliTaq Gold polymerase (Applied Biosystems), 0.01  $\mu$ M of each primer, 1.5 mM of  $MgCl_2$ , 1  $\mu$ l of GeneAmp 10x buffer II (Applied Biosystems), in a 10  $\mu$ l volume. After 3 min at 95°C, 30 cycles were done at 94°C for 30 s, at 54°C for 30 s, at 72°C for 15 s, and then a final extension step at 72°C for 3 min. For the –G238A polymorphism the right primer was biotin labeled and 5'-AGACCCCCCTCGGAAT-3'

was used as the sequencing primer. For the –G308A polymorphism the left primer was biotin labeled and 5'-CCTGGAGGCTGAACCCCGTC-3' was used as the sequencing primer. The initial concordance between the two genotyping methods was 97.6%. Discordant samples were re-genotyped by Pyrosequencing, with 100% concordance with the original Pyrosequencing read.

For evaluation of linkage in TNF stratified family subsets, the previously published genome scan data were used (Brzustowicz et al. 2000). Genotypes were available from 288 subjects from the original 22 pedigrees for the 381 markers from the Weber Version 6.0 Screening Set. These genotypes were generated both in our laboratory and in the laboratories of the Center for Inherited Disease Research (CIDR), as previously described (Brzustowicz et al. 2000).

### **2.2.3 Error-checking and statistical analysis**

Genotyping errors are known to affect family-based tests of association (Mitchell et al. 2003), and we therefore undertook several error-checking steps. Genotype data from TNF -G308A and -G238A were first checked for Mendelian inconsistencies using the program Pedcheck (O'Connell and Weeks 1998). Second, the genotyping error probabilities were estimated with five runs of Simwalk v2.82 (Sobel and Lange 1996; Sobel et al. 2001; Sobel et al. 2002), using different starting conditions. Sixteen samples with a probability of mistyping  $\geq 0.25$  were re-genotyped with Pyrosequencing. For 13 samples, repeat genotyping resolved the apparent errors. Data for three other genotypes were removed from further analysis due to ambiguity of the Pyrosequencing reads. Five Simwalk2 runs

were performed on the data after error checking, with a variety of initial analysis parameters, to identify the most likely haplotypes. Genotypes from both SNPs were used simultaneously for haplotype generation. The resulting haplotypes were compared across runs to identify and remove any haplotypes with markers that could not be definitively phased. Six haplotypes were removed because they could not be unambiguously phased. 723 fully phased haplotypes were defined in this sample, including 658 haplotypes for subjects with available genotyping data and 65 inferred definitive haplotypes for subjects without genotyping data. No recombination events were detected between TNF -G308A and -G238A in our sample. These haplotypes were arranged into an input format for the Trimhap program. The error-checking steps for the genome scan data used are as previously described (Brzustowicz et al. 2000).

The trimmed haplotype test for linkage disequilibrium was performed using Trimhap (MacLean et al. 2000). The test is based on the construction of the sequence of ancestral haplotypes, analysis of identity by descent in the pedigree, and calculation of haplotype-sharing score for each haplotype in the sample. Due to the complexity of the pedigree structures and therefore the haplotype distribution in the sample, the reported p-value is based on a specified number of random rapid permutation replications. The replicates are formed by shuffling all observed haplotypes among the existing pedigrees within the sample without changing the pattern of the inheritance to avoid the interference of the linkage signal with the linkage disequilibrium value. The genetic models for the analysis were the same as those used for the genome scan (Brzustowicz et al. 2000) and are summarized in Table 2. The following additional parameters were specified for the



analysis: 200 generations since the ancestral mutation event,  $10^{-5}$  mutation rate per marker per generation, 0.01 error rate per marker, 10,000 replicates for permutation analysis, proportion of the linked founder haplotypes is 1.0, and proportion of linked founder haplotypes descended from a given ancestor is 0.2.

Table 2. Genetic Models for Genome Scan

Model	Frequency of Disease Allele	Penetrance of Disease Homozygote	Penetrance of Heterozygote	Penetrance of Normal Homozygote
Narrow-Dominant	0.0045	0.75	0.50	0.001
Broad-Dominant	0.007	0.90	0.80	0.009
Narrow-Recessive	0.065	0.50	0.0015	0.0015
Broad-Recessive	0.10	0.60	0.01	0.01

For our original genome scan for linkage, branches of extended pedigrees that were connected through more than one individual without available DNA were removed from the main pedigrees and analyzed as separate pedigrees, to minimize inflations of the LOD score due to errors in pedigree structure, including undetected non-paternity (Brzustowicz et al. 2000). This resulted in three small branches (total of 23 individuals) being removed from three pedigrees. However, for association analysis, consideration of these small branches as independent families could inflate the evidence for association. To avoid these possible errors, we reanalyzed our data excluding these three small branches. This did not significantly change the results of the association analysis and therefore for the remainder of analysis these branches were included as separate families.

Several factors may affect the significance of these association analysis results, including multiple testing under narrow and broad phenotype definitions and dominant and recessive modes of inheritance and the complexity of these pedigree structures, including the presence of one pedigree with an inbreeding loop. We therefore evaluated the significance of results from the Trimhap analysis with a simulation study. 10,000 replicates with linkage disequilibrium (LD) between the marker loci preserved as in the original data but without linkage or LD to the affection status locus were generated. First, we calculated the conditional probabilities of observing each of the two alleles at the –G238A SNP given each of the two alleles at the –G308A SNP, using all the founder haplotypes stably defined by our Simwalk analyses. Next, the genotypes for the first SNP were simulated without regard to affection status using the program Simulate (Terwilliger et al. 1993; Terwilliger and Ott 1994), using the allele frequencies observed in our sample. Genotypes for the second SNP were then generated conditional on the allele present at the first SNP, using the probabilities calculated from all founders. Finally, each replicate was analyzed by Trimhap under the same four conditions as the real data to produce four nominal p-values, for each of the genetic models: narrow-dominant, narrow-recessive, broad-dominant, and broad-recessive. The distribution of the simulation study results was assembled to allow empiric evaluation of the real data.

Furthermore, we stratified the 22 pedigrees with genotypes available from the original genome scan into two groups for additional linkage analysis. The first group, H1 positive, included families that segregate a relatively rare haplotype H1 (-308A, -238G), and the second group included families that did not have this haplotype. Two-point linkage

analysis was performed on each subset separately using the Vitesse 2.0 program (O'Connell and Weeks 1995). Heterogeneity testing was conducted using the HOMOG program (Ott 1986). The same genetic models originally used for the genome scan (6) were used for this analysis. All markers from the original genome scan were reanalyzed for linkage in the two subsets. Since a number of markers produced LOD or HLOD scores  $>3.0$  in our original genome scan, we wanted to develop a criterion for evaluation of results that would consider not just the absolute magnitude of the subset LOD/HLOD score, but also the significance of any increase in the subset LOD/HLOD over the LOD/HLOD of the entire sample. Therefore, at each marker, the maximum LOD and HLOD scores from each subset were compared to the results that had been obtained for the total sample. The difference between the whole sample LOD and HLOD and the higher of the two subset LOD and HLOD scores was recorded as  $\Delta\text{LOD}$  and  $\Delta\text{HLOD}$ , respectively, for that marker.

To assess the significance of the increase in subset LOD/HLOD scores, we conducted another simulation study. The program Simulate was used to generate 1,000 replicates of full autosomal genome scans under the null hypothesis of no linkage, using actual allele numbers, allele frequency, and recombination fractions for each marker used for our actual scan. Then each of the replicates was analyzed with Vitesse 2.0 and HOMOG, under the same four genetic models as the original genome scan (Brzustowicz et al. 2000). The pedigrees were then divided into two subsets, based on the presence (16 families) or absence (6 families) of the H1 haplotype in the real pedigree data. Each subset in each simulated replicate was again analyzed under the four models as the real

data. In each subset, the maximum LOD and HLOD score was recorded for each marker and, if greater or equal to 3.0, was compared to the maximum LOD and HLOD values at the same marker under the same model in the whole replicate. For each replicate, the maximum values of  $\Delta$ LOD and of  $\Delta$ HLOD from all subset LOD/HLOD scores  $> 3.0$  were recorded for each of the two subsets and arranged into a table to allow empiric evaluation of the results.

## **2.3 Results**

### **2.3.1 Haplotype construction and trimmed haplotype analysis**

Multiple runs of Simwalk defined three TNF promoter haplotypes in this sample, assigned the labels H1 (-308A, -238G; frequency: 0.18), H2 (-308G, -238G; 0.78), and H3 (-308G, -238A; 0.04). The results of the Trimhap analysis indicated association of TNF promoter haplotype H1 with both the narrow and broad SZ phenotypes. All four tested models yielded nominal p-values of  $< 0.05$  and for three of them the p-values were  $< 0.01$ . The most interesting result was obtained with the narrow definition of the phenotype under the dominant model of inheritance (nominal  $p=0.0052$ ), which corresponded to an empiric p-value of 0.073 when calculated by considering only the probability of obtaining a single nominal p-value of equal or smaller size from among the four p-values generated for each replicate. However, we observed that for some of the simulated replicates, only one of the four models produced a nominally significant p-value. Therefore, we also calculated the significance of observing this overall pattern of three nominal p-values  $< 0.01$  within a single unlinked/unassociated replicate. This chance was equal to 0.026, supporting the association of TNF promoter haplotype H1 with SZ in

these families. The output results of Trimhap test and simulations are summarized in Table 3.

Table 3. Results of TRIMHAP Test and Simulations: Association of Schizophrenia Phenotypes with TNFA promoter Haplotypes

Models	TRIMHAP test, p-value	10,000 simulations, p-value
Narrow-Dominant	0.0052	0.073
Narrow-Recessive	0.0329	0.281
Broad-Dominant	0.0082	0.105
Broad-Recessive	0.0056	0.077
Overall probability	Three values $\leq 0.01$	0.026

### 2.3.2 Linkage analysis in stratified samples

Examining the Trimhap output, we observed that the associated haplotype H1 was present only in a subset of the families in our sample. We therefore stratified the available genotyped pedigrees, for which the autosomal genome scan data were available, into two groups based on the presence or absence of the TNF H1 haplotype.

The subset of H1-positive families comprised 16 families with 206 genotyped subjects, and in the smaller H1-negative subset there were six families with 75 genotyped subjects. In H1-negative subset marker locus D1S1609 located at 1q44 reached a LOD/HLOD value of 3.01 with  $\Delta$ LOD equal to 2.87 and  $\Delta$ HLOD equal to 1.67 (Table 4).

In H1-positive subset, two of the three LOD/HLOD score of 3.0 or greater that were obtained upon the stratification were in the 1q22 region known to contain a SZ

susceptibility locus in our sample (Brzustowicz et al. 2000). The D1S1677 locus showed a significant increase in LOD score, while the LOD score for D1S1679, site of the peak in the original and fine-mapping studies (Brzustowicz et al. 2000; Brzustowicz et al. 2002), remained virtually unchanged using this smaller sample (Table 4). The other locus, D3S3045, located on 3q13.12 reached a LOD/HLOD value of 3.30 with  $\Delta$  LOD of 1.19 and  $\Delta$  HLOD of 0.90 (Table 4).

Table 4. Increase in LOD/HLOD Scores in Subsets of Families and Significance Values Based on 1,000 Simulations

Marker	Subset	Cytogenetic Position	Model	LOD ( $\phi$ ) Stratified Sample	LOD ( $\phi$ ) Unstratified Sample	$\Delta$ LOD (p)	HLOD ( $\alpha$ , $\phi$ ) Stratified Group	HLOD ( $\alpha$ , $\phi$ ) Unstratified Group	$\Delta$ HLOD (p)
D1S1609	H1(-)	1q44	BD	3.01 (.01)	0.15 (.3)	2.86 ( <b>0.025</b> )	3.01 (1, .01)	1.34 (.25, 0)	1.67 (0.102)
D1S1679	H1(+)	1q22	NR	5.69 (.01)	5.77 (.05)	-0.08 (0.137)	5.82 (.85, 0)	5.80 (.95, .05)	0.02 (0.176)
D1S1677	H1(+)	1q22	NR	3.65 (.05)	2.15 (.1)	1.50 ( <b>0.037</b> )	3.65 (1, .05)	2.26 (.8, .1)	1.39 ( <b>0.035</b> )
D3S3045	H1(+)	3q13.12	NR	3.30 (.1)	2.11 (.2)	1.19 (0.064)	3.30 (1, .1)	2.40 (.75, .1)	0.90 (0.086)

Table 4 summarizes the results of the stratified linkage analysis and provides the significance level of the LOD/HLOD score increases as empiric p-values obtained from the simulation analysis. The results demonstrate that among the previously unreported loci from our sample that reach LOD scores of 3.0 or higher in one of the TNF haplotype stratified subsets, there is one locus, D1S1609, which has a statistically significant increase in LOD score as compared to the whole sample.

## 2.4 Discussion

This study has demonstrated the association of a TNF promoter haplotype with both the narrow and broad definition of SZ-associated phenotypes using a family-based trimmed haplotype linkage disequilibrium test (Trimhap). We further showed that stratification of our sample based on TNF haplotypes followed by reanalysis of linkage to SZ throughout the genome yielded significant evidence for a locus on chromosome 1q44 that is linked to SZ phenotypes and was previously undetected in this sample as a whole. We also illustrated that simulation studies are pivotal in evaluating the significance of results obtained with newer statistical methods, particularly when the structure of the sample is complex, and when multiple, but not independent, tests are performed. Simulation studies are also necessary to evaluate linkage results after sample stratification, since the traditional interpretation of LOD scores in comparison to a fixed threshold may not be sufficient to fully evaluate the significance of LOD/HLOD increases observed within the subsets.

Many hypotheses regarding the etiology of SZ have been proposed, one of which involves an immunological theory. The progress in immunological research techniques over the past two decades and the development of genetic methods for the investigation of polymorphisms in the genes related to the immune system has revived this theory. These developments have revealed the role of the components of the immune system in normal behavior and psychosis (Muller 2004). A recent review article has summarized the proven effects of key cytokines in the central nervous system, their possible function with respect to SZ, and the results of original studies elucidating the changes in cytokine

systems in individuals with schizophrenia (Hinze-Selch and Pollmacher 2001). Clinical reports on the beneficial effects of the anti-inflammatory COX-2 inhibitors in combination with the regular antipsychotic treatment on the total SZ psychopathology provide additional evidence that the immune dysfunction seen in individuals with schizophrenia may be part of the etiology and/or pathophysiology of the disorder (Muller et al. 2002; Muller et al. 2004).

In light of the immunological theory of SZ, the major histocompatibility complex has long been proposed as a candidate locus that may influence the susceptibility to SZ. The MHC spans approximately 4 million base pairs of DNA and has been mapped to the distal portion of 6p21.3. MHC genes are divided into three groups: Class I or HLA A, B and C; Class II or HLA DP, DQ and DR; and Class III (located between Classes I and II).

There are many genes of potential interest in MHC region that demonstrated association with SZ phenotypes in previous studies – NOTCH4 (Wei and Hemmings 2000; Anttila et al. 2003; Skol et al. 2003; Luo et al. 2004), TNXB (Wei and Hemmings 2004b), DRB1 (Wright et al. 1996; Arinami et al. 1998; Akaho et al. 2000; Li et al. 2001), DQB1 (Nimgaonkar et al. 1993; Nimgaonkar et al. 1995; Nimgaonkar et al. 1997). We wanted to select a single gene from the region to test for association to limit the multiple testing performed. The TNF gene (OMIM 191160) is located in the HLA III complex, chromosome 6p21.3, and is in linkage disequilibrium with genes in HLA I, II, and III (Hajeer and Hutchinson 2001; Selvaraj et al. 2001). Plasma TNF levels may be higher in patients with SZ than controls (Naudin et al. 1997), with levels normalizing in SZ on



treatment with antipsychotic medications (Monteleone et al. 1997; Kowalski et al. 2001). Another study has reported that TNF concentrations demonstrate a significant correlation with Brief Psychiatric Rating Scale and Scale Assessment of Positive Symptoms scores (Erbagci et al. 2001).

Recently, it was shown that the -308A allele is present significantly ( $p=0.0042$ ) more often in Northern Italian individuals with SZ than healthy controls (Boin et al. 2001). An association study of -G308A TNF in a mixed sample of Caucasian SZ sib-pairs and parent-offspring trios provided evidence for significant association with the -308G allele with SZ (Schwab et al. 2003). If the -G308A polymorphism is not the causative risk mutation but merely in linkage disequilibrium with the true risk mutation, then differences in the associated allele in these two populations could be explained by differences in the population genetics of these two samples. This is supported by the reported difference in the allele frequencies of this polymorphism, ranging from 0.11 for the minor allele in Northern Italians to 0.19 in the mixed Caucasian sample from Germany, Hungary, and Israel. Association to TNF may be stronger in Caucasians populations, with Japanese (Hashimoto et al. 2004), Chinese (Tan et al. 2003; Tsai et al. 2003), Korean (Pae et al. 2003) and some Asian-Pacific populations (Handoko et al. 2003) failing to show association between TNF promoter markers and SZ.

TNF plays an important role in initiation and regulation of the inflammatory process. Changes in expression may trigger an anomalous response to infection, which could lead to a subtle brain injury at critical stages during development and contribute to the onset of

SZ latter in life. As recently reviewed, immunopathological findings are common in individuals with SZ who sometimes show signs of infectious factors and a certain degree of non-specific inflammatory reactions that are consistent with a possible role of TNF dysfunction in disease etiology through an infection or inflammatory mechanism (Rothermundt et al. 2001). Recent research indicates the possible role of glial TNF and other cytokines in synaptic strength control at excitatory synapses (Beattie et al. 2002) and apoptosis of oligodendrocytes through glutamate excitotoxicity (Takahashi et al. 2003). This provides a different kind of mechanistic link to SZ that would be compatible with the increasing genetic evidence for the glutamate hypothesis (Harrison and Owen 2003; Sawa and Snyder 2003).

Up to 2005, no other association study of TNF promoter polymorphisms with SZ has analyzed haplotypes in extended pedigrees. This approach provides the opportunity to increase the information content of the biallelic markers and elevate the quality control of the genotypes through robust methods of error detecting. In addition, this is the first study of TNF that investigated a polymorphism other than -G308A (Saviouk et al. 2004).

To decrease the number of tests we chose to evaluate haplotypes in a single test rather than each SNP separately. We chose a trimmed haplotype method of association analysis (MacLean et al. 2000) since it can be used in extended pedigrees and it evaluates haplotype data as a whole without a need to convert the haplotypes into a multiallelic pseudomarker which would then be analyzed as unique independent alleles. Despite the strengths of this approach and the built-in permutation test of Trimhap, we have also

demonstrated the utility of simulations to accurately evaluate the significance of test results when multiple tests are performed on complex pedigree structures.

The review of the literature shows no prior use of trimmed-haplotype method for evaluation of the linkage disequilibrium since its introduction. There are several reasons for this: there is a tendency to use population-based samples, sib-pairs, trios and nuclear families in association studies rather than extended pedigrees; there is a tendency to evaluate the multiple markers over short genetic distances rather than haplotypes; the algorithm of the simulation studies is more complex for the tests performed on extended pedigrees that use haplotype information with certain degree of linkage disequilibrium between markers along the chromosome. For a complex disease like SZ, population-based studies of unrelated individuals comprised into a case and control groups could be both practical due to the ease of the subject collection and powerful. However, there is an extensive debate about the optimum study design, and multiple concerns are been expressed that this kind of studies leads to a hard-to-detect population stratification with biased or spurious results (Cardon and Palmer 2003). There are several advantages in using family based data. Family-based sample allows to use a robust test of linkage to search for the regions in human genome that contribute to the phenotype etiology, it is more practical in inferring the haplotypes in the region of interest, and perform genotype quality control tests. Moreover, there is a greater similarity of the effects from contributing loci on phenotypes of individuals from the same family and the extension of the number of those individuals should contribute to the value of genotype-phenotype association. On the other hand, the pedigrees with multiple individuals prevent from the

statistical analysis of the data as independent cases with the decrease in the power of the statistical method. The power further decreases as multiple tests being performed on several markers in independent tests. To avoid this, the use of the haplotype data maybe advised to evaluate the association of the group of the markers covering a short genetic distance in a single test. To evaluate the significance of our results obtained from our sample using four non-independent tests with two phenotype definitions and two modes of inheritance for each phenotype, we conducted a simulation study. We generated 10,000 replicates of our genotyping data. For each replicate, we used the original pedigree structures and affection status information. The genotypes for the first SNP were generated under the “no linkage” hypothesis using Simulate software (Terwilliger et al. 1993; Terwilliger and Ott 1994) with the allelic frequencies as in real data. The genotypes for the second SNP were generated with the notion of the tight linkage disequilibrium between both SNPs with allelic frequencies for the second SNP dependent on the specific allele at the first SNP. The absence of association in the absence of linkage is assured by the TRIMHAP internal haplotype shuffling mechanism when evaluating the replicates. Each replicate was analyzed by the trimmed haplotype method and under the same conditions as the real data. Therefore, each replicate produced four p-values for narrow-dominant, narrow-recessive, broad-dominant, and broad-recessive models. When using only the most significant out of four values from 10,000 tests in the conservative evaluation, we find that the chance to obtain a p-value of 0.0052 from unlinked non-associated data is equal to 0.073 (95% CI 0.067-0.078). However, accounting for the fact that the four tests are not independent and there is a correlation between the four p-values obtained from a single replicate we evaluated the chance of

observing an unlinked and not-associated replicate with three p-values of equal or less than 0.01 as obtained from the test on the real data. This chance is equal to 0.026 (95%CI 0.023-0.029). The chance of observing three p-values of less or equal to 0.01 with the fourth p-value of less or equal to 0.05 was 0.025 (95%CI 0.022-0.029) and did not add much to the significance of the results.

The output of the TRIMHAP analysis revealed that the associated haplotype H1 is present only in a subset of the families in our sample. We decided to test a possibility that TNFA promoter markers distribution in our sample suggests the sample stratification and evaluate the effect of this stratification on linkage results throughout the genome. We stratified the available genotyped pedigrees into two groups of families for which whole autosomal scan data was available, with and without H1 haplotype of TNFA. An example of stratification of a data set on the basis of HLA genotypes (DR3 and DR4) in order to separate the families with different degrees of genetic susceptibility and influenced by different genetic factors was shown in the successful attempt to identify causative locus for insulin-dependent diabetes mellitus on chromosome 11q (Hashimoto et al. 1994).

The reanalysis of our genome scan data in subsets of families stratified by TNF haplotypes produced only a four loci that exceeded a LOD score threshold of 3.0. Only two of these, D1S1609 and D1S1677, exhibited a statistically significant increase in LOD score over the results from the entire sample. D1S1609, located on 1q44, was found to be linked to the broad phenotype under a dominant mode of inheritance in the small subset not segregating haplotype H1. Linkage of SZ to the telomeric portion of chromosome 1

has been reported in a large family with a balanced translocation (1;11) (q42;q14.3) (Blackwood et al. 2001). The family was followed for 20 years and showed an increase incidence of DSM-IV defined SZ, schizoaffective disorder, and recurrent major depression in family members with the translocation. Linkage between these three phenotypes and the translocation was detected with a LOD score of 7.1. Linkage with seven cases of SZ alone (other disorders coded unknown) was also significant (LOD score 3.6). In the isolated population from the northeastern part of Finland a maximum LOD score of 3.82 was detected in a three-stage genome scan at locus D1S2891, located approximately 35 cM centromeric from locus D1S1609 (Hovatta et al. 1999). Linkage was obtained to SZ/SAD using a dominant affecteds-only model. Another study performed on 134 affected sib-pairs from Finland detected linkage with a LOD score of 2.62 to the region between markers D1S439 and D1S1656 (Ekelund et al. 2000).

Interestingly, this result was obtained using a broad phenotype definition and dominant model of inheritance – the same conditions under which we obtained significant results for linkage to D1S1069, approximately 20 cM more distal on chromosome 1. More recently, the same authors conducted a chromosome 1 screening for SZ loci in samples consisting of subjects from a northeastern isolate of Finland and from the rest of the country (Ekelund et al. 2001). They found strong evidence of linkage at marker D1S2709 (LOD=3.21) located at 1q42.2, about 17 cM centromeric from D1S1609. These results were obtained from the sample that did not include the northeastern isolate. In the combined sample, the authors obtained a maximum LOD score of 2.71 at the same locus.

In both cases, linkage was obtained with a SZ spectrum phenotype and a dominant model of inheritance.

Another interesting observation in our study relates to the locus on chromosome 1q22, previously identified during the genome scan analysis of these family samples (Brzustowicz et al. 2000; Brzustowicz et al. 2002). The maximum heterogeneity LOD score of 6.5 with a Z-max support interval of <3cM was obtained approximately 80 cM away from locus D1S1609. Upon stratification on the basis of TNF promoter haplotypes, virtually the entire signal at 1q22 was found to fall within the subgroup that does segregate the H1 haplotype, without a significant change in LOD/HLOD at D1S1679 and a significant strengthening of the signal at the adjacent D1S1677 marker. Review of the literature and the observation that the two chromosome 1 regions (1q22 and 1q44) appear to be linked to different subgroups of families strongly suggests that there are two distinct SZ susceptibility loci segregating in our sample, one associated more strongly with a narrow phenotype (1q22) and the other with a broad phenotype (1q44). The relationship of these loci to TNF remains unclear. It is not known if there may be an interaction with TNF with one or both of these loci, or if the different TNF promoter haplotypes are merely serving as a proxy for another MHC locus or other population differences. Additional studies on these population subgroups will clearly be needed.

## **Chapter 3. Association of Synapsin 2 with schizophrenia in families of Northern European ancestry**

### **3.1 Introduction**

Synapsins are a family of three genes in higher vertebrates whose products are associated with the cytoplasmic surface of the synaptic vesicles and implicated in synaptogenesis and neuronal development, neurotransmitter release, and the localization of nitric oxide (NO) synthase to the proximity of NO targets in presynaptic neurons. All synapsins have a similar domain structure at the amino terminal region, which is composed of short A and B domains and a longer C domain. Domain A contains a phosphorylation site for protein kinase A and  $\text{Ca}^{++}$ /calmodulin-dependent protein kinase I and regulates neurotransmitter release in a phosphorylation dependent manner. Domain C accounts for more than half of the synapsin sequences, and is the most highly conserved domain with over 50% homology between vertebrate and invertebrate synapsins. Together with domain E, domain C is responsible for binding to the actin scaffold and maintaining the vesicle pool in the periphery. Domains D-I make up the carboxyl-terminal region, which varies among the different isoforms. As a result of alternative splicing, synapsin genes are known to be transcribed into three isoforms named “a”, “b”, and “b-like” with a structurally different C-terminal part of the molecule. Synapsins “a” are grouped together since they share a conservative domain E. Domains F and I are found in the “b” type of synapsins. Domains B, D, G, H, and J demonstrate an abundance of proline, glutamine, alanine, and serine and contain a site for phosphorylation by mitogens-activated protein



kinase and  $\text{Ca}^{++}$ /calmodulin-dependent protein kinase II (Hosaka and Sudhof 1998; Hilfiker et al. 1999; Hilfiker et al. 2005).

A family of tissue inhibitors of metalloproteinase genes (TIMP) is associated physically with the synapsin family. TIMPs inhibit the matrix metalloproteinases, a group of zinc-binding endopeptidases, and are expressed in many tissues, with highest expression in the placenta. The TIMP4 gene (OMIM 601915) is located within the sixth intron of Syn2 and transcribed in the opposite direction. TIMP1 (OMIM 305370) is located within the sequence of Syn1 on chromosome X, and TIMP3 (OMIM 188826) resides within Syn3 on chromosome 22. While the evolutionary development of both synapsins and TIMP genes through duplications explains the physical link between the two families, there is currently no strongly established functional interaction between them (Olson et al. 1998; Pohar et al. 1999).

In humans, the Syn2 gene (MIM 600755) is located on chromosome 3p25 and is translated into two proteins of 547 (Syn2a) and 478 (Syn2b) aminoacids. It exhibits high homology across a broad range of major phyla within the animal kingdom with conserved functionality (Kao et al. 1999), though the whole synapsin family does not appear to be required for survival, as shown by knockout experiments (Gitler et al. 2004). Brain and spinal cord are the major sites of expression.

Many theories regarding the etiology of SZ emphasize the misregulation of neurotransmitters at the synapse. When an action potential reaches a nerve terminal,

calcium ions enter via voltage-gated ion channels, triggering the fusion of vesicles to the plasma membrane and the subsequent release of neurotransmitters into the synaptic cleft (Greengard et al. 1993). There are two pools of synaptic vesicles present in the nerve terminal: a releasable pool of vesicles floating freely in the cytoplasm that can fuse to the plasma membrane following an action potential, and a reserve pool of vesicles that are reversibly tethered to the actin-based cytoskeleton. These reserved vesicles effectively replenish those that have undergone fusion, lessening the synaptic depression. Synaptic vesicles, the associated synapsin protein, and actin filaments form a complex that is anchored to the cytoskeleton. The phosphorylation of synapsin is believed to cause the dissociation of this complex, thereby increasing the density of free synaptic vesicles in the cytoplasm (Greengard et al. 1993; Hosaka and Sudhof 1998; Augustine et al. 1999).

Another important function of synapsins that relates to SZ is their ability to localize NO in proximity of its target. Neurally produced NO is a highly reactive molecule with a broad spectrum of functions that involve neurotransmitter release and extension of neuronal processes. As NO cannot be stored in vesicles, it must be synthesized by neuronal NO synthase (nNOS) on demand. To minimize the undesired reactivity of NO molecules in neurons, adapter proteins are used for the localization of nNOS. One such adapter protein is the nitric oxide synthase 1 (neuronal) adaptor protein encoded by the NOS1AP gene (MIM605551), previously known as the C-terminal PDZ domain ligand of nNOS or CAPON, (Jaffrey et al. 2002), which was recently identified as a major candidate susceptibility gene for SZ in a Canadian population of Northern European descent (Brzustowicz et al. 2000; Brzustowicz et al. 2002; Brzustowicz et al. 2004; Xu et

al. 2005) and in Han Chinese (Zheng et al. 2005). Synapsins are known to colocalize with CAPON and nNOS in neurons and the absence of the Syn1 and Syn2 genes in knockout mice markedly alters the subcellular localizations of these molecules (Jaffrey et al. 2002).

Several published studies have investigated the mRNA expression profile of Syn2 in the brains of subjects affected with SZ. A microarray expression profile of the prefrontal cortex revealed that Syn2 transcript levels were significantly decreased in nine out of ten subjects with SZ as compared to ten matched controls (Mirnics et al. 2000). Although this finding was not confirmed by real-time PCR and immunoblotting experiments in another sample (Imai et al. 2001), another Western immunoblotting study found a decrease in synapsin (IIa and IIIa) expression in the hippocampus of individuals with SZ (Vawter et al. 2002). Syn2 transcript levels were significantly up-regulated in immunoblotting experiments in rats following chronic haloperidol treatment (Chong et al. 2002), implying a possible role in reaction to perturbations of the dopamine system. More recently it has been shown in the rat that Syn2 expression may be up or down regulated by manipulations of the dopamine D1 and D2 receptors, further supporting the theory of neurotransmitter misregulation in the etiology of psychotic phenotypes (Chong et al. 2006).

Though no significant linkage results have been reported in the area of the Syn2 gene, a suggestive LOD score of 2.34 was reported in this region from an affecteds only genome scan analysis of 57 multiplex SZ families (Pulver et al. 1995). Recently, two association studies of Syn2 polymorphisms and SZ reported highly significant results in Han Chinese

using case-control (Chen et al. 2004b) and transmission-disequilibrium (Chen et al. 2004a) approaches. In addition, significant haplotype association was observed in Korean sample (Lee et al. 2005).

In this study we used a data set of 37 multiplex SZ families of Northern European ancestry to investigate linkage and association to the Syn2 locus. Four microsatellite markers were used for the linkage analysis and 20 single nucleotide polymorphism markers (SNPs) that spanned almost the entire Syn2 gene were used for two distinct tests of association.

## **3.2 Materials and Methods**

### **3.2.1 Subjects**

The sample of families used in this study was obtained from the National Institute of Mental Health (NIMH) SZ Genetic Initiative Collection. SZ pedigrees were ascertained by three independent medical sites (Columbia University, Harvard University, Washington University). The subjects were diagnosed according to DSM-III-R and DSM-IV classifications with the following systematic and comprehensive examination of affected individuals and their relatives using the Diagnostic Interview for Genetic Studies (Nurnberger et al. 1994; Faraone et al. 1996; Cloninger et al. 1998). Nuclear and extended pedigrees have been ascertained which have at least two individuals affected with SZ who are first-degree biological relatives. Data on family structure and individual family members, including psychiatric diagnosis and other clinically relevant

information, as well as lymphoblastoid cell lines and DNA, are stored, maintained and distributed by the NIMH Center for Genetic Studies. All data and biological material is stored and distributed without any links to personal identifying information. To reduce the impact of genetic heterogeneity on association with the SZ phenotype, families of exclusively Northern European ancestry were selected for this study. This set includes 292 individuals (98 founders) in 37 pedigrees with an average family size of 7.9 subjects (ranging from 4 to 28) and an average number of generations of 2.3 (ranging from 2 to 4). 229 DNA samples were available for genotyping from the cell repository at Rutgers University. For this study, a single SZ phenotype definition was used with subjects diagnosed with SZ or SAD designated as affected. Subjects unavailable for assessment were designated phenotype unknown. The remaining individuals, including those with SZ spectrum diagnoses, were designated as unaffected. Overall, 89 subjects were assigned affected, 153 unaffected, and 50 unknown phenotypes. Written informed consent was obtained from all participants after explanation of possible consequences according to the protocols of NIMH Human Genetic Initiative.

### **3.2.2 Genotyping**

The dbSNP database was used to select SNPs rs308969, rs308964, rs308965, rs931676, rs3817004, rs17035945, rs308952, rs99365, rs308950, rs308953, rs795009, rs795010, rs795011, rs3755724, and rs794999 for PCR amplification and genotyping assays. Three additional SNPs were identified by sequencing intron 6 of the Syn2 gene in a set of 16 random founders from the sample described above (ss35528974, ss35528972, and ss35528973). SNPs rs308969 (intron 2), rs308964 (intron 3), rs308965 (intron 4),

rs931676 (intron 5), rs3817004, rs17035945, rs308952, rs99365, rs308950, rs308953, ss35528974 (intron 6), rs795009 (intron 8), rs795010 (intron 9), rs795011 (intron 10) were genotyped using simplex Pyrosequencing<sup>TM</sup> assays on the automated PSQ HS96A platform (Ronaghi et al. 1998; Ahmadian et al. 2000). PCR primers were designed using Primer3 (Whitehead Institute) and the sequencing primer used for the Pyrosequencing assay was designed using the Pyrosequencing SNP Primer Design Software v1.0 (Pyrosequencing). PCR reactions contained 40 ng of template DNA, 0.5 U AmpliTaq Gold polymerase (Applied Biosystems), 0.01  $\mu$ M of each primer, dNTPs (200  $\mu$ M each, Invitrogen), 1.5 mM of  $MgCl_2$ , 1  $\mu$ l of GeneAmp 10x buffer II (Applied Biosystems), in a 10  $\mu$ l volume. After 3 min at 95°C, 30 cycles were performed at 94°C for 30 s, at 50-60°C for 30 s, and at 72°C for 15 s, followed by a final extension step at 72°C for 3 min.

DNA fragments for SNPs rs3755724, ss35528972, ss35528973 (intron 6), rs794999 (exon 13) were amplified using a recently described multiplex PCR approach that minimizes primer complementarity, especially between their 3'-bases (Wang et al. 2005). Multiplex PCR was performed in 30- $\mu$ l of PCR mix containing 1x PCR buffer (50 mM KCl, 100 mM Tris-HCl, pH 8.3, 1.5 mM  $MgCl_2$ , and 100  $\mu$ g/ml gelatin), dNTPs (200  $\mu$ M each, Invitrogen), primers (20 nM each), 0.5 U AmpliTaq Gold polymerase (Applied Biosystems) and 20ng of template DNA. The samples were heated to 94°C for 15 min, followed by 40 PCR cycles of 40 sec at 94°C, 2 min at 55°C, and 5 min of ramping from 55°C to 70°C with 0.01°C /s increase. A final extension step was carried out at 72°C for 3 min. PCR amplifications were performed with the PTC-200 Programmable Thermal Controller (MJ Research). A DNA fragment containing SNPs rs598704 and rs598747

(intron 2) was amplified as a single PCR product. PCR reactions contained 40 ng of template DNA, 1U AmpliTaq Gold polymerase (Applied Biosystems), 0.01  $\mu$ M of each primer, 2mM of MgCl<sub>2</sub>, 1 $\mu$ l of GeneAmp 10x buffer II (Applied Biosystems), in a 10  $\mu$ l volume. After 10 min at 94°C, 40 cycles were performed at 94°C for 4 s, at 50°C for 60s, ramping from 50°C to 72°C with 0.2°C/s increase, at 72°C for 45 s, followed by a final extension step at 72°C for 3 min.

These 6 SNPs were genotyped using the Ligase Detection Reaction (LDR) combined with Luminex flow cytometry (Iannone et al. 2000; Bortolin 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 complementary to the sequence 3' to the SNP, 5'-phosphorylated, and ending with a 3' universal tag (CTATCTTTAACTACAAATCTAAC). LDRs were performed in a 20  $\mu$ l volume containing 2  $\mu$ l of multiplex PCR product, 1  $\mu$ l of rs598704-rs598747 PCR product, 6 U Taq DNA Ligase (New England Biolabs), 0.15 pmol of allele specific and common primers for each SNP, 2  $\mu$ l of 10x Taq DNA Ligase buffer (New England Biolabs), and distilled water. LDR was carried out at 95°C for 60 s followed by 22 cycles of 95°C for 15 s and 58°C for 2 min. The bead hybridization step was performed with 0.5  $\mu$ l 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'-biotinalated universal oligonucleotide (GTTAGATTTGTAGTTTAAAGATAG-biotin) complementary to the universal tag at the 3' end of the common SNP-specific primer, and 46.02  $\mu$ l of

hybridization buffer (3 M tetramethylammonium chloride, 50 mM Tris-HCl, pH 8.0, 3mM EDTA, pH 8.0, 0.1% SDS). After heating to 95 °C for 60 s, the hybridization reaction was carried out at 37°C for 20 min. Fluorescent labeling was performed by adding 0.12 µl of 1mg/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.

To facilitate the detection of SNP genotyping errors and to assess linkage in the Syn2 area, four microsatellite markers spanning 4 Mb and located at the 5'-end (D3S4545, D3S3680), within intron 2 (D3S1259), and at the 3'-end (D3S3701) of the Syn2 gene were genotyped using WellRED labeled oligonucleotides (Proligo®) in conjunction with automated fluorescent fragment analysis on the CEQ8000 (Beckman Coulter).

PCR, pyrosequencing and LDR primers are listed in Table 5.

### **3.2.3 Error-checking and statistical analysis**

As genotyping errors are known to affect family-based tests of association (Mitchell et al. 2003), we undertook several error-checking steps. Genotype data from all Syn2 SNPs and microsatellite markers were first checked for Mendelian inconsistencies using the program PEDCHECK (O'Connell and Weeks 1998). Second, the genotyping error probabilities were estimated with five runs of SIMWALK v2.82 (Sobel and Lange 1996; Sobel et al. 2001; Sobel et al. 2002) under different starting conditions using all genotyped SNP and microsatellite markers. Three genotypes with a probability of



Table 5. PCR, pyrosequencing, and LDR reaction primers for Syn2 genotyping

SNP	Chr.3 position <sup>a</sup>	Method	PCR size	Primer label <sup>b</sup>	Primer sequence <sup>c</sup>
rs598747	12087010	LDR_Luminex	492	PCR_L	ATGGTTAATGACGTTGAGTATCACA
				PCR_R	GTGTTGAAGGTCTCAAACATGATCT
				Allele_A_Bead72	tcatttacctttaatccaataatcattggcaccacaccttctacaa
				Allele_G_Bead73	atcaaatctcatcaattcaacaatattggcaccacaccttctacag
				Common	/P/-tgagttgcgtgtggccccggctatctttaaactacaaatctaac
rs598704	12087053	LDR_Luminex	492	PCR_L	ATGGTTAATGACGTTGAGTATCACA
				PCR_R	GTGTTGAAGGTCTCAAACATGATCT
				Allele_A_Bead74	tacacatcttacaactaatttcagagcacctgggtgctgctgaca
				Allele_G_Bead75	aatcataaccttcaatcttttacagagcacctgggtgctgctgacg
				Common	/P/-gaggccctgtgaacccaagctatctttaaactacaaatctaac
rs308969	12152083	Pyrosequencing	220	PCR_L	AAAGGTAAATGTCTAGACCAGTGCT
				PCR_R	/Bio/-TGTCTATATTGGAGCTAATGGACCT

				Pyro_Seq	TGCAAATTCAGTCATC
rs308964	12158011	Pyrosequencing	122	PCR_L	GGGAAATGGAAACCTAGAGAGTACA
				PCR_R	/Bio/-CAGTTTCAACATAAAAGCACTAGGTC
				Pyro_Seq	GAAAGCAGAACTAAAACTA
rs308965	12158741	Pyrosequencing	212	PCR_L	TGATGTGAGTTGTGCAGAAATAGTAG
				PCR_R	/Bio/-ACTCTGTTTTCCAAGGGAAATGTAT
				Pyro_Seq	ACAGACTGAGAGCTCACTT
rs931676	12163443	Pyrosequencing	194	PCR_L	/Bio/-ACATCCTCATTGGCTTGCAGTA
				PCR_R	ACAAGAAGGGCTTACTGCATCTT
				Pyro_Seq	CATGGCTTGTACACAGA
rs99365	12169085	Pyrosequencing	220	PCR_L	CTTTTCTCTGCTGTAGCATCTAGC
				PCR_R	/Bio/-CCACAAAGCCTTTTTCTTACAGAG
				Pyro_Seq	ACCTACCGTGCTTT
rs17035945	12169628	Pyrosequencing	162	PCR_L	GTAGAGGATACACAGCCACAGTATG
				PCR_R	/Bio/-CTTTGTCTTAATCGATCTGGTAGGG
				Pyro_Seq	TGTCAAACCACCTTCTG
rs308952	12170622	Pyrosequencing	150	PCR_L	/Bio/-GACTCTCTTTAAAGGGTAGCTGTGTT
				PCR_R	CTTGAGATCTGCACTGTATGAAGTT

				Pyro_Seq	CCATCACAGGAGGCAGAC
rs3817004	12170674	Pyrosequencing	150	PCR_L	/Bio/- GACTCTCTTTAAAGGGTAGCTGTGTT
				PCR_R	CTTGAGATCTGCACTGTATGAAGTT
				Pyro_Seq	CAATACAGTCTATAGGCC
ss35528972	12172255	LDR_Luminex	133	PCR_L	CATTTCTCCCCACCCTCAGTTAG
				PCR_R	CGCACCTCCTTCCTAAGCACC
				Allele_A_Bead40	ctttctacattattcacaacattagacctccctgaaggcaggga
				Allele_T_Bead41	ttactacacaataactcatcaatgacctccctgaaggcaggga
				Common	/P/-catgttctcatttccctgcctatctttaaactacaaatctaac
ss35528973	12172299	LDR_Luminex	104	PCR_L	CATTTCTCCCCACCCTCAGTTAG
				PCR_R	CGCACCTCCTTCCTAAGCACC
				Allele_G_Bead42	ctatctcatatttcactataaacgtacctccatgcctagcagcg
				Allele_A_Bead43	ctttcaattacaataactcattacgtacctccatgcctagcagca
				Common	/P/-ggctagacacacagaggcagctatctttaaactacaaatctaac
ss35528974	12172660	Pyrosequencing	192	PCR_L	/Bio/-TAAGGACTGTGCCTTGTTACTGAAT
				PCR_R	GATCTAAACTGGCCTGAAAACATAA
				Pyro_Seq	AAGAAAAAGCACAGCAG
rs308953	12172997	Pyrosequencing	180	PCR_L	TTAGACTCAAGCTCCTGTTAAGTCC

				PCR_R	/Bio/-ACCGTTTCACTATTTTAAGGACAGG
				Pyro_Seq	CAGTTTTAGAGAGGAGACTT
rs3755724	12175906	LDR_Luminex		PCR_L	ACGCTGGGAATGAGACGAGCTA
				PCR_R	GTTCTATTACTGTTTGCTGTTGCTT
				Allele_C_Bead48	aaacaaacttcacatctcaataatcttcttcagctgcaggaagtgc
				Allele_T_Bead49	tcatcaatcttcaatttacttaccttcttcagctgcaggaagtgt
				Common	/P/-ttcaatgccctatttatgaggctctatctttaaactacaaatctaac
rs308950	12177866	Pyrosequencing	228	PCR_L	/Bio/-TGTCTAATGCAGAGAAAATTGACAG
				PCR_R	CTCCGTGGAATCCTACACATATTTT
				Pyro_Seq	GTTCCCAGGGTCACA
rs795009	12183671	Pyrosequencing	201	PCR_L	/Bio/-ACTCCTTCTCTCAACTCACCTGTCT
				PCR_R	AAGCAGGTGTGGAAAGCAA
				Pyro_Seq	AAAATTCTGGAAAGTT
rs795010	12183995	Pyrosequencing	226	PCR_L	/Bio/-ATAAAACACAAAAGGCCCAAGTAG
				PCR_R	GCTATAAAGGAATACTTGAGGCTAGG
				Pyro_Seq	TGGTATGTGCAGTCTTTA
rs795011	12186046	Pyrosequencing	220	PCR_L	/Bio/-ATAGGATCTTTGTCCCTTCCTTCTA
				PCR_R	CACATGCTCCTAATCAGAGATTTAAG

				Pyro_Seq	CCCTGGCACGGGTA
rs794999	12204015	LDR_Luminex	91	PCR_L	TTCTTCCTCCTCCTCGGCTC
				PCR_R	CTGGGCCTCTGCCAGGGAGCTGCT
				Allele_A_Bead60	aatctacaaatccaataatctcatggccggggggccccacca
				Allele_G_Bead61	aatcttaccattcataatcttcaggccggggggccccaccg
				Common	/P/-cccacggagatgcaccctccctatctttaactacaaatctaac
D3S1259	12073681	Microsatellite	196	PCR_L	/D3-PA/-gctggactatattgaaact
				PCR_R	TTTCAGTGAGCCAAGATCGT
D3S4545	8559807	Microsatellite	192	PCR_L	/D4-PA/-ctgtgatcacaccactgcag
				PCR_R	TTCGGTATTCTGTGTCAGAGC
D3S3680	11700958	Microsatellite	126	PCR_L	/D3-PA/-aaggaattgcaaatgaaatagaaa
				PCR_R	GCCTGGTCCCTAACATAACT
D3S3701	12592517	Microsatellite	171	PCR_L	/D4-PA/-ccccagaacttaagcaaaa
				PCR_R	TGTTGGAGAATCTGCCAGAC

a- Position on chromosome 3 according to The UCSC Human Genome Browser, May 2004 assembly

b- Labels for allele specific primers for LDR assay accompanied by FlexMap™ bead number.

c- Primer sequences are in 5'-3' direction.

Labels:

/P/- 5' phosphorylation.

/D2-PA/, /D3-PA/, /D4-PA/ - 5' WellRED labeled oligonucleotides (Proligo®)

/Bio/ - 5' biotin label on PCR primer for pyrosequencing assay

mistyping  $\geq 0.25$  were regenotyped and since the apparent errors were not resolved, they were removed from further analysis. Overall, all of the genotypes for a single subject with multiple Mendelian errors and 5 other genotypes in the remainder of the sample were removed from the final analysis due to Mendelian inconsistencies and high probability of mistyping.

The PEDSTATS program was used to characterize the family structures and to assess deviations from Hardy-Weinberg equilibrium (Abecasis et al. 2002).

Parametric two- and multi-point linkage analyses of the microsatellite markers and the phenotype locus were performed using FASTLINK v.4.1P (Cottingham et al. 1993; Schaffer et al. 1994). Heterogeneity testing was conducted using the HOMOG program (Ott 1986). Parametric linkage analysis was conducted, as it is more powerful than nonparametric methods and is a robust method for detecting linkage despite errors or simplifications in the analyzing model, as long as both a dominant and a recessive model are used (Durner et al. 1999). Dominant and recessive genetic models and the narrow phenotype definition were the same as used previously (Brzustowicz et al. 2000; Saviouk et al. 2004).

Association between the genotyped SNPs and the phenotype was assessed using two different methods. Allelic transmission of markers from parents to affected offsprings was evaluated by the Transmission Disequilibrium Test (TDT) using the TRANSMIT software (version 2.5.4) (Clayton 1999). TRANSMIT can analyze single marker data as

well as multi-locus phase-unknown haplotypes and allows for unknown parental genotypes. Rare haplotypes with frequency less than 0.03 were aggregated by using the “-c3” option. Multiple nuclear families from a single pedigree were allowed (“-mf”) with robust estimation of the variance of the vector score (“-r”). Reported p-values for association were based on up to 10,000,000 internal bootstrap procedures.

To estimate the linkage disequilibrium (LD) between SNP markers, and the significance of association between SNP markers and the phenotype locus in pedigrees of various structures, we used an extension of the pedigree disequilibrium test (PDT) (Martin et al. 2000) implemented in the program PDTPHASE, which is a part of the UNPHASED package (Dudbridge 2003) of association analysis programs. We used the “missing genotypes” and “equal weight to all families” options for our analyses. The PDTPHASE output was used to report global p-values for association of individual SNPs with the disease phenotype based on 1,000 permutations and their corresponding transmission statistics.

To assess the effect of linkage in the area on the results of TRANSMIT and PDTPHASE a simulation study was conducted. Two SNPs with minor allele frequencies (MAF) of 0.1 and 0.5, respectively, were simulated by SLINK (Ott 1989) with 0%, 25%, 50%, 75%, and 100% of families linked ( $\alpha$ ) at  $\theta = 0.1$  to the affection locus using the original affection status and pedigree structures but without any association between the markers and the affection locus. For each SNP, MAF, and value of  $\alpha$ , 10,000 replicates were generated and analyzed using TRANSMIT and PDTPHASE under the same conditions as

in the real data. For  $MAF=0.1$  and  $\alpha=0$ , an additional 75,000 replicates were generated to estimate small empirical p-values for TRANSMIT. Output of the simulation was arranged into a table to allow empiric evaluation of the results.

### 3.3 Results

All of the tested microsatellite and SNP markers were in Hardy-Weinberg equilibrium among the founders ( $p \geq 0.70$ ) and in the whole sample ( $p \geq 0.08$ ). Four groups of SNPs appeared to be in four different, partially interdigitated, haplotype blocks in complete LD ( $D'=1$ ,  $r^2=1$ ) and therefore were considered as four single markers for subsequent analyses. Block 1 consisted of rs308969, rs308964, rs308965, and ss35528974 which spread through introns 2, 3, 4, and 6. Block 2 included rs931676 in intron 5, and ss35528973 and rs308953 in intron 6. Three SNPs in intron 6, rs99365, rs308952, and rs308950, were grouped into Block 3. Block 4 was formed by rs795009, rs795010, and rs795011, covering introns 8, 9, and 10. Seven SNPs fell outside of these defined LD blocks and so were included individually in further analysis.

LD between the eleven markers defined above was analyzed using PDTPHASE. Table 1 demonstrates that all SNPs exhibit high level of LD between each other. For most of the markers  $D'=1$ , implying that transmission of markers can be analyzed jointly, using haplotypes.

No significant ( $LOD \geq 3$ ) or suggestive ( $LOD \geq 2$ ) linkage results were obtained in linkage analysis with the microsatellite markers in the Syn2 area. A maximum two-point



Table 6. LD between SNP markers in Syn2 gene

SNP markers	rs598747	rs598704	Block 1	Block 2	Block 3	rs17035945	rs3817004	ss35528972	rs3755724	Block 4	rs794999
rs598747		1	1	1	1	1	1	0.92	0.86	0.87	0.89
rs598704	0.36		1	1	1	1	1	0.91	0.76	1	1
Block 1	0.58	0.21		1	1	1	1	0.90	1	1	1
Block 2	0.02	0.20	0.01		1	1	1	1	1	0.45	1
Block 3	0.92	0.33	0.65	0.02		1	1	0.86	1	1	1
rs17035945	0.04	0.41	0.02	0.49	0.04		1	1	0.84	0.53	0.82
rs3817004	0.25	0.09	0.01	0.005	0.01	0.28		1	1	1	1
ss35528972	0.26	0.09	0.42	0.01	0.01	0.25	0.003		1	0.86	0.92
rs3755724	0.07	0.15	0.05	0.05	0.08	0.08	0.01	0.03		0.88	0.90
Block 4	0.38	0.74	0.30	0.06	0.17	0.45	0.13	0.11	0.14		1
rs794999	0.35	0.85	0.25	0.24	0.33	0.38	0.11	0.11	0.17	0.84	

D' measures are in the top-right part and  $R^2$  measures are in the bottom-left part of the table.

heterogeneity LOD (HLOD) score of 1.93 was obtained at marker D3S3434 ( $\theta=0$ ) under a recessive model of inheritance and with 35% of families linked. Multi-point analysis using all of the genotyped microsatellites in a five-point parametric linkage analysis did not produce an increase in LOD or HLOD values, with a maximum HLOD of 1.21 at D3S3434 under a recessive model and 25% of families linked. The addition of SNPs data did not significantly affect the outcome of the multipoint linkage analysis. Results of the two-point linkage analysis under homogeneity and heterogeneity for microsatellite markers in the *Syn2* region are presented in Table 7.

Table 7. Maximum two-point LOD scores under homogeneity and heterogeneity for microsatellite markers in *Syn2* region

Model	Loci	cM	Max LOD	$\theta$	Max HLOD	$\theta$	$\alpha$
Dominant	D3S4545	0	0.22	0.2	0.69	0	0.3
	D3S3680	7.4	0.48	0.2	0.49	0.2	0.9
	D3S1259	8.9	0	0.5	0	0.5	1
	D3S3701	11.8	0.56	0.2	<b>1.06</b>	0	0.25
Recessive	D3S4545	0	0.97	0.2	<b>1.93</b>	0	0.35
	D3S3680	7.4	0.08	0.3	0.10	0.3	0.7
	D3S1259	8.9	0	0.5	0.05	0.1	0.1
	D3S3701	11.8	0.09	0.3	0.43	0.05	0.2

cM - Map position in centimorgans from the first marker (D3S4545)

$\theta$ - Recombination fraction;

Max LOD - maximum LOD score under homogeneity;

Max HLOD - maximum LOD score under heterogeneity;

$\alpha$  - Proportion of linked families.

LOD values of  $> 1.0$  are in bold.

The PDTPHASE and TRANSMIT statistics for each marker are provided in Table 8.

Single marker transmission disequilibrium to affected and unaffected siblings

(PDTPHASE) demonstrated the most interesting results for Block 3 and rs17035945,

both in intron 6, where significant transmission disequilibrium was observed at both markers (nominal  $p=0.014$  and  $p=0.021$ , respectively). Additionally, slight overtransmission of the common allele to affecteds was observed for SNP rs598747 in intron 2 ( $p=0.034$ ) and slight overtransmission of the rare allele to affecteds was detected for markers in Block 2 ( $p=0.037$ ). Analyses of allelic transmissions from parents to affected subjects (TRANSMIT) demonstrated significant disequilibrium for Block 2 (nominal global  $p=0.0000005$ ), Block 3 ( $p=0.00024$ ), rs598747 ( $p=0.0039$ ), ss35528972 ( $p=0.0042$ ), and rs3817004 ( $p=0.0097$ ).

Although we did not demonstrate suggestive linkage ( $\text{LOD} \geq 2.0$ ) in the area, a review of modern literature on the genetics of complex traits provides numerous examples where any LOD score greater than 1.0 is presented as “worthy of attention”. Therefore, we conducted a simulation study to assess how various strength linkage signals could affect the results of the TRANSMIT and PDTPHASE association tests. Two SNPs with MAF of 0.1 and 0.5 were analyzed for evidence of association in simulated datasets of the same family structure as our sample, with varying proportions of families linked to either simulated SNP. Overall, our data shows that for pedigrees of this structure TRANSMIT and PDTPHASE p-values are not distorted by the presence of linkage in the area (Table 9). However, for all tests the TRANSMIT bootstrap-based p-values seem to be anticonservative with a p-value of 0.05 or less being seen in approximately 7% of replicates for MAF=0.5 and 8% for MAF=0.1 when unassociated data was analyzed, regardless of the degree of linkage in the sample. Interestingly, the anticonservative nature of the TRANSMIT p-values increased as the probability of obtaining smaller and

Table 8. Transmission statistics to affected and nonaffected siblings (PDTPHASE) and from parents to affected subjects (TRANSMIT)

SNP markers	Location	Alleles	Frequency (first allele)	Transmission		$\chi^2$	p-value	
				Affected	Nonaffected		PDTPHASE	TRANSMIT
rs598747	Intron 2	C/T	0.8438	261	243	4.50	<b>0.034</b>	<b>0.0039</b>
rs598704	Intron 2	C/T	0.6574	214	212	0.29	0.62	0.70
Block 1 rs308969 rs308964 rs308965 ss35528974	Intron 2 Intron 3 Intron 4 Intron 6	T/C G/A G/C T/C	0.9011	278	270	2.38	0.12	0.34
Block 2 rs931676 ss35528973rs308953	Intron 5 Intron 6 Intron 6	T/C G/A A/G	0.9041	289	296	3.74	<b>0.037</b>	<b>0.0000005</b>
Block 3 rs99365 rs308952 rs308950	Intron 6 Intron 6 Intron 6	C/T G/A G/C	0.8563	273	254	7.80	<b>0.014</b>	<b>0.00024</b>
rs17035945	Intron 6	C/T	0.8224	264	284	4.4	<b>0.021</b>	0.09
rs3817004	Intron 6	A/G	0.9552	311	300	3.65	0.13	<b>0.0097</b>
ss35528972	Intron 6	A/T	0.9456	279	271	3.33	0.058	<b>0.0042</b>
rs3755724	Intron 6	C/T	0.6695	181	183	0.03	0.86	0.42
Block 4 rs795009 rs795010 rs795011	Intron 8 Intron 9 Intron 10	A/C A/T A/C	0.7296	221	222	1.06	0.59	0.30
rs794999	Exon 13	G/A	0.6962	213	208	0.08	0.78	0.42

Table 9. Frequency of observing target p-values using TRANSMIT and PDTPHASE in an area of linkage with various proportions of linked families, based on 10,000 simulations for each condition tested.

Observed p-value <sup>a</sup>	Method	Proportion of linked families ( $\alpha$ )									
		0		0.25		0.5		0.75		1	
		0.5 <sup>b</sup>	0.1 <sup>b</sup>	0.5 <sup>b</sup>	0.1 <sup>b</sup>	0.5 <sup>b</sup>	0.1 <sup>b</sup>	0.5 <sup>b</sup>	0.1 <sup>b</sup>	0.5 <sup>b</sup>	0.1 <sup>b</sup>
0.05	TRANSMIT	0.067	0.085	0.072	0.084	0.071	0.081	0.071	0.078	0.068	0.070
0.05	PDTPHASE	0.038	0.033	0.039	0.035	0.038	0.033	0.035	0.036	0.035	0.034
0.01	TRANSMIT	0.020	0.033	0.022	0.032	0.025	0.03	0.023	0.028	0.019	0.023
0.01	PDTPHASE	0.006	0.004	0.007	0.004	0.010	0.010	0.006	0.0039	0.006	0.0039
0.005	TRANSMIT	0.013	0.023	0.015	0.022	0.015	0.021	0.014	0.018	0.013	0.016
0.005	PDTPHASE	0.0021	0.0018	0.0028	0.0018	0.0017	0.0016	0.0019	0.0016	0.0023	0.0012
0.001	TRANSMIT	0.0049	0.0119	0.005	0.0119	0.0058	0.0105	0.0045	0.0089	0.0047	0.0029
0.001	PDTPHASE	0.0003	0.0002	0.0004	0.0003	0.0004	0.0001	0.0004	0.0004	0.0003	0.0002

a – The frequency was calculated for observing this or a smaller p-value in PDTPHASE and TRANSMIT analysis of simulated replicates with no association and varying degrees of linkage

b - Frequency of minor allele

Table 10. Haplotype analysis with markers covering exclusively introns 5 and 6 of *Syn2*: Block 2 (rs931676), Block 3 (rs99365), rs17035945, rs3817004, ss35528972, rs3755724.

	PDTphase statistics			Transmit statistics				
Haplotype	Transmission		p-value	Haplotype Probability <sup>c</sup>	Transmission to affecteds		$\chi^2$	p-value
	A <sup>a</sup>	NA <sup>b</sup>			O <sup>d</sup>	E <sup>d</sup>		
T-T-C-G-A-C	5	16	<b>0.04</b>	0.05	4	8	4.20	<b>0.0000043</b>
T-C-C-A-A-C	95	89	0.59	0.38	59	60	0.03	0.86
C-C-T-A-A-C	19	12	<b>0.02</b>	0.07	18	13	4.83	<b>&lt;0.00000001</b>
T-C-T-A-A-C	28	17	0.20	0.08	15	14	0.07	0.68
T-T-C-A-A-C	9	14	<b>0.04</b>	0.04	6	5	0.16	0.27
T-T-C-A-T-C	29	32	<b>0.04</b>	0.05	6	10	4.50	<b>0.0015</b>
T-C-C-A-A-T	126	125	0.76	0.31	55	53	0.25	0.63
Global p- values			0.087	<b>0.0066</b>				

a, b – Transmission to affected and non-affected siblings

c – Haplotype probabilities as defined by transmit

d, e- Observed and expected transmissions

p-values  $\leq 0.05$  are in bold; global p-values are based on 1,000,000 bootstraps for TRANSMIT and 1,000 permutations for PDTPHASE.

smaller p-values by chance was examined. P-values of 0.001 were seen approximately 50 times more often than expected by chance when  $MAF=0.5$  and 92 times more often when  $MAF=0.1$ . Overall, inflation of the TRANSMIT p-values was greatest when the  $MAF=0.1$  and all families were unlinked. For this case, a nominal bootstrap p-value of 0.0202 would be equivalent to an empiric p-value of 0.05, while a nominal p-value of 0.00038 would be equivalent to an empiric p-value of 0.01, and a nominal p-value of 0.00001 would be equivalent to an empiric p-value of 0.005.

PDTPHASE performance was closer to expected from its reported statistic with a p-value of 0.05 or less observed in approximately 3.6% of the replicates regardless of the degree of linkage or  $MAF$ . The PDTPHASE p-values were almost always overly conservative, with the least conservative p-values occurring with the  $MAF=0.5$  and 25 to 50% of the sample linked. Based on the least conservative condition observed, a nominal p-value of 0.062 would be equivalent to an empiric p-value of 0.05. Table 4 summarizes the results of the simulation study.

A limited number of haplotype analyses were performed on the data. First, we performed a PDTPHASE haplotype analysis with markers rs5987747, Block2 (rs931676), Block 3 (rs99365) and rs170035945, each of which demonstrated some evidence of association with SZ (nominal  $p < 0.05$ ) in the single marker test. One out of the four observed haplotypes, haplotype C-C-T-C, showed a significant transmission disequilibrium with 19 transmissions to affected and 12 transmissions to non-affected siblings ( $p=0.024$ ), although the global permutation-based p-value for all haplotypes was not significant

( $p=0.056$ ). TRANSMIT haplotype analysis with markers rs598747, Block 2 (rs931676), Block 3 (rs99365), rs3817004, and ss35528972 (nominal  $p < 0.05$  in single marker TRANSMIT tests) did not yield any significant results for any of 5 observed haplotypes. Since the majority of markers with evidence for association under the single marker tests fall within intron 5 and intron 6, we performed haplotype analysis with markers only from this area of the gene. Seven haplotypes were observed for markers Block 2 (rs931676), Block 3 (rs99365), rs17035945, rs3817004, ss35528972, and rs3755724 in both the TRANSMIT and PDTPHASE tests. Three of the observed haplotypes produced evidence of association with SZ in both tests. The most interesting results were obtained for haplotype C-C-T-A-A-C that demonstrated the strongest association with both the TRANSMIT ( $p < 0.00000001$ ) and PDTPHASE ( $p=0.02$ ) tests, with overtransmission to affected individuals. The global  $p$ -value for all haplotypes tested was significant only for the TRANSMIT test ( $p=0.0066$ ). Table 10 summarizes results of both haplotype tests using markers in intron 5 and 6 of the Syn2 gene.

### **3.4 Discussion**

In this study we investigated linkage and association of Syn2 gene polymorphisms with SZ using four microsatellite markers and twenty SNPs. We failed to identify significant ( $\text{LOD} \geq 3.0$ ) or suggestive ( $\text{LOD} \geq 2.0$ ) linkage to the area in this sample. However, family-based association analysis of the transmission of Syn2 SNPs individually and as haplotypes from parents to affected offspring and transmission disequilibrium between affected and unaffected siblings provided evidence that Syn2 is associated with the development and/or pathogenesis of this debilitating disorder.



Analysis of twenty SNPs spanning 117 kb in the Syn2 gene revealed a complex LD/haplotype structure of the gene. We observed four groups of SNPs in tight LD blocks with  $D'=r^2=1$ . Physically, these blocks ranged in size with the largest spreading over 20.6 kb and covering almost 10% of the gene (Block 1), and the smallest encompassing only 2.4 kb (Block 4). While in our study Block 4 appeared as a discrete haplotype unit, the other blocks interdigitated significantly. The largest block (Block 1) encompassed the proximal 96.5% of the 9.6 kb Block 2 and the proximal 40.7% of the 8.8 kb Block 3, while the distal 40.9% of Block 2 overlapped with the proximal 44.6% of Block 3. We demonstrated that strong LD encompassed almost the entire gene, with the majority (39 of 55) of non-redundant marker pairs being in complete LD ( $D'=1$ ), a large number (14 pairs) demonstrating very strong LD ( $D'$  from 0.76 to 0.92) and only two marker pairs with  $D'<0.6$  ( $D'=0.45$  for Block 2 vs Block 4 and  $D'=0.53$  for rs17035945 vs Block 4). Public LD databases, such as that provided by Perlegen Sciences and Hapmap, reveal a similarly complex pattern of LD in this region, although with differences in the details of the LD/haplotype structures observed, presumably due to differences in the markers and populations used for the different analyses.

Out of eleven SNPs and SNP block markers analyzed for association with SZ, four showed disequilibrium of transmission to affected subjects and their unaffected siblings and five demonstrated deviation of transmission from parents to affected offspring. Although these results of association were obtained in an area without significant evidence of linkage to SZ in this sample, in light of the mildly positive LOD scores

(maximum HLOD of 1.9) we wished to explore the possible effect of linkage on the tests of association. A simulation study to assess the effect of linkage on the results of the tests of association revealed that the PDTPHASE and TRANSMIT statistics appear to be independent of the effect of linkage for this sample. While TRANSMIT appeared to be anticonservative when calculating p-values by its internal bootstrap procedure, our simulation analysis demonstrated that the observed associations with SZ are still highly significant. According to the most conservative scenario observed in our simulation results, an empiric p-value of 0.05 is equivalent to a nominal p-value of 0.02 in TRANSMIT and of 0.06 in PDTPHASE. Five out of eleven SNP markers reached this level of empiric significance for each test; markers rs598747, Block 2, Block 3, and ss35528972 were empirically significant in both tests, while markers rs17035945 and rs3817004 were empirically significant in only PDTPHASE or TRANSMIT, respectively.

While three of the SNPs tested produced nominal p-values  $<0.05$  with both PDTPHASE and TRANSMIT, more SNPs were detected as associated using TRANSMIT than PDTPHASE, and the significant p-values obtained with TRANSMIT were one to five orders of magnitude smaller than the PDTPHASE p-values for the same markers. Part of this difference appears to be due to the increasingly large distortion of the TRANSMIT nominal p-values for smaller values. So while, under the most conservative scenario, a nominal p-value of 0.05 occurred in 8.5% of the replicates by chance, a nominal p-value of 0.001 occurred 1.2% of the time, and a nominal p-value of 0.0001 occurred 0.7% of the time. However, even accounting for this inflation does not appear to fully explain the

differences in the results. Further differences can be explained by the different statistical approaches of the two methods. TRANSMIT, a TDT based method, evaluates the transmission of markers from parents to affected offspring. It calculates a score vector averaged over all possible configurations of parental haplotypes and transmissions. Data from unaffected siblings and siblings with unknown phenotype is used only to narrow the possible parental genotypes and haplotype configurations. PDTPHASE is based on the PDT test (Martin et al. 2000) that uses a broader range of information from an extended pedigree by including unaffected siblings into the statistical analysis of association. For the PDT, a measure of linkage disequilibrium is defined for each triad and each discordant sib pair within a pedigree, and an average is determined for each pedigree. The difference in what is considered the fundamental unit for each test (heterozygous parents for TDT, triads and discordant sib pairs for the PDT) can also lead to differences in the test statistics. For example, in the case of triads with two heterozygous parents, the test statistic for the TDT can be double that of the PDT in the situation where the allelic transmission of the two heterozygous parents is concordant (Martin et al. 2000). We assume that Syn2 is a susceptibility gene that is neither necessary nor sufficient for the development of SZ. Individuals inheriting certain alleles of this gene are at increased risk for developing the SZ phenotype. Environmental factors or susceptibility alleles at other genes may also be required before a sufficient threshold is reached for the phenotype to manifest, resulting in apparent reduced penetrance of the Syn2 disease-associated allele. The use of risk allele carriers who do not manifest the illness by the PDT-based tests, but not the TDT-based test, could also contribute to a weaker association result for the PDT in situations with greatly reduced penetrance. While TRANSMIT appears to have greater

power to detect the association present between Syn2 and SZ in this sample, small p-values generated by this program must be evaluated with great caution due to the anticonservative nature of the internal bootstrap procedure.

Overall, 11 markers were tested for association. Given the strong marker to marker association in this region, considering these as 11 independent tests would be overly conservative. While it unclear if the PDTPHASED results would reach significance if corrected for multiple testing, our simulations do indicate that the TRANSMIT results are significant. Applying the overly conservative Bonferroni correction would require a p-value of 0.0045 to reach study-wide significance. Our simulation results suggest that to obtain an empiric TRANSMIT p-value of 0.005 would require a nominal p-value of 0.00001. Thus even with a Bonferroni correction, the Block 2 nominal p-value of 0.0000005 would reach study-wide significance.

Haplotype analysis demonstrated that simply combining all markers with evidence of association under the single marker tests was not helpful in identifying a haplotype that is likely to harbor SZ associated polymorphism within the Syn2 gene. One explanation could be that the associated SNPs are in LD with more than one susceptibility allele, so combining them all into a single analysis with markers spanning over 90 kb was not beneficial. Most of the associated SNP makers were located in introns 5 and 6 which are known for their evolutionary conservation due to the presence of the TIMP4 gene in intron 6 of Syn2. A positional haplotype analysis approach that densely covered a 14.4 kb interval from this area identified seven haplotypes consisting of markers from introns

5 and 6 of Syn2, with one of these haplotypes significantly overtransmitted to affected individuals.

Although the majority of the SZ associated SNPs and haplotypes within the Syn2 gene fall into the area of the TIMP4 gene, TIMP4 seems to be an unlikely functional candidate for SZ. The expression profile of the TIMP family is diverse and includes multiple tissues, including the central nervous system. The literature on this family is limited, and fails to report a significant association of TIMP genes with SZ on genetic or functional levels (Hung et al. 2001). Moreover, the review of the clinical manifestations caused by alterations within the TIMP family (TIMP1 [OMIM305370], TIMP2 [OMIM188825], TIMP3 [OMIM188826], TIMP4 [OMIM601915]) reveals a single established human phenotype, Sorsby fundus dystrophy, that does not resemble SZ or any other psychotic illnesses. However, TIMP4 cannot be ruled out as a susceptibility gene on the basis of our association data. The nested relationship of the TIMP and synapsin family members will likely necessitate a functional approach to differentiate the possible role of Syn2 and TIMP4 in the etiology of SZ.

This sample represents the first population of Northern European descent to exhibit an association between Syn2 and SZ. Recently, evidence of SZ associated polymorphisms in case-control and family based studies were found in the Han Chinese (Chen et al. 2004a; Chen et al. 2004b) and Korean (Lee et al. 2005) populations. Further association studies may provide a more precise location of the SZ associated polymorphism(s) within the Syn2 gene. Functional studies of polymorphisms identified through association

studies should aid in the identification of the SZ risk-allele within this region.

Interestingly, samples from both Northern European descent (Brzustowicz et al. 2004) and Han Chinese (Zheng et al. 2005) populations have also demonstrated association between SZ and NOS1AP, a gene that is functionally linked with Syn2 (Jaffrey et al. 2002). A combined influence of NOS1AP and Syn2 on SZ susceptibility is plausible and warrants further investigation.

## **Chapter 4. Bayesian reanalysis of NIMH Chinese genome screen reveals multiple novel schizophrenia and affective illnesses susceptibility loci**

### **4.1 Introduction**

The linkage and association studies of large cohorts aimed at identifying SZ susceptibility loci demonstrated the difficulties for reaching significant results and consistent failures to replicate previously identified significant findings in smaller cohorts. Such studies involve in a collection of large samples and usually demand collaborative efforts by multiple research groups. However, differences may exist between the subsets of large cohorts recruited at different diagnostic centers, that include, but no limited to, ethnic heterogeneity and diagnostic discrepancies at the different medical sites (Brzustowicz 2007). Simulation studies further demonstrate that big cohorts pooled from multiple sites result in a decreased power to detect linkage if variations in diagnostic procedures across the recruitment cites or other clinical differences across subsets exist (Huang and Vieland 2001; Vieland et al. 2001).

An example of a reduced power to detect linkage in a large SZ cohort was recently demonstrated in a genome scan performed on a cohort of 606 Han Chinese families (Faraone et al. 2006). The authors presented evidence of suggestive linkage to chromosome 10q22.3 with a nonparametric LOD score of 2.88 that was the largest reported LOD in this study. After review of the study we have identified several issues

that may have contributed to the low power to detect linkage. Firstly, the available clinical data demonstrate quite an extensive clinical heterogeneity expressed as heavy comorbidity with SZ, that included multiple cases of substance abuse, presence of affective disorders, organic mental syndromes, and non-DSM-IV defined culturally related psychopathology with unknown effects on SZ diagnostic precision. Also, the further diagnostic reliability comes under question considering the limited experience of the interviewers who were college graduates majoring in psychology and psychiatric nursing. Limited quality control of the genotype data, which included only the Mendelian inconsistency analysis provided further opportunity to refine the linkage signal in this sample. Marshfield maps utilized for the linkage analysis in this study were not suitable for a Han Chinese ancestry sample, as the available public databases, including Marshfield, commonly provide map distances evaluated in Caucasian populations only. Nonparametric linkage analysis employed by the authors is also proven to be of the limited power, comparing to a parametric one (Goldgar 2001).

We have performed the reanalysis of evidence for linkage in the same Han Chinese sample trying to address at least some of the issues that may have contributed to the low power in the original report (Faraone et al. 2006). We have reviewed all of the available clinical data and tried to identify the situations that may have presented a diagnostic challenge. We have redefined the phenotypes of the subjects with heavy comorbidity, including those that abuse drugs, other than alcohol and nicotine, organic mental syndromes, and uncertain diagnostic codes not observed in DSM-IV. Further, we believe that milder forms of psychosis seen in SZ-related personality disorders, like schizotypal



personality disorder, might have presented a challenge to non-psychiatrists with a limited experience in differential diagnosis between SZ, personality disorders, and other psychopathology (Jane et al. 2006; Lindsay et al. 2007). Subjects with cluster A personality disorders were removed from the pool of affected and non-affected individuals, and their phenotypes were redefined to unknown. The presence of affective diseases within the sample provided further evidence of potentially undesirable clinical heterogeneity, thus the families with subjects affected by SAD and BPD were separated into a heterogeneous subgroup. We also have estimated the sample specific genetic map distances between the genotyping markers to reduce the inflation or deflation of linkage evidence in this cohort. Quality controls procedures were employed to detect the likely errors in the data otherwise not seen with a Mendelian inconsistency checks only.

We decided to assess the evidence for or against linkage to SZ in this sample with a newly developed Bayesian method of posterior probability of linkage, or PPL (Vieland 1998). Studies demonstrate several advantages of PPL as compared to the traditional p-value or LOD score statistics. PPL is virtually “model-free”, as it does not require the user to predefine a genetic model of the studied phenotype, but instead scans through a network of feasible model parameters that include the disease gene allele frequencies, penetrance values for disease allele homozygotes and heterozygotes, and heterogeneity values integrating those trait parameters out of the final result instead of maximizing over them. However, since this statistics is based on likelihood, any kind of pedigree structure can be used in the analysis. Since a low prior probability is incorporated in the analysis, posterior probabilities from one data set can be introduced as priors when analyzing

another set of families, accumulating evidence for and against linkage across multiple subsets of data virtually without penalties for heterogeneity across subsets and without a need for post-hoc adjustments to the significance level. This process is known as Bayesian sequential updating. As described in this chapter, the PPL method can be used for a multipoint analysis, but was also developed for the analysis of quantitative traits, LD mapping, and evaluation of interaction between the causative genes. Another advantage of PPL analysis is an ease of interpretation of the output values. Probabilities, which range from a scale of 0 to 100%, can be interpreted as strength of a belief, in this case a belief that a particular chromosomal region is linked or not linked to SZ. 0% probability implies an impossibility of the underlying hypothesis, and 100% probability refers to a definite certainty. Thus PPL provides an effective scale for linkage measure with two set reference points, which exhibits more characteristics of monotonicity than either p-values or LOD scores. Because of the direct measure of evidence of linkage, PPL is not reported within a predefined concept of significance and therefore it does not require replication and is easier to interpret in the settings of multiple tests. PPL is performed via KELVIN software named after Baron Kelvin William Thomson (1824-1907), an author of an absolute temperature scale. Further theoretical details and practical application of PPL can be found in the following references (Elston and Lange 1975; Vieland 1998; Wang et al. 1999; Wang et al. 2000; Vieland et al. 2001; Logue et al. 2003; Logue et al. 2006; Vieland 2006; Govil and Vieland 2008).

## 4.2 Methods

### 4.2.1 Subjects and phenotypes

Genotypes and diagnostic data for families of Han Chinese ancestry were obtained from the NIMH Genetic Initiative. A detailed description of diagnostic methods and genotyping procedures is provided by Faraone et al., 2006. Firstly, we reviewed the available clinical information for each subject in the study and assigned a phenotypically unknown status to the subjects with organic mental syndromes, mental retardation, active substance dependence other than nicotine or alcohol. Overall, some 28 nuclear families were removed from further PPL analysis, where subjects affected with SZ had one or more of the listed comorbid conditions; however, those families were utilized for marker to marker genetic map distance and allele frequency estimations. Furthermore, upon review of the remaining psychiatric nosology, we identified 20 families where, in addition to probands with SZ, subjects with SAD and BPD were present. To reduce the impact of clinical and, hopefully, genetic heterogeneity, we separated these 20 families into a “heterogeneous” (HET) subgroup to be analyzed with PPL independently from a “schizophrenia” (SZ) subgroup, in which all of the affected subjects suffer from SZ exclusively. As a result, the SZ subgroup for the PPL analysis comprised 558 two-generation families with 2,530 individuals (1,116 founders, 1,067 females) with an average family size of 4.53, and the HET subgroup consisted of 20 two-generation families with 92 individuals (40 founders, 48 females) and an average family size of 4.6 as reported by PEDSTATS (Wigginton and Abecasis 2005). Genotypes were available for 2,224 individuals (821 founders, 964 females) in SZ subgroup, and 80 individuals (29 founders, 44 females) in the HET subgroup.

A hierarchy of phenotypic classifications comprising all of the observed major psychotic illnesses was constructed, ranging from a narrow definition of illness, through a continuum of schizoaffective manifestations, both depressive and manic, to the BPD as the broadest psycho-affective entity, focusing on only the most clinically conspicuous psychotic embodiments. In detail, all of the subjects with schizotypal and paranoid personality disorders, non-specified psychosis and subjects with delusional disorder were assigned an unknown phenotype. For phenotype 1, all of the subjects with DSM-IV defined SZ were assigned an affected status. Additional three phenotypes were applied to the HET subgroup: phenotype 2a included as affecteds those subjects with SAD (manic and depressive subtypes), phenotype 2B included those with schizoaffective disorder depressive type (SADD) only, and phenotype 3 included subjects with all three psycho-affective spectrum nosologies: SZ, SAD, and BPD. In total, the SZ subgroup included 1,160 affected and 930 unaffected subjects with an additional 440 individuals having an unknown phenotypic status. In the HET subgroup, we observed 31 unaffected subjects under all phenotypic categories; with 28 affected individuals under phenotype 1, 42 affecteds under phenotype 2a, 34 and 47 affecteds under phenotypes 2b and 3, respectively. SADD was seen in 6 subjects, SAD bipolar (SADB) or SAD unspecified type in 8 subjects, and BPD in 5 subjects.

#### **4.2.2 Genotypes quality control and sample-specific genetic maps**

Both genotyping errors (Mitchell et al. 2003) and imprecise estimates of map distances (Daw et al. 2000) negatively influence linkage analysis. For this reason, we conducted a

chain of analyses to minimize these undesirable confounding factors. First, we used PEDCHECK to confirm the absence of the Mendelian inconsistencies in the data (O'Connell and Weeks 1998). Then, we estimated the allelic frequencies for all of the available microsatellite markers with MENDEL (Lange et al. 1988; Lange et al. 2005). KELVIN's mapping function was utilized for the marker to marker map distance estimation to construct the sample specific genetic map using the entire available sample of 606 families. Further, the genotyping error probabilities were estimated with three runs of SIMWALK2 v2.91 (Sobel and Lange 1996; Sobel et al. 2001; Sobel et al. 2002) under different starting random seeds. 927 genotypes (0.11%) demonstrated a consistent probability of error of 25% or higher and were removed from the PPL analysis, leaving 786,105 genotypes in SZ subgroup, and 28,813 genotypes in HET subgroup, distributed over 375 microsatellite markers. Finally, the allele frequencies and mapping positions were reevaluated on the entire cleaned data with MENDEL and KELVIN, respectively.

#### **4.2.3 PPL analysis and sequential updating**

The linkage of genomic regions to SZ phenotypes was evaluated using the Bayesian statistics implemented in PPL analysis and delivered via KELVIN software which assumes a prior probability of linkage at 2% (Elston and Lange 1975). The genetic model space was restricted by assigning the disease allele frequency discrete values (0.001, 0.01, 0.1, 0.3, 0.5, and 0.8), setting the penetrance values at homozygous and heterozygous disease marker genotypes (ranging from 0 to 0.9 with a 0.1 increment at each step and 0.999 as a final value), and assigning heterogeneity  $\alpha$  values (ranging from 0.05 to 1.0 at 0.05 increment at each step). The genome was analyzed at 1 cM resolution

utilizing each phenotype against the three closest microsatellites along chromosomes, with 10 cM flanking each of 44 telomeric markers. The posterior probabilities reported by KELVIN serve as predictive measures of accumulated evidence for and against linkage at each genomic position and are expressed numerically as an average over the entire genetic model space without maximization. Bayesian sequential updating of the results allowed the further refinement of evidence derived from different subgroups (Govil and Vieland 2008). Overall, 3,778 autosomal genomic positions were separately evaluated for PPL in the SZ and HET subgroups and then sequentially updated; in addition, evaluation was performed in the pooled sample (SZ and HET subgroups together, 578 families) to compare the results with the sequentially updated values at the points of interest. The computational details of PPL are described elsewhere (Vieland 1998; Wang et al. 1999; Wang et al. 2000; Vieland et al. 2001; Logue et al. 2003).

### **4.3 Results**

Table 11 demonstrates the number of PPL values exceeding or equaling a series of thresholds in each analyzed subsample (SZ and HET) and the sequentially updated data under each phenotype definition.

In the SZ subgroup, 84.2% of the autosomal genome demonstrated an absence of or negative evidence for linkage (PPL of  $\leq 2\%$ ); in the HET subgroup, depending on phenotype definition, 59.2-72.8% of the genome is not linked to any studied phenotypic marker.

Our preliminary simulation studies utilizing PPL suggest that a PPL of 10% is a rare event, occurring approximately 0.6% of the time when non-linked data is analyzed.

Therefore we set a 10% threshold as a value worthy attention.

Analyzed under a single phenotype definition (phenotype 1), the SZ subgroup produced 43 PPL values over or equal to 10%, forming four discernable peaks in the autosomal genome. Chromosome 10q22.3-q22.31 revealed the highest PPL value for the SZ subgroup, which reaches 32.1% at a genetic position of 107 cM between markers

Table 11. Number of PPL above or equal to 2%, 10%, 20%, and 30% under each phenotype definition

Sample	SZ	HET				Sequential Update			
Phenotype	P1	P1	P2A	P2B	P3	P1	P2A	P2B	P3
PPL $\geq$ 0.02	598	1524	1159	1376	1026	752	715	701	669
PPL $\geq$ 0.1	43	0	13	0	26	48	48	42	61
PPL $\geq$ 0.2	11	0	0	0	12	11	11	11	22
PPL $\geq$ 0.3	1	0	0	0	2	1	1	2	3

D10S2327 (101 cM) and D10S2470 (113.55 cM). Distal to this, on chromosomal region 10q26.12-q26.13, is another peak that reaches 16.7% at the position of 152 cM, between D10S1230 (148.71 cM) and D10S1656 (155.86 cM). Chromosome 10q22.3-q22.31 corresponds to the largest non-parametric z score of 2.88 for marker D10S2327 in the original genome scan, however the finding on 10q26.12-q26.13 is barely discernable

from the noise in the original report (Faraone et al. 2006). Little or no evidence of linkage to chromosome 10 is derived from the HET subgroup. When updated sequentially, the 10q22.3-q22.31 peak is preserved with only a slight increase in PPL to 33.8% at 107 cM under phenotype 2b, when SZ and SADD patients are considered to be affected. Pooled results in this area stand at 35.8% at the same location and phenotype definition and are closely matching the sequentially updated results. For 10q26.12-q26.13, the maximum PPL value of 19.4% comes from 152 cM region under phenotype 1, where only subjects with SZ are considered affected, but not BPD or SAD patients. If sequential updating is used to evaluate the data in the region, the PPL finding stands at 16.5% under the same phenotype and at the same location. Figure 1 and 2 demonstrate the chromosome 10 results in the SZ, HET, pooled samples and upon the sequential update over SZ and HET subgroups for phenotypes 1 (SZ) and 2b (SZ and SADD), respectively.

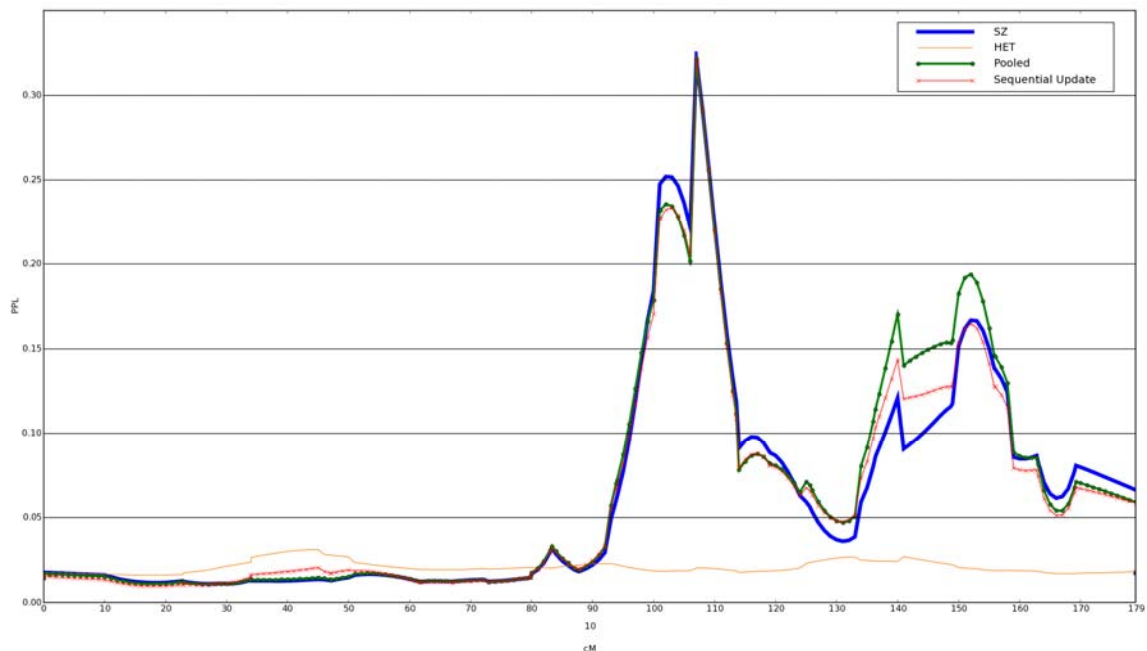


Figure 1. Chromosome 10 PPL scan results, phenotype 1



In the SZ subgroup, a peak with a maximum PPL value of 11.6% is observed over D13S793 (85.42 cM) located at 13q32.1. Sequentially updated and pooled PPL results are comparable in this area and stand at 11.5% and 11.6%, respectively. Chromosome 13 findings for phenotype 1 in the SZ and HET subgroups as well as sequentially updated are demonstrated in Figure 3. This is a novel finding in this sample since no distinguishable peak is observed in the original report (Faraone et al. 2006).

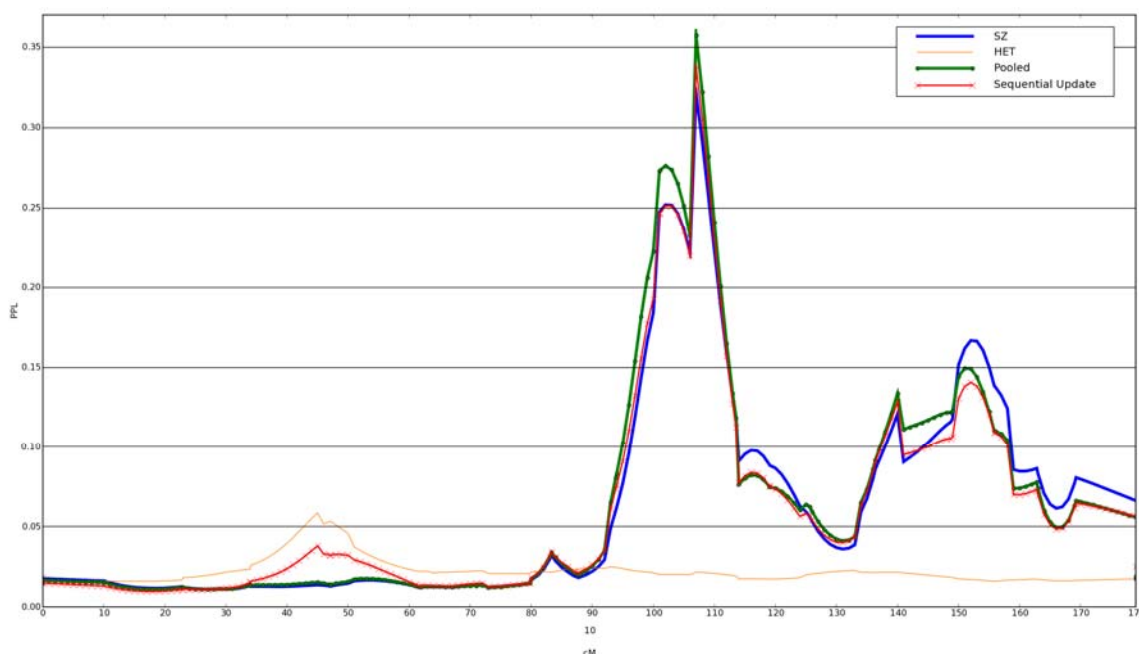


Figure 2. Chromosome 10 PPL scan results, phenotype 2b

Comparable in magnitude finding was seen on 19q13.33 over D19S246 (68.82 cM) with PPL of 11.9% in SZ subgroup. Little evidence for linkage comes from the HET subgroup in this region (max PPL of 2.25% is seen over the 68.12-71 cM area under phenotype 3); however, the results of sequential updating are comparable with pooled sample analysis and stand at 13.2% and 14.7%, respectively, at the same location with phenotype 3 (SZ, SAD, BPD) providing the strongest support. Figure 4 depicts the PPL results on

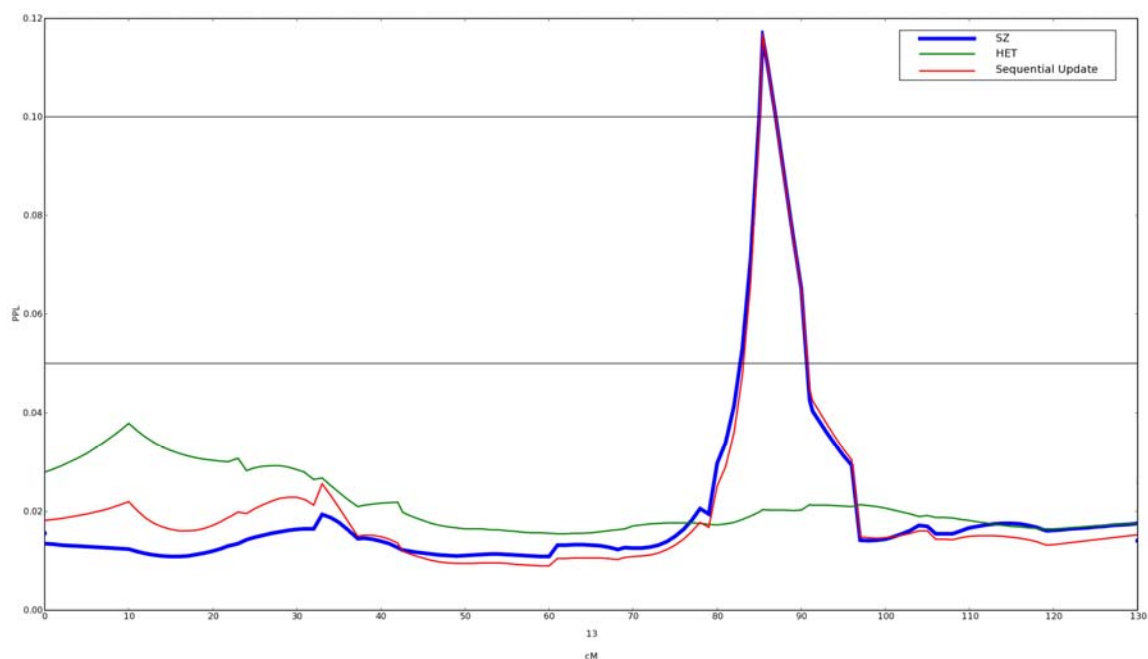


Figure 3. Chromosome 13 PPL scan results, phenotype 1

Comparable in magnitude finding was seen on 19q13.33 over D19S246 (68.82 cM) with PPL of 11.9% in SZ subgroup. Little evidence for linkage comes from the HET subgroup in this region (max PPL of 2.25% is seen over the 68.12-71 cM area under phenotype 3); however, the results of sequential updating are comparable with pooled sample analysis and stand at 13.2% and 14.7%, respectively, at the same location with phenotype 3 (SZ, SAD, BPD) providing the strongest support. Figure 4 depicts the PPL results on chromosome 19 in the SZ, HET samples and upon the sequential update.

Despite its small cohort size, the HET subgroup demonstrates the second most noticeable peak in this study on chromosome 3q29. Interestingly, the entire magnitude of the reported PPL value of 30.5% in the HET sample and in the sequentially updated results

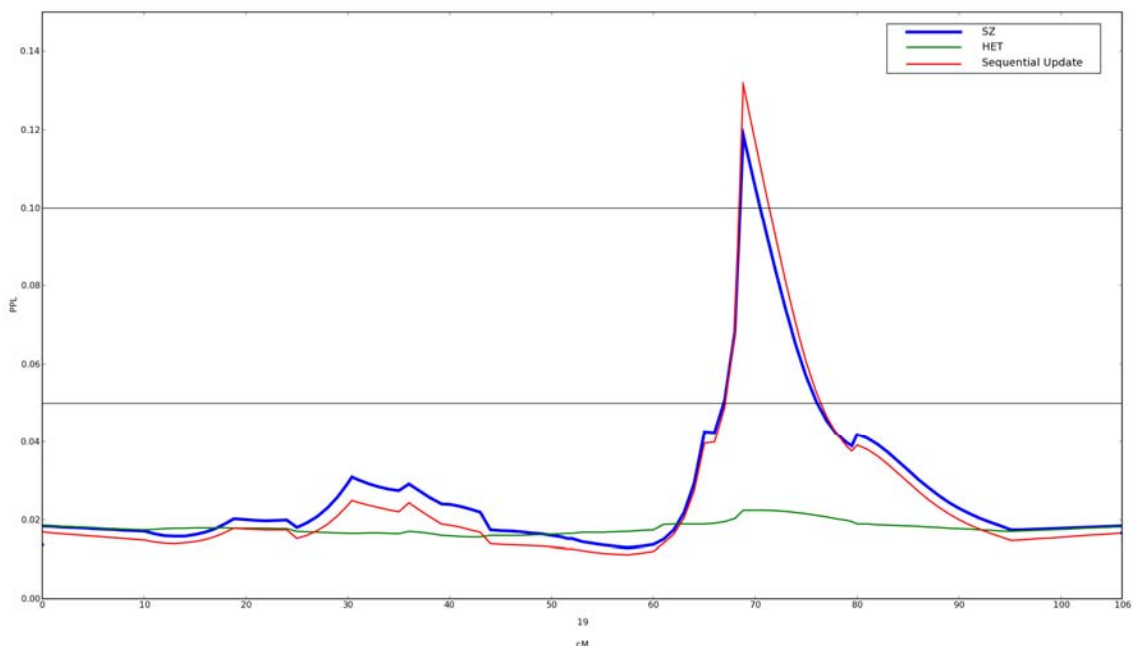


Figure 4. Chromosome 19 PPL scan results, phenotype 3

comes exclusively from the HET subsample, particularly when the phenotype 3 definition is used. As the proportion of affected subjects with affective issues increases within the presented psychotic-affective phenotype framework, the more evidently is linkage observed in the sample. Data fail to demonstrate any salient linkage when only SZ subjects are being considered affected – a maximum PPL of only 2.12% is observed under phenotype 1 in the HET subsample. As schizoaffective conditions being included into the phenotypic definitions, the evidence of linkage within the data initially increases only minimally when only the subjects with SADD were being included under phenotype 2b. Further, as patients with SADB switch their status from unknown to affected under phenotype 2A, the PPL vaults to 12.8% in the HET sample alone. With BPD included into the search for genes involved in psychosis across the psychotic-affective spectrum illnesses under phenotype 3, the PPL value reaches 30.5%. Pooled sample analysis fails

to provide any distinguishable results in this sample, demonstrating that smaller subsets stratified on the basis of clinical presentation can be more powerful in detecting linkage rather than larger cohorts where genetic heterogeneity becomes more apparent in multifactorial settings (Brzustowicz 2007). The most distal marker on chromosome 3, D3S1311 (204.01 cM), is the site of the second largest peak in this study. Figure 5 demonstrates the results for chromosome 3 in the SZ, HET, pooled samples and after sequential update over SZ and HET subgroups under the phenotype 3 definition (SZ, SAD, BPD).

Smaller peaks were seen in three additional areas of the human genome in this study; however they fail to reach an interesting threshold of 10% in the sequentially updated or pooled data. Particularly, chromosomal region 2q14.1 demonstrates a 9.6% chance of

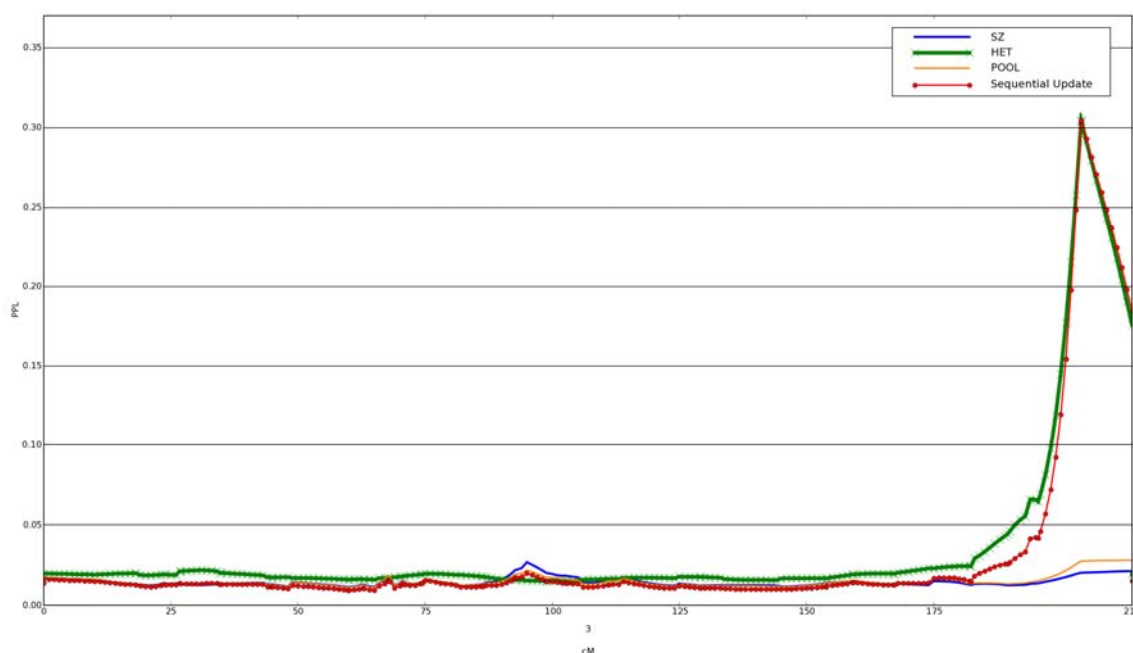


Figure 5. Chromosome 3 PPL scan results, phenotype 3

harboring a SZ gene, as seen in the SZ subsample. The HET subgroup provides only evidence against linkage, with the PPL values falling below the 2% prior probability value under every tested phenotypic definition. In the entire sample, the evidence for linkage stands at 6.6% when the subgroups are pooled and at 7.5% if they are sequentially updated. This peak was noted in the original linkage scan performed on this dataset with a non-parametric z score reaching a suggestive value of 2.31 at marker D2S410.

Moreover, two peaks just above the 10% threshold are seen on 5q22.1-q23.1 and 14q21.1-14q22.2 in the HET subgroup; however the SZ subsamples provide no data in support of linkage in these areas and, therefore, no discernable signal in the pooled sample is observed. Chromosome 5q22.1-q23.1 demonstrates a PPL value of 12.27% in the HET and 5.8% in sequentially updated data under phenotype definition 3 at the position of 116 cM, between markers D5S2501 (111.93 cM) and D5S1505 (119.45 cM). These results are less prominent under phenotype 2A (10%), and fall below 5% under phenotypic definitions that are absent of mania manifesting illnesses (phenotype 1). On 14q21.1-14q22.2, it is the combination of SZ, SADD, and SADB that accounts for a signal of 10.11% in the HET subgroup (phenotype 2A), with a PPL below 5% if only subjects with SZ (phenotype 1) or opposite, subjects with SZ, SAD, and BPD (phenotype 3) are considered as affected. The largest observed PPL value comes from the 44 cM position, between loci D14S306 (35.55 cM) and D14S587 (46.84 cM) in the HET subgroup, that translates into a modest PPL of 6.5% after sequential updating over marker D14S587 using the phenotype 2A definition.

Figures 6-9 provide the graphs for the PPL autosomal genome scan in the HET and SZ subgroups under all of the tested phenotypic classifications as well as the sequentially updated results. Pooled results are not shown on the graphs, since they closely mimic the results of the sequential updating, with the exception of the areas mentioned above.

Appendix 1 table provides detailed results for all of the 3,788 chromosomal positions under all of the phenotypic definitions used in the study in the SZ and HET subgroups, pooled sample, and the results of sequential updating. Table in appendix 2 displays the sample specific genetic maps calculated with KELVIN.

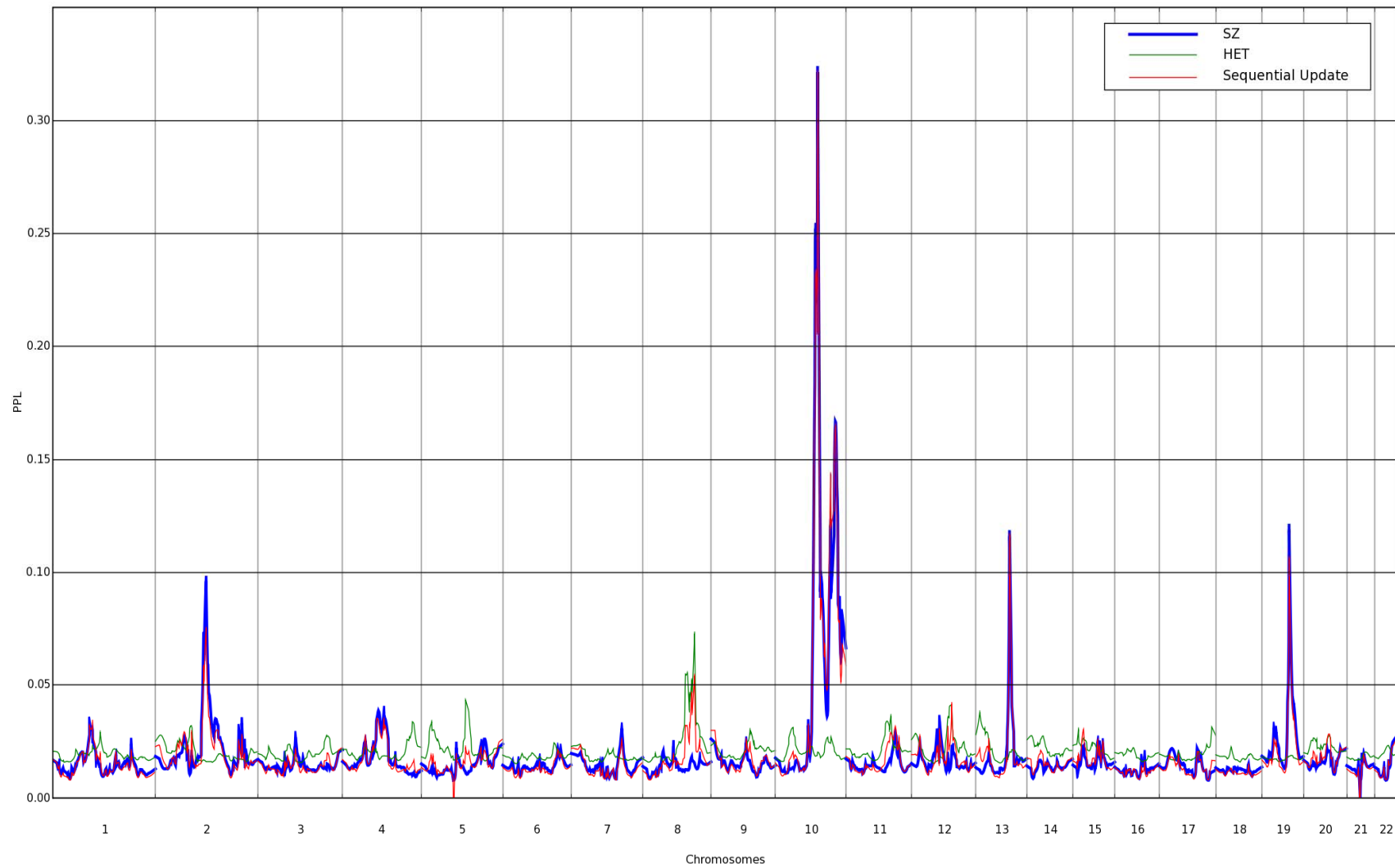


Figure 6. PPL genome scan results, phenotype 1

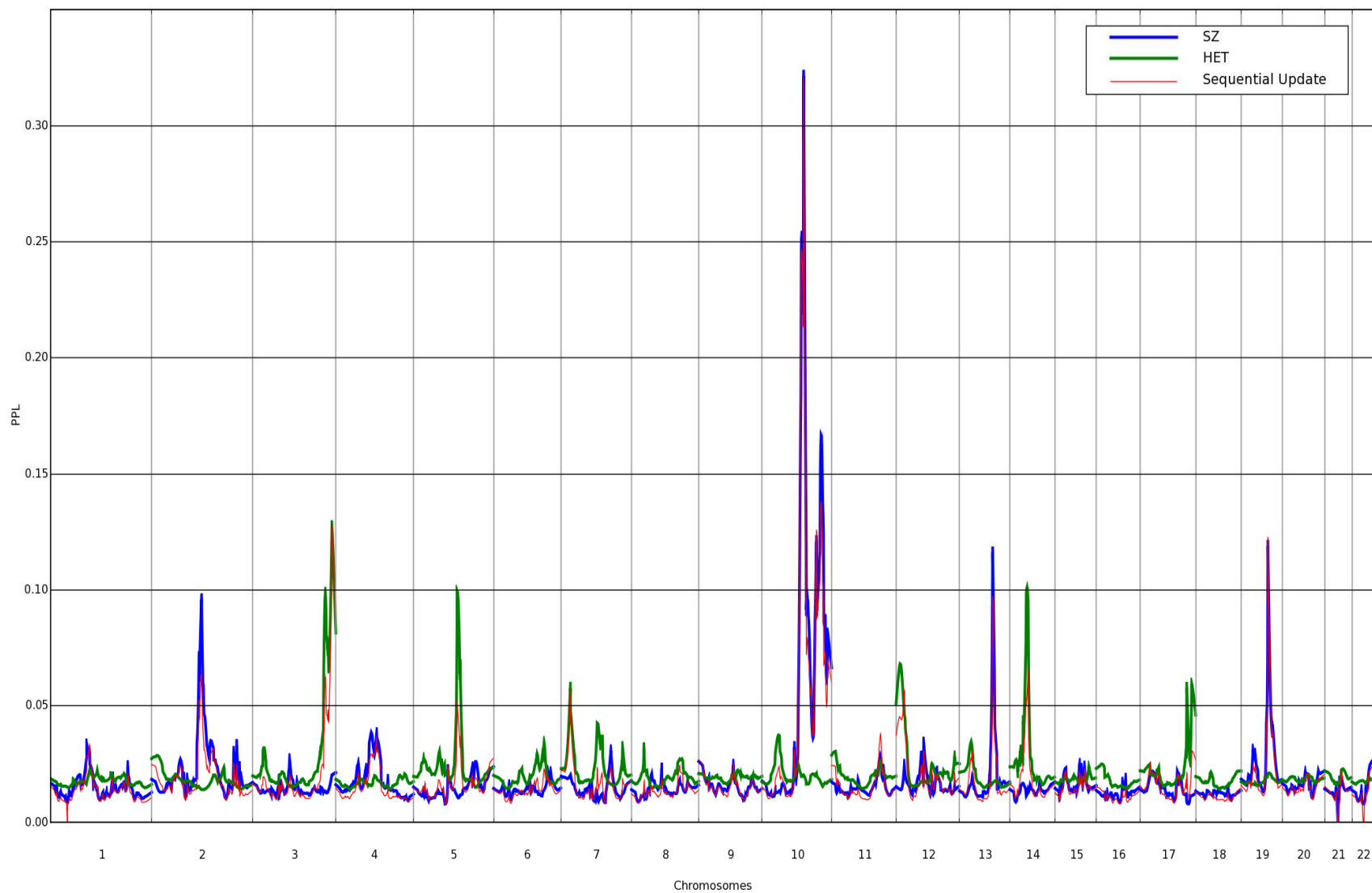


Figure 7. PPL genome scan results, phenotype 2a



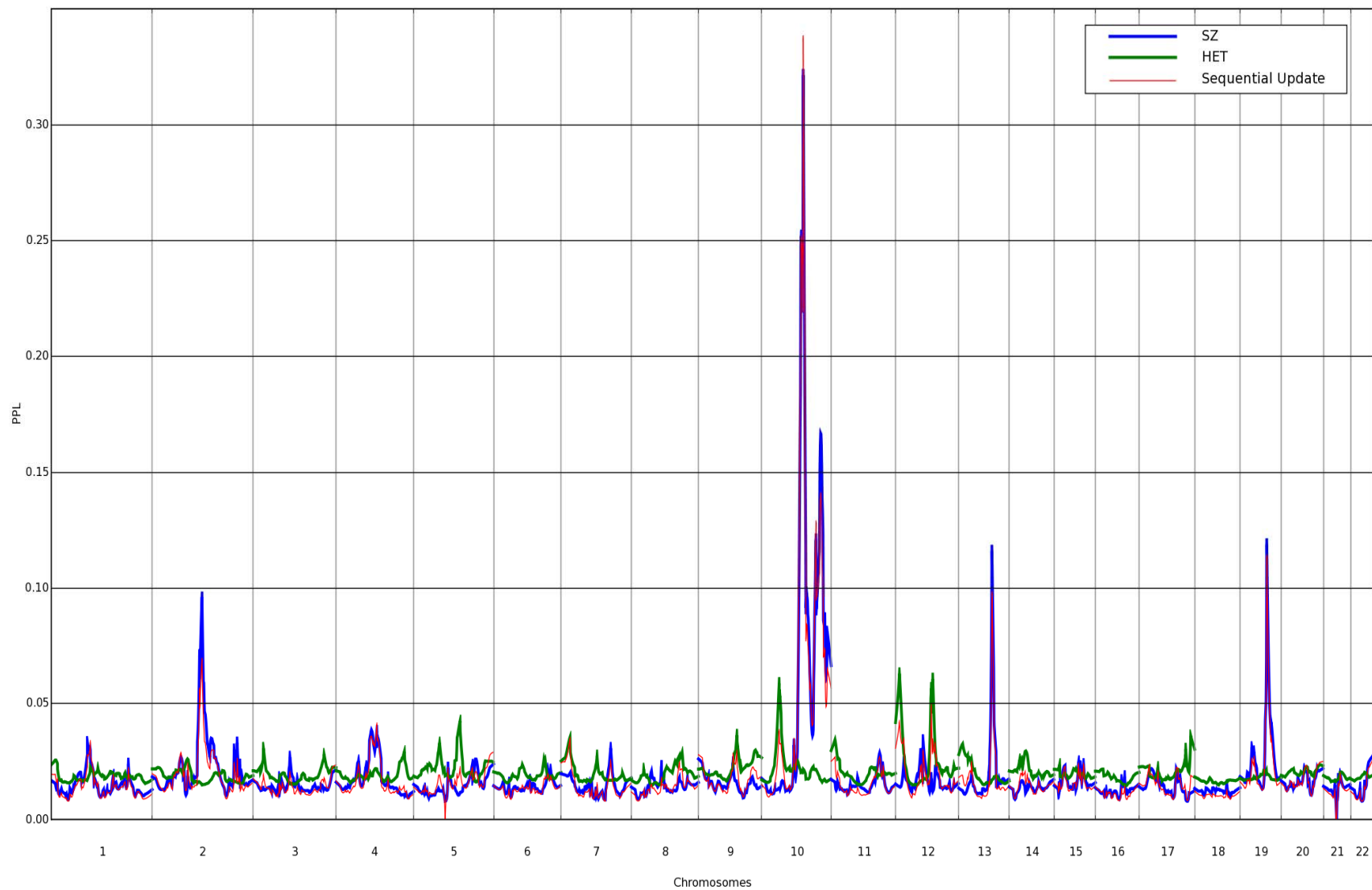


Figure 8. PPL genome scan results, phenotype 2b

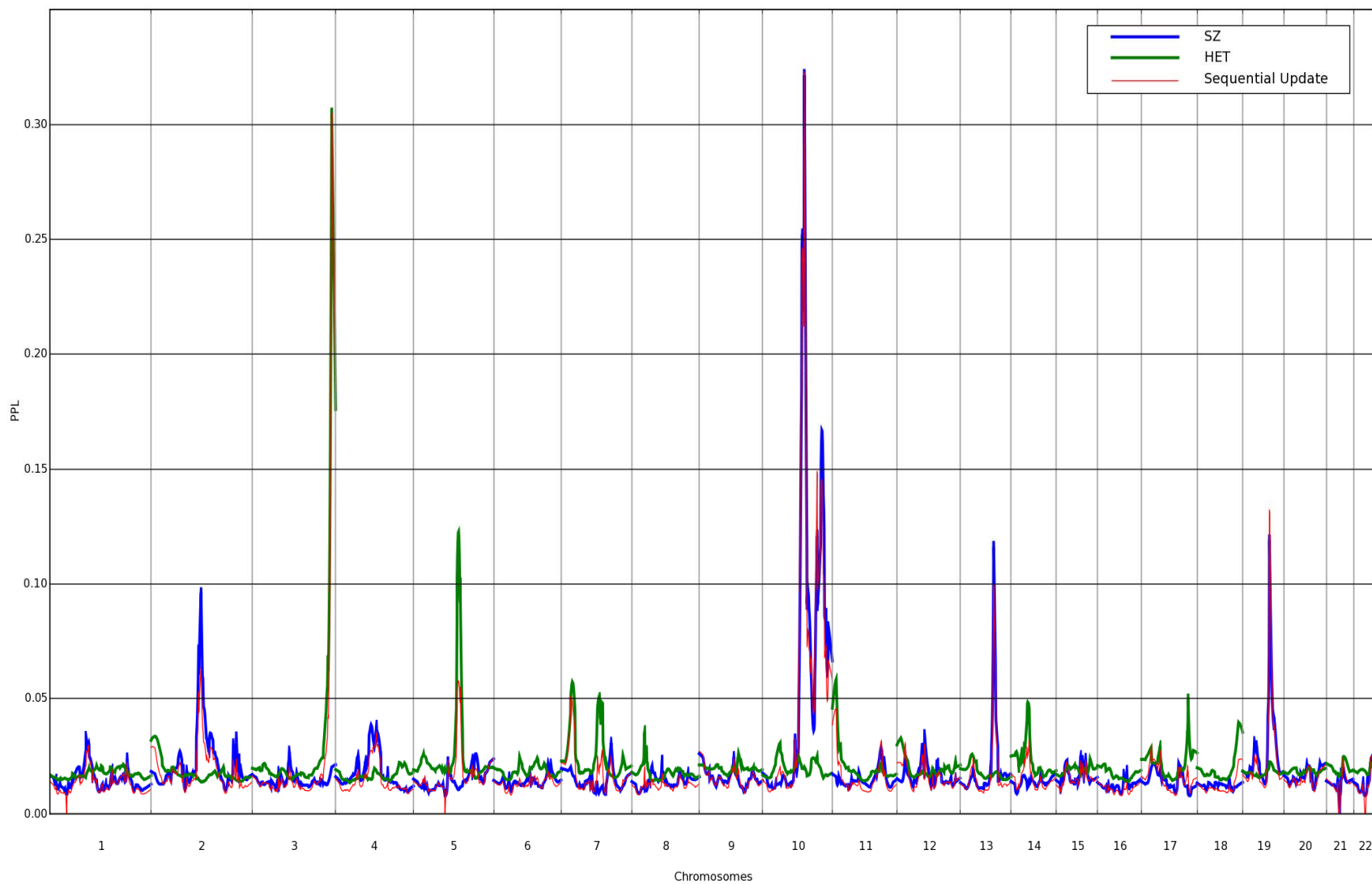


Figure 9. PPL genome scan results, phenotype 3

## 4.4 Discussion

The goal of this research was to reevaluate the evidence of linkage to SZ phenotypes in a large Chinese sample offered through the NIMH SZ Genetics Initiative. The review of clinical data revealed several potential problems within the pedigree sample. We observed the presence of psychopathologies that potentially could have influenced the ability to definitely distinguish SZ from other related disorders possibly resulting in an unnecessary increase in phenocopy and heterogeneity rates. For this reason, we redefined as “unknown” the phenotypic status of those individuals who, besides a diagnosis of SZ, SADD, SADB, or BPD, were also reported as suffering from mental retardation, unspecified substance abuse, non-specified psychosis, or an unspecified psychopathology. After the exclusion of 28 families that had no remaining affected individuals due to phenotype changes to unknown, we obtained a sample of 578 families suitable for linkage analysis; the small group of 28 genotyped pedigrees were utilized for allele frequency and genetic map distance estimation, but not for the PPL analysis. Furthermore, a group of 20 families appeared to be clinically distinguishable from the rest of the group due to presence of individuals with SAD and BPD along with the subjects with SZ. Genetic and neuroimaging studies suggest a genetic overlap between SZ and BPD, and SAD is argued to be an intermediate phenotypic expression between the two nosologies (Kempf et al. 2005; Lake and Hurwitz 2007). However, linkage and association studies suggest that there may be a group of genes that predispose one to a classic schizophrenic psychosis that is different from a group of genes predisposing to both SZ and a mood disturbance with psychotic features (Craddock et al. 2005). To address this issue and provide an opportunity to evaluate the linkage signals for both

groups of genes, these 20 families were segregated into a heterogeneous HET subgroup. Fortunately, PPL analysis allows for such heterogeneity within a subset and differences across subsets without loss of power (Vieland 1998). Moreover, subsetting into smaller groups may be superior to analysis of larger cohorts when multifactorial phenotypes are being studied (Brzustowicz 2007).

It is known that the genetic distances between markers in the human genome vary considerably between the sexes (Robinson 1996; Barlow and Hulten 1998; Barlow et al. 2002; Tease et al. 2002) as well as between individual male (Yu et al. 1996) and female humans (Broman et al. 1998; Kong et al. 2002). It has also been shown that the rates of recombinations are different across ethnic groups (Jorgenson et al. 2005). Such differences result in the misspecification of map intervals if genetic maps constructed for one ethnicity are used for multipoint linkage analysis in a sample belonging to another ethnic group. Genetic map misspecifications may result in a bias of LOD scores in multipoint linkage analysis with a corresponding loss of power in the presence of linkage, and also result in a potentially larger negative or positive bias when linkage is absent. Moreover, an underestimation of map distance biases the LOD score downward and an overestimation of map distance biases the LOD score upward (Daw et al. 2000). Using the genotyping information for the entire sample of 606 families, we estimated the sex-averaged sample-specific recombination functions  $\theta$  for 22 autosomes. These fractions were converted to the Kosambi centimorgan (cM) map positions for each marker and were utilized in Simwalk2 runs to evaluate the probabilities of erroneous genotypes and

also for the PPL analysis. The values for the estimated map distances can be found in appendix 2.

The two peaks that highlight the areas with the most substantial evidence for linkage to SZ phenotypes are located on chromosomes 10q22.3-q22.31 and 3q29 and reach maximal posterior probabilities of 32.1% and 30.5%, respectively. The 10q22.3-q22.31 peak has been identified in the original genome scan for SZ in this sample and reached the highest, though non-significant, non-parametric linkage z score of 2.88 (Faraone et al. 2006). Previously, a maximum non-parametric linkage score of 4.27 was identified between markers D10S1677 and D10S1753, aligning to the same genomic area on 10q22.3-10q23.31, in an Ashkenazi Jewish cohort, consisting of 29 multiplex families with 83% of affected subjects suffering from SZ and 17% from SAD (Fallin et al. 2003). Furthermore, this region was also recently implicated in susceptibility to bipolar disorder in Ashkenazi Jewish pedigrees (Venken et al. 2008). Meta-analysis of linkage studies of BPD also points to the nearby region of 10q11.21 as a place that ranked second in the genome to most likely harbor a susceptibility gene when investigated against a “very narrow” phenotypic definition that included BPD I and SADB (Segurado et al. 2003). Recently, the GRID1 gene (OMIM: 610659) on 10q23.1-q23.2, that encodes a delta-1- ionotropic glutamate receptor which is a subunit of a glutamate receptor channel that mediates an excitatory synaptic transmission and is involved in synaptic plasticity, has been shown to be associated with SZ in both family-based (Fallin et al. 2005) and case-control studies (Guo et al. 2007). Another candidate gene, NRG3 (OMIM: 605533), Neuregulin 3, on 10q23.1 was reported to be associated with SZ in a case-control study

(Benzel et al. 2007), while also interacting with NRG1 – a well studied potential SZ risk locus (Tosato et al. 2005; Harrison and Law 2006).

Chromosomal region 3q29 yielded a PPL of 30.5% that came exclusively from the HET subgroup. The signal is strongest when the affected population includes subjects with SZ, as well as subjects with both forms of SAD and BPD. In the SZ sample, we do not observe any convincing evidence for linkage in this region. This particular peak clearly demonstrates the advantage of PPL and sequential updating over the traditional methods of linkage analysis: the use of mood disturbances as clinical criteria for sample stratification is superior in handling the sample heterogeneity even if the clinical criterion used may be imperfect (Govil and Vieland 2008). After sequential updating over the SZ and HET subsamples the evidence of linkage remains the same, while pooled sample failed to provide a distinct signal in this area. This, in part, explains the lack of linkage to this 3q29 genomic region in the original report (Faraone et al. 2006). We hypothesize that 3q29 harbors a susceptibility factor that predisposes to both illnesses on the psychosis-mood spectrum, SZ and BPD, as well as to the intermediate nosologies like SADD and SADB. Interestingly, it is a combination of families with subjects affected with SZ, SAD, and BPD that have provided linkage support to this area in the past. The highest reported non-parametric linkage score of 3.74 ( $p=0.0003$ ) and a parametric LOD score of 1.69 were observed with marker D3S1265 in a cohort of eight Austrian families where the affected cases included SZ, SADB, SADB, BPD, and major recurrent depression (Bailer et al. 2002). Furthermore, an NPL score of 4 was obtained in a follow up studies

involving the same pedigrees and additional microsatellite markers (Schosser et al. 2004) and SNPs (Schosser et al. 2007).

Another peak on chromosome 10q26.12-q26.13 reaches 19.4% in the SZ subsample and 16.5% upon sequential updating with the HET subgroup PPL results. This peak is in close proximity to the peak described above at 10q22.3-q22.31 and may have resulted from a statistical artifact that split a single peak in the area into two discernable peaks due to the difference in information content of the underlying genotyping data. However, as seen in appendix 1, we observe a gradual decrease of the 10q22.3 peak as we proceed along the chromosome to PPL values of 3-4% and then a similar monotonic increase without any “jumps” that would indicate that the information content dramatically changes between different markers used in the scan along chromosome 10. Furthermore, a review of the literature suggests that both peaks were seen previously in linkage studies, in addition to less significant peaks in between these two areas of chromosome 10 that may have resulted from overlapping linkage signals that propagated from the surrounding areas of linkage. Compelling evidence of a linked locus on 10q26 comes from a study of genetic isolates from the Russian Northern Caucas province of Dagestan that yielded a significant parametric LOD score of 3.4 under a dominant model of inheritance between markers D10S1213 and D10S1248 (10q26.13-q26.3) (Bulayeva et al. 2007). Phenotypic definitions used in this study concentrate around SZ and SZ-like psychotic conditions and ensure that a significant proportion of subjects lack affective illnesses except for SAD; however the diagnostic system used appears to be different from those commonly utilized in Western psychiatric classifications. Another finding on the chromosomal region

10q26.12-q26.3 came from a relatively isolated population in the Faroe Islands that demonstrated significant haplotype sharing among affected subjects with both SZ and BPD (Ewald et al. 2002). A maximum NPL score of 3.12 ( $p=0.0013$ ) between markers D10S1483 and D10S217 support the notion of a susceptibility locus for bipolar disorder on 10q25-q26 as well (Cichon et al. 2001). “In between” reports demonstrate linkage to 10q24.32 (Levinson et al. 1998) and 10q25.2 (Mowry et al. 2000) as a “broad peak” using non-parametric linkage analysis in 43 Caucasian families ascertained for SZ, as well as to the marker D10S187 (10q25.3) with a NPL of 3.24 ( $p=0.0008$ ) in 21 Arab Israeli families under a broad phenotype definition that included SZ, SAD, schizotypal features, and a few subjects with BPD and major depression with psychotic features (Lerer et al. 2003).

Karyopherin beta-3 (KPNB3), or Ran-binding protein 5 (RANBP5) (OMIM: 602008) is a nuclear transport factor that is involved in the trafficking of ribosomal proteins and has been shown to be associated with SZ in family-based tests of association in British (Wei and Hemmings 2004a) and Chinese trios (Hu et al. 2005; Liu et al. 2007). It may exert its effects through the interaction with another karyopherin KPNA3 (OMIM: 601892) (Zhang et al. 2006), possibly via immunological mechanisms and an involvement of aberrations in influenza or cytomegalovirus life cycles (Carter 2008). RANBP5 is located on 13q32 and appears to be the closest candidate gene to the area on 13q32.1 where we observed a peak of 11.6% within the SZ subgroup that is practically unchanged after sequential updating or in the pooled sample results. DAOA is another candidate that is being studied extensively as a risk locus for both SZ and BPD; however it is located



over 8 Mb telomeric from the peak in our study. Though the limited power of non-parametric linkage analysis conceals this linkage signal in the original report (Faraone et al. 2006), this area appears to provide one of the most convincing demonstrations of a SZ spectrum susceptibility locus in other genome scans (Blouin et al. 1998; Brzustowicz et al. 1999; Brzustowicz et al. 2000; Christian et al. 2002; Faraone et al. 2002; Liu et al. 2003a; Potash et al. 2003; Shaw et al. 2003; Mulle et al. 2005).

Chromosomal region 19q13.33 yielded a PPL score of 11.9% in the SZ subgroup that slightly increases in the pooled sample to 14.7% and 13.2% if the SZ subgroup scores are sequentially updated over the HET subgroup PPL values. As well as the previously discussed peaks, this region has been shown to suggest linkage to SZ spectrum phenotypes. Recently, suggestive evidence of linkage to bipolar disorder was obtained from 10 Belgian multigenerational families of Ashkenazi Jewish ancestry with a heterogeneity LOD score of 2.01 (Venken et al. 2008) and mild evidence of linkage for SZ was seen in pedigrees of Scottish ancestry (Macgregor et al. 2004). A group of several candidate genes in the area demonstrated positive association with SZ, likely due to the linkage disequilibrium across the region. This group includes PLA2G4C (Tao et al. 2005), GRIN2D (Makino et al. 2005), APOE (Harrington et al. 1995; Igata-Yi et al. 1997; Chen et al. 1999; Lee et al. 2001; Liu et al. 2003b), BLOC1S3 (Morris et al. 2008), XRCC1 (Saadat et al. 2008), and NUMBL (Passos Gregorio et al. 2006).

Other smaller peaks reach a value of 10% within the SZ (2q14.1) or HET subgroups (5q22.1-q23.1 and 14q21.1-14q22.2); however the pooled and the sequentially updated

results failed to provide evidence for linkage exceeding 10%. Further PPL genome studies are necessary to enhance or decrease the existing evidence for linkage to SZ spectrum illnesses in these parts of human genome.

We have demonstrated that thoroughly considering clinical information and stratifying large samples into subgroups based on pertinent manifestations of illnesses, making efforts to reduce the phenocopy rates by screening out the subjects/pedigrees with heavy comorbidities, employing a conservative approach to genotyping, utilizing ethnic-specific genetic maps, and using the PPL together provide an excellent approach to evaluate the evidence for and against linkage in the human genome. Using an NIMH SZ Chinese family collection we were able to reveal SZ linked loci that were not evident in the original report where traditional non-parametric analysis was applied (Faraone et al. 2006), but were previously seen in a variety of linkage scans for both SZ and BPD. We demonstrated that sequential updating is a convenient and statistically rigorous way to accumulate the linkage evidence across subsets of families with inter-subset clinical heterogeneity that is not possible with other approaches. Genetic analysis with PPL and sequential updating may provide a useful combination of tools for further research in the field of SZ spectrum diseases, as well as for a variety of illnesses with a multifactorial complex inheritance pattern thus eliminating the need for complicated meta-analysis studies.

## Chapter 5. General discussion

In this dissertation we investigated the associations between the polymorphisms within TNF and Syn2 genes and SZ phenotypes and provided an example of a novel Bayesian method of linkage analysis that offers several advantages over the classic parametric and nonparametric linkage analysis strategies.

Using restriction fragment length polymorphism and pyrosequencing methods, we genotyped two TNF gene promoter SNPs (-G308A, -G238A) and analyzed the haplotype structure in 24 Canadian families of Celtic (23) and German (1) origins. Our results demonstrate that after correction for multiple testing based on simulations of 10,000 replicates of unlinked/unassociated data, there is evidence for association ( $p=0.026$ ) of a specific haplotype (-308A, -238G) with SZ and SZ spectrum disorders with a family-based trimmed haplotype linkage disequilibrium test (Trimhap). Stratifying the 22 families with genome scan data by TNF promoter haplotypes followed by reanalysis of linkage to SZ throughout the genome, we identified few loci that exhibit a considerable increase in LOD/HLOD scores. A locus on chromosome 1q44 (D1S1609) demonstrated a significant increase ( $p=0.025$ ) in LOD score from 0.15 to 3.01 with a broad definition of the SZ phenotype and a dominant mode of inheritance. This result replicates a previously reported positive result of linkage of SZ spectrum disorders to this area of the genome. We also illustrated that simulation studies are necessary in accurately evaluating the significance of results obtained with newer statistical methods, when multiple, but not independent, tests are performed, and when sample stratification is utilized to reduce the impact of heterogeneity or assess the interaction between loci. Another interesting finding

of this study is that despite the subsetting of the original larger sample into two groups defined by the presence or absence of the specific TNF haplotype the linkage signal on 1q22 observed in the original study in this sample (Brzustowicz et al. 2000; Brzustowicz et al. 2002) was found to fall within the subgroup that does segregate the H1 haplotype, without a significant change in LOD/HLOD at D1S1679 and a significant strengthening of the signal at the adjacent D1S1677 marker. It is not known if there may be an interaction with TNF with the locus on 1q22 or if the different TNF promoter haplotypes are merely serving as a proxy for another MHC locus or other population differences. However, this study provides the first evidence that subsetting of larger family samples may decrease the effects of sample heterogeneity and therefore reveal novel SZ susceptibility loci that remain hidden in the larger family sets where truly negative signals from one family effectively override the truly positive signals in other families.

Recently, the NOS1AP gene was proposed as a strong SZ candidate (Brzustowicz et al. 2004) that resides within the linkage signal obtained on 1q22 in our study (Saviouk et al. 2004) and in the original linkage genome scan performed on this sample (Brzustowicz et al. 2000). If the relationship between TNF and NOS1AP genes are unclear, the interaction between the NOS1AP and Syn2 genes are well established (Jaffrey et al. 2002; Sanchez-Islas and Leon-Olea 2004). Therefore, in our second study that is described in chapter 3 we tested if the Syn2 gene may be involved into the pathogenesis of SZ. The Syn2 gene is located on 3p25 in humans and is implicated in synaptogenesis, neurotransmitter release, and the localization of nitric oxide synthase to the proximity of its targets. 37 pedigrees of exclusively Northern European ancestry from the NIMH

Human Genetics Initiative collection were used. Four microsatellites and twenty SNPs were genotyped. Linkage (FASTLINK) and association (TRANSMIT, PDTPHASE) between markers and SZ were evaluated. A maximum heterogeneity LOD of 1.93 was observed at marker D3S3434 with a recessive mode of inheritance. Significant results were obtained for association with SZ using TRANSMIT (minimum nominal  $p=0.0000005$ ) and PDTPHASE (minimum nominal  $p=0.014$ ) using single marker analyses. Haplotype analysis using markers in introns 5 and 6 of Syn2 provided a single haplotype that is significantly associated with SZ using TRANSMIT (nominal  $p<0.00000001$ ) and PDTPHASE (nominal  $p=0.02$ ). Simulation studies confirm the global significance of these results, but demonstrate that the small p-values generated by the bootstrap routine of TRANSMIT can be consistently anticonservative. Review of the literature suggests that Syn2 is likely to be involved in the etiology or pathogenesis of SZ.

This study again demonstrated the pivotal role of simulations in evaluating the significance of the family-based tests of association. Trimhap and TRANSMIT both demonstrated a propensity for anti-conservative interpretation of the association data, therefore we advise against the utilization of those methods in further studies unless they are accompanied by rigorous simulations. Nominal results of the PDTPHASE method closely match the expected performance as evaluated by the simulations. We demonstrated that PDTPHASE is not affected by the presence of linkage in the family sample, neither it is sensitive to the allele frequencies of the biallelic markers which are used to test the association of a gene with a phenotype. The slight over-conservative nature of the method that we revealed through the simulations provide considerably less

concern in interpreting the results of the association than the unexpected anticonservative nominal p-values of Trimhap and TRANSMIT that increase the type I error rate.

The fourth chapter study relates to a recent linkage scan for SZ in the NIMH HGI Chinese family collection as reported by Faraone et al. (2006). In this original study, the largest NPL z score of 2.88 for D10S2327 in a sample of 606 two-generation families of Han Chinese ancestry was revealed, however it did not reach a study-wide significance.

We have reanalyzed the genome using the posterior probability of linkage (PPL). We split the sample into two subsets: those without any family members with affective diagnoses (SZ subgroup); and those with SZ, SAD, and BPD (HET subgroup).

Genotypes were cleaned using PEDCHECK and SIMWALK. Though we did not detect any Mendelian inconsistencies in the publically available genome scan data for this sample, 0.11% of the genotypes were removed from the further analysis due to a high chance of being erroneous based on multiple Simwalk runs to evaluate for spurious excess recombination events. Sample specific genetic maps were constructed since most of the available public genetic maps, including the Marshfield map used in the original study, are constructed utilizing the families of Caucasian ancestry. Three phenotypic definitions were tested in our re-analysis study that range from a “purely psychotic clinical manifestation” (SZ; phenotype 1) to a combination of psychotic and affective manifestations seen in SAD (SZ and SAD; phenotype2) and BPD (SZ, SAD, and BPD; phenotype 3). SZ and HET groups were analyzed by four-point PPL analysis, and the results from each group were combined via pooling and sequential updating. The results confirmed the linkage peak on 10q22 with a PPL of 32.1% after updating. In addition we

observed a peak of 30.5% over D3S1311 on 3q29 coming primarily from the HET group. Our results confirmed the previously reported linkage peak and yielded novel linkage findings in this family sample.

As in the TNF study, this study highlights the use of sample stratification to reduce the effects of genetic heterogeneity. In the TNF study, the presence of a certain haplotype that is associated with SZ served as a stratification criterion; in the Bayesian reanalysis study the differences in clinical manifestations within a group of a SZ spectrum disorders was used to segregate the families. Both approaches appeared to be efficient in reducing the effects of genetic heterogeneity and revealed the new loci throughout the genome that were not detected in the original linkage scans (Brzustowicz et al. 2000; Faraone et al. 2006).

We also would like to emphasize that our successful approach to the phenotypic definitions proved to be useful in SZ linkage studies. Contrary to the traditional Kraepelinian dichotomy employed by modern psychiatry that is reflected in the current version of DSM, multiple accounts of evidence have surfaced in recent years that support an idea that there is a continuum of clinical manifestations and thus the etiopathophysiological factors between psychotic states and affective pathology with psychotic features. In particular, it is hypothesized that there is a set of genes that influence the manifestation of psychosis and this set of genes maybe at least partially shared between the subjects with a functional psychotic states independent of the categorical definition of the subject's psychopathology. In other words, the genes that

predispose to SZ can be shared between the subjects with SZ and SAD, as well as with subjects with BPD, particularly if psychosis is a part of their clinical picture. Moreover, this set of genes to a lesser degree may be shared with subjects that suffer from the cluster A personality disorders. Further, deficits in reality testing of lesser magnitude, like those seen in a postpartum psychosis, can be caused by some of those genes, but the smaller overall dosage effect of those genes may be insufficient for the development of a classic functional psychotic disease.

As demonstrated in the fourth chapter, we identified some families in the original Chinese NIMH family sample that have multiple affected subjects suffering from either DSM-IV defined SZ, SAD, or BPD. The subset of those families yielded a strong linkage signal on chromosome 3q29, comparable in magnitude to the major linkage finding on chromosome 10 seen in the SZ subgroup as well as in the pooled sample, despite the HET subset's much smaller size. The review of the literature not only demonstrates the previous linkage to this area, but also emphasized that this locus seemed to be specifically important in the families with psychopathologies from the entire psycho-affective spectrum that includes SZ, SAD, and BPD.

Majority of current linkage studies on SZ or BPD traditionally employ the categorical definitions of these psychopathologies. This approach ultimately demonstrates the uncertainty of the hierarchical placement of SAD, since this disorder is commonly included in the linkage scans of SZ and BPD. We hypothesize that this indiscriminate inclusion of SAD may hinder the gene search for SZ and BPD, enhancing the effects of



genetic heterogeneity. In the light of the continuum hypothesis we would not advise to exclude subjects or families with SAD from the further linkage studies, however, we would recommend to accommodate SAD and BPD nosologies within SZ spectrum phenotypes through subsetting of the families and possible multiple phenotypic definitions.

Fortunately, as we demonstrated in the fourth chapter, this can be achieved through the use of novel linkage analysis approaches that employ Bayesian statistics. The PPL allows us to use such subsetting without a penalty for breaking up the larger cohorts. The evidence for and against linkage can be evaluated in each subset separately, resulting in a single posterior probability value that is free of genetic model parameters. Further, the evidence from each subset can be combined via sequential updating. This approach would not penalize our final results if a particular gene is important in a single clinical subset only or if it is involved in the etiology of the psychotic states of multiple clinically heterogeneous subsets but with different genetic dosage. A gene with a variable dosage effect in different subsets could potentially be detected with a parametric linkage analysis, but the genetic models that maximize the LOD scores in those subsets are likely to be different and multiple tests would likely be required to detect such a gene.

Since there is no a predefined concept of significance in PPL analysis, multiple tests can be used without a correction. That allows us to employ multiple phenotypic definitions in our research of the diseases with a complex inheritance. As we demonstrated in the fourth chapter, multiple phenotypic definitions can be useful in heterogeneous settings when the

relationship between the different disorders under particular phenotypic definitions is not quite clear.

Based on our experience we recommend a following approach to the linkage analysis studies for complex phenotypes like SZ to help decrease the negative effects of the clinical and genetic heterogeneity:

- Careful approach to clinical data to reduce the phenocopy rates
- If possible, focusing of syndromal diagnosis of symptom components, rather than traditional categorical definition of disease entities
- Subsetting of the family sample based on the observation of particular syndromes within pedigrees, for example, families with psychosis, families with psychosis and mania, etc.
- Utilization of the PPL to evaluate linkage evidence in each phenotypic subgroup and use of sequential updating to derive results for the entire heterogeneous sample

In addition, attention should be paid to other issues that we discuss in this dissertation. In particular, genotyping data quality control beyond the Mendelian inconsistency checks should be applied, ethnic specific genetic maps should be used for linkage analysis, and simulations should be applied to establish a true significance of family-based association studies and linkage studies that employ multiple but not independent tests, especially when traditional rather than Bayesian statistical techniques are used.

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CHR	cM	SZ	HET				POOL				Seq Update			
		Phen1	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3
1	0	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
1	1	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
1	2	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
1	3	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
1	4	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
1	5	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
1	6	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
1	7	.02	.02	.02	.03	.02	.02	.02	.02	.02	.01	.02	.01	.02
1	8	.02	.02	.02	.03	.02	.02	.02	.02	.02	.01	.02	.01	.02
1	9	.02	.02	.02	.03	.02	.02	.02	.02	.02	.01	.02	.01	.02
1	10	.02	.02	.02	.03	.02	.02	.02	.02	.02	.01	.02	.01	.02
1	1.8	.02	.02	.02	.03	.02	.02	.02	.02	.02	.01	.02	.01	.02
1	11	.02	.02	.02	.03	.02	.02	.01	.02	.01	.02	.01	.01	.02
1	12	.01	.02	.02	.03	.02	.01	.01	.01	.01	.01	.01	.01	.02
1	13	.01	.02	.02	.03	.02	.01	.01	.01	.01	.01	.01	.01	.02
1	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
1	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
1	15.92	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
1	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	18	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	19	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	20	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	21	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	22	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	23	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	24	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	24.61	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	25	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	26	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	28	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	29	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	30	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	31	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
1	32	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	33	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	34	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
1	69	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	70	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	71	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	72	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	73	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	74	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	75	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	76	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	77	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
1	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
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1	80.11	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
1	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
1	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
1	83	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
1	84	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01
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1	88	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
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1	99	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
1	99.73	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
1	100	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
1	100.53	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
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1	103	.02	.02	.02	.02	.02	.03	.03	.03	.02	.03	.03	.03	.02





		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
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1	176	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
1	177	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
1	178	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.02
1	178.77	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.02
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1	184	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
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1	187	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
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1	190	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	190.32	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	191	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
1	192	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
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1	197	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.02
1	198	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	198.59	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	199	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	200	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	201	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	202	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
1	203	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
1	204	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
1	205	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
1	205.64	.02	.02	.02	.02	.02	.02	.01	.02	.02	.01	.01	.01	.01

[illegible]





CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
2	16	.01	.03	.03	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02
2	17	.01	.03	.03	.02	.03	.02	.02	.01	.02	.02	.02	.02	.02
2	18	.01	.03	.03	.02	.03	.01	.02	.01	.02	.02	.02	.01	.02
2	19	.01	.03	.03	.02	.03	.01	.02	.01	.02	.02	.02	.01	.02
2	20	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
2	21	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
2	22	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
2	23	.01	.02	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
2	24	.01	.02	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
2	25	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
2	26	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
2	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
2	27.48	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
2	28	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
2	29	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	30	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	31	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	32	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	33	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	34	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	35	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	36	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	37	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01
2	38	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	38.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	39	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	40	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	41	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	42	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	43	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	44	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	45	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	46	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	46.92	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	47	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	48	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02
2	49	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	50	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
2	51	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
2	52	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
2	53	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	54	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	55	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	56	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	56.43	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	57	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	58	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	59	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	60	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	61	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
2	62	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
2	63	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	64	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	65	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	66	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	66.36	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	67	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	68	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	69	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
2	70	.02	.02	.02	.02	.02	.03	.02	.03	.02	.03	.02	.03	.02
2	71	.03	.02	.02	.02	.02	.03	.02	.03	.02	.03	.02	.03	.02
2	72	.03	.02	.02	.02	.02	.03	.03	.03	.02	.03	.02	.03	.02
2	73	.03	.02	.02	.02	.02	.03	.03	.03	.02	.03	.02	.03	.02
2	73.92	.03	.02	.02	.02	.02	.03	.03	.03	.02	.03	.02	.03	.02
2	74	.03	.02	.02	.02	.02	.03	.03	.03	.02	.03	.02	.03	.02
2	75	.03	.02	.02	.02	.02	.03	.03	.03	.02	.03	.02	.03	.02
2	76	.03	.02	.02	.02	.02	.03	.02	.03	.02	.03	.02	.03	.02
2	77	.03	.02	.02	.02	.02	.03	.02	.03	.02	.03	.02	.03	.02
2	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
2	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
2	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
2	83	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
2	83.12	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
2	84	.01	.03	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01
2	85	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01









		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
2	223	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.02	.02	.01
2	223.22	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.02	.02	.01
2	224	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.02	.02	.02
2	225	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.02	.02	.02
2	226	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.02	.02	.02
2	227	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
2	228	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
2	229	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
2	230	.02	.02	.01	.02	.01	.02	.02	.02	.01	.01	.01	.01	.01
2	230.78	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
2	231	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
2	232	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
2	233	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
2	234	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
2	235	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
2	236	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
2	237	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
2	238	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	239	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
2	240	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	241	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	242	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	242.07	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	243	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	244	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	245	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	246	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	247	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	248	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	249	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	249.73	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	250	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
2	251	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01
2	252	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	253	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
2	254	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	255	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	256	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	257	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01



CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
2	258	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	259	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
2	260	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
3	0	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	1	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	2	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	3	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	4	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	5	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	6	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	7	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	8	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	9	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	10	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.01
3	11	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
3	12	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.02	.01
3	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.02	.01
3	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.02	.01
3	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	18.07	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	22	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	23	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
3	23.49	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	24	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	25	.01	.02	.02	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	26	.01	.02	.02	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	26.69	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	27	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	28	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	29	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	30	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
3	31	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.02	.01







		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
3	134	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	135	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	136	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	137	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	138	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	139	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	140	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	141	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	142	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	143	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	144	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	145	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	146	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	147	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	148	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	149	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	150	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	151	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	152	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	153	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	153.92	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	154	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	155	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	156	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	157	.01	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01
3	158	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
3	159	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01
3	159.24	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01
3	160	.01	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01
3	161	.01	.02	.02	.02	.02	.01	.02	.01	.01	.01	.02	.01	.01
3	162	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	163	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	164	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	165	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	166	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	167	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	167.31	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
3	168	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
3	169	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	170	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	171	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	172	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	173	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	174	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
3	175	.02	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	176	.02	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	177	.01	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	178	.01	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	179	.01	.03	.04	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
3	180	.01	.03	.04	.03	.02	.01	.02	.01	.02	.02	.03	.02	.02
3	181	.01	.03	.04	.03	.02	.01	.01	.01	.01	.02	.02	.02	.02
3	182	.01	.03	.04	.03	.02	.01	.01	.01	.01	.02	.02	.02	.02
3	182.35	.01	.03	.04	.03	.02	.01	.01	.01	.01	.02	.02	.02	.01
3	183	.01	.02	.07	.03	.03	.01	.01	.01	.01	.02	.04	.02	.02
3	184	.01	.02	.08	.03	.03	.01	.01	.01	.01	.01	.05	.02	.02
3	185	.01	.02	.09	.03	.03	.01	.01	.01	.01	.01	.06	.02	.02
3	186	.01	.02	.1	.03	.04	.01	.01	.01	.01	.01	.06	.02	.02
3	187	.01	.02	.1	.02	.04	.01	.01	.01	.01	.01	.06	.02	.02
3	188	.01	.02	.1	.02	.04	.01	.01	.01	.01	.01	.06	.02	.03
3	189	.01	.02	.09	.02	.04	.01	.01	.01	.01	.01	.05	.01	.03
3	189.5	.01	.02	.08	.02	.04	.01	.01	.01	.01	.01	.05	.01	.03
3	190	.01	.02	.08	.02	.05	.01	.01	.01	.01	.01	.05	.01	.03
3	191	.01	.02	.08	.02	.05	.01	.01	.01	.01	.01	.05	.01	.03
3	192	.01	.02	.08	.02	.05	.01	.01	.01	.01	.01	.05	.01	.03
3	193	.01	.02	.07	.02	.06	.01	.01	.01	.01	.01	.04	.01	.03
3	194	.01	.02	.08	.02	.07	.01	.01	.01	.01	.01	.05	.01	.04
3	195	.01	.02	.07	.02	.07	.01	.01	.01	.02	.01	.05	.01	.04
3	195.53	.01	.02	.07	.02	.06	.01	.02	.01	.02	.01	.04	.01	.04
3	196	.01	.02	.07	.02	.07	.01	.02	.01	.02	.01	.05	.01	.05
3	197	.01	.02	.07	.02	.08	.01	.02	.01	.02	.01	.05	.01	.06
3	198	.02	.02	.08	.02	.1	.02	.02	.02	.02	.02	.06	.02	.07
3	199	.02	.02	.08	.02	.12	.02	.02	.02	.02	.02	.06	.02	.09
3	200	.02	.02	.09	.02	.15	.02	.02	.02	.02	.02	.07	.02	.12
3	201	.02	.02	.1	.02	.18	.02	.02	.02	.02	.02	.08	.02	.15
3	202	.02	.02	.11	.02	.22	.02	.02	.02	.02	.02	.1	.02	.2
3	203	.02	.02	.12	.02	.26	.02	.03	.02	.03	.02	.11	.02	.25



CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
4	26	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	27	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	28	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	29	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	30	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	30.7	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	31	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	32	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	33	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	34	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	35	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	36	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	37	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	38	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	39	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
4	40	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
4	41	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
4	41.67	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
4	42	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
4	43	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
4	44	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
4	45	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
4	46	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
4	47	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
4	48	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
4	48.21	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
4	49	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
4	50	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
4	51	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
4	52	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
4	53	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
4	54	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
4	55	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
4	56	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
4	57	.02	.02	.02	.02	.02	.03	.02	.02	.02	.03	.02	.02	.02
4	57.83	.03	.02	.02	.02	.02	.03	.02	.02	.02	.03	.02	.02	.02
4	58	.03	.02	.02	.02	.02	.03	.02	.02	.02	.03	.02	.02	.02
4	59	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02





[illegible]



[illegible]

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
4	200	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	0	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01
5	1	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	2	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	4	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	5	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	7	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	9	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	10	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	18.48	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	20	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	21	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	22	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	23	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	24	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.01	.01	.01
5	24.61	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
5	25	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.01
5	26	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.01
5	27	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.01	.01	.01
5	28	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.01	.01	.01
5	29	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
5	29.32	.01	.03	.03	.02	.03	.01	.01	.01	.01	.02	.02	.01	.02
5	30	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.02	.01	.01
5	31	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	32	.01	.03	.03	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
5	33	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
5	69	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
5	70	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.02	.02	.01
5	71	.01	.02	.03	.03	.02	.01	.01	.01	.01	.01	.01	.02	.01
5	72	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	73	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	74	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	75	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	75.89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	76	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	79	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	80	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	81	.01	.02	.02	.02	.02	.01	.01	.01	.01	0	.01	0	0
5	82	.01	.02	.02	.02	.02	.01	.01	.01	.01	0	.01	0	0
5	83	.01	.02	.02	.02	.02	.01	.01	.01	.01	0	.01	.01	.01
5	84	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	88	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
5	88.55	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	89	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	90	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	91	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	92	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	93	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	94	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	94.17	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	95	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	96	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
5	97	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
5	98	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
5	99	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
5	99.69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
5	100	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
5	101	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.02
5	102	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	103	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02





CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
5	137	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	138	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
5	139	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
5	140	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
5	140.75	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
5	141	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
5	142	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	143	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	144	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	145	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	146	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	147	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	148	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	149	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	150	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	151	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	152	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	153	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	154	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	155	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	155.57	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	156	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	157	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	158	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	159	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	160	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	161	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	162	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	163	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	164	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	165	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	166	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	167	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	168	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02
5	169	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
5	169.52	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01
5	170	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
5	171	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
5	172	.02	.02	.02	.02	.02	.02	.01	.02	.02	.01	.01	.01	.01
5	173	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
5	174	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
5	174.64	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
5	175	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
5	176	.01	.02	.02	.02	.02	.01	.01	.02	.01	.01	.01	.01	.01
5	177	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	178	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	179	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	180	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	181	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
5	182	.01	.02	.02	.02	.02	.01	.01	.02	.01	.01	.01	.02	.01
5	183	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	184	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	184.67	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	185	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	186	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	187	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	188	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	189	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	190	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	191	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	192	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
5	193	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02
5	194	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02
5	195	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02
5	196	.02	.02	.02	.03	.02	.02	.03	.03	.02	.02	.03	.03	.02
5	196.27	.02	.02	.02	.03	.02	.02	.03	.03	.02	.02	.03	.03	.02
5	197	.02	.02	.02	.03	.02	.02	.03	.03	.02	.02	.03	.03	.02
5	198	.02	.02	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	199	.02	.02	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	200	.02	.02	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	201	.02	.02	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	202	.02	.02	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	203	.02	.02	.02	.02	.02	.02	.03	.03	.02	.03	.03	.03	.02
5	204	.02	.02	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.02
5	205	.02	.02	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.02
5	206	.02	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.02

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
6	0	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	1	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	2	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	4	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	5	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	7	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	9	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	10	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	22	.02	.02	.02	.02	.02	.01	.01	.02	.01	.01	.01	.01	.01
6	23	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	24	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	25	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	25.15	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	26	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	28	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	29	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	30	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	31	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	32	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	33	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
6	34	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
6	35	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
6	36	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
6	69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	70	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	71	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	72	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	73	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	74	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	74.16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	75	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	76	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	79	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	80	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	81	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	82	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	83	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	84	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	85	.02	.02	.02	.02	.02	.01	.01	.02	.01	.01	.01	.01	.01
6	85.55	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01
6	86	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01
6	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	88	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	90	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	91	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	92	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	93	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
6	93.41	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
6	94	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
6	95	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	96	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	97	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	98	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	99	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
6	99.74	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
6	100	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
6	101	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
6	102	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.02

[illegible]

[illegible]







CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
7	68	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	70	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	71	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
7	72	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
7	72.68	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
7	73	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
7	74	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	75	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	76	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	78.81	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.01
7	79	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
7	80	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	81	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	82	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	83	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	84	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	87	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	88	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	88.32	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	89	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	90	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	91	.01	.02	.03	.02	.04	.01	.01	.01	.01	.01	.01	.01	.01
7	92	.01	.02	.04	.03	.04	.01	.01	.01	.01	.01	.02	.01	.02
7	92.63	.01	.02	.04	.03	.05	.01	.01	.01	.01	.01	.02	.02	.02
7	93	.01	.02	.04	.03	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	94	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	95	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	96	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	97	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.01	.01	.02
7	98	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	99	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.02
7	100	.01	.02	.03	.02	.04	.01	.01	.01	.01	.01	.02	.01	.02
7	100.49	.01	.02	.03	.02	.04	.01	.01	.01	.01	.01	.02	.01	.02

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
7	101	.01	.02	.03	.02	.04	.01	.01	.01	.01	.01	.02	.01	.02
7	102	.01	.02	.04	.02	.04	.01	.01	.01	.01	.01	.02	.01	.02
7	103	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.03
7	104	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.03
7	105	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.03
7	106	.01	.02	.04	.02	.05	.01	.01	.01	.01	.01	.02	.01	.03
7	107	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
7	107.03	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
7	108	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	109	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	110	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
7	111	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	112	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	113	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	114	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	115	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	116	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	117	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
7	118	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.02
7	119	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
7	119.8	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	120	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	121	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	122	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	123	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	124	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	125	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	126	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	127	.03	.02	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02
7	127.77	.03	.02	.02	.02	.02	.03	.02	.03	.03	.03	.02	.03	.02
7	128	.03	.02	.02	.02	.02	.03	.02	.03	.03	.03	.02	.02	.02
7	129	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	130	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	131	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	132	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	133	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	134	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
7	135	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01
7	136	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
7	137	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	138	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	138.22	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	139	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	140	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	141	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	142	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	143	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	143.44	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	144	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	145	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	146	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	147	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	148	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	149	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	150	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	151	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	152	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	153	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	154	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	155	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	156	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	156.1	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	157	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
7	158	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.01
7	159	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	160	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	161	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	162	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	163	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	164	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
7	165	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01
7	165.61	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01
7	166	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.01
7	167	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	168	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	169	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	170	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02

		SZ	HET				POOL				Seq Update			
CHR	cM	Phen1	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3
7	171	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	171.33	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	172	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	173	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	174	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	175	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
7	176	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
7	177	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	178	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	179	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	180	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
7	181	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
8	0	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	1	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	2	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	4	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	5	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	7	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	9	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	10	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	22	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	23	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	24	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	24.71	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
8	25	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	26	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	28	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	29	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	29.12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	30	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	31	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	31.02	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	32	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
8	33	.01	.02	.03	.02	.04	.01	.01	.01	.01	.01	.02	.01	.02
8	34	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	35	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	36	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
8	37	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
8	38	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
8	38.07	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
8	38.67	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	39	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	40	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	40.4	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	41	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	42	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	43	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	44	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	45	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	46	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	46.63	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	47	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01
8	48	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
8	49	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
8	50	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
8	51	.02	.02	.02	.01	.01	.02	.02	.02	.02	.02	.02	.01	.01
8	52	.02	.02	.01	.01	.01	.02	.02	.02	.02	.02	.02	.02	.01
8	53	.02	.02	.01	.01	.01	.02	.02	.02	.02	.02	.02	.02	.01
8	54	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
8	55	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
8	56	.02	.02	.01	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
8	57	.02	.02	.01	.02	.01	.02	.02	.02	.02	.01	.01	.01	.01
8	57.08	.02	.02	.01	.02	.01	.02	.02	.02	.02	.01	.01	.01	.01
8	58	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
8	59	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
8	60	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
8	61	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
8	62	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
8	63	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
8	64	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
8	65	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	66	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	66.9	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	67	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	68	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	69	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	70	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	71	.01	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	72	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	72.73	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	73	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	74	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
8	75	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
8	76	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01
8	77	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
8	77.65	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
8	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
8	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
8	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	83	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	84	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	88	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	88.62	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01
8	89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
8	90	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01
8	91	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	92	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	93	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	94	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	95	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	95.67	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	96	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	97	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	98	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	99	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	100	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
8	101	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	102	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	103	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	104	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	105	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	105.81	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	106	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	107	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	108	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	109	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	110	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	111	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	112	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	113	.01	.06	.02	.03	.02	.01	.01	.01	.01	.03	.01	.02	.01
8	113.47	.01	.06	.02	.03	.02	.01	.01	.01	.01	.03	.01	.02	.01
8	114	.01	.05	.02	.03	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	115	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	116	.01	.05	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	117	.01	.04	.02	.02	.02	.01	.01	.01	.01	.03	.01	.01	.01
8	118	.01	.04	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01
8	119	.01	.05	.03	.03	.02	.02	.02	.02	.02	.03	.02	.02	.01
8	119.6	.02	.04	.03	.03	.02	.02	.02	.02	.02	.03	.02	.02	.01
8	120	.02	.04	.03	.03	.02	.02	.02	.02	.02	.03	.02	.02	.02
8	121	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02
8	122	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02
8	123	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
8	124	.02	.05	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.02
8	125	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02
8	126	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02
8	127	.02	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.02
8	128	.02	.06	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.01
8	129	.02	.06	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.01
8	130	.02	.07	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.01
8	131	.02	.07	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.01
8	131.2	.02	.07	.03	.03	.02	.02	.02	.02	.02	.05	.02	.02	.01
8	132	.01	.06	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02	.01
8	133	.01	.05	.02	.03	.02	.02	.02	.01	.01	.04	.02	.02	.01
8	134	.01	.04	.02	.02	.02	.01	.01	.01	.01	.03	.01	.02	.01
8	135	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	135.21	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	136	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	137	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	138	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	139	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	140	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
8	141	.01	.03	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
8	142	.01	.03	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
8	143	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	144	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.01
8	144.52	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.01
8	145	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	146	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	147	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	148	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	149	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	150	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
8	151	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	152	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
8	153	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
8	154	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
8	155	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
8	156	.01	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01
8	157	.01	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01
8	158	.01	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
9	21	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	22	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	23	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	24	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	25	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	26	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	28	.02	.02	.02	.02	.02	.01	.01	.02	.01	.01	.01	.01	.01
9	29	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
9	30	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
9	31	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.02
9	32	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	33	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	33.5	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	34	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	35	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	36	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.01
9	37	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	38	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	39	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	40	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	41	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	42	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	43	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	43.53	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	44	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	45	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	46	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	47	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
9	48	.01	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
9	49	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
9	50	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
9	51	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	51.39	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	52	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	53	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	54	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
9	55	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
9	56	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
9	57	.01	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.01
9	58	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	59	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	60	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	61	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	62	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	62.89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	63	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	64	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	65	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	66	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	67	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	68	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	70	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	71	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	72	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	72.3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	73	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	74	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	75	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	75.6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
9	76	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
9	77	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
9	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
9	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
9	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02
9	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	83	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	84	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	85	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	86	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	87	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	88	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	88.37	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
9	89	.02	.02	.02	.02	.02	.02	.02	.03	.02	.03	.02	.03	.02



[illegible]







CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
10	67	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	67.03	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	68	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	70	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	71	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	72	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	73	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	74	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	75	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	76	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	79	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	79.8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
10	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
10	83	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
10	83.31	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
10	84	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
10	85	.02	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.03	.03
10	86	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
10	87	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	87.72	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	88	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	89	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
10	90	.02	.02	.02	.02	.02	.02	.03	.03	.03	.02	.02	.03	.03
10	91	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
10	92	.03	.02	.02	.02	.02	.03	.03	.04	.04	.03	.03	.04	.03
10	93	.05	.02	.02	.03	.02	.06	.07	.07	.07	.06	.06	.06	.06
10	93.85	.06	.02	.02	.02	.02	.07	.08	.08	.08	.07	.07	.07	.07
10	94	.06	.02	.02	.02	.02	.07	.08	.08	.09	.07	.08	.08	.07
10	95	.08	.02	.02	.02	.02	.09	.1	.1	.11	.08	.09	.09	.09
10	96	.1	.02	.02	.02	.02	.11	.13	.13	.13	.1	.11	.11	.11
10	97	.12	.02	.02	.02	.02	.13	.15	.15	.16	.12	.13	.13	.13
10	98	.14	.02	.02	.02	.02	.15	.18	.18	.19	.14	.15	.16	.15
10	99	.17	.02	.02	.02	.02	.17	.2	.21	.21	.16	.17	.18	.17

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
10	100	.18	.02	.02	.02	.02	.18	.22	.22	.23	.17	.19	.19	.19
10	101	.25	.02	.02	.02	.02	.23	.27	.27	.28	.23	.24	.25	.24
10	101.1	.25	.02	.02	.02	.02	.23	.27	.27	.28	.23	.24	.25	.24
10	102	.25	.02	.02	.02	.02	.24	.27	.28	.28	.23	.25	.25	.25
10	103	.25	.02	.02	.02	.02	.23	.27	.27	.28	.23	.25	.25	.25
10	104	.25	.02	.02	.02	.02	.23	.26	.27	.27	.23	.24	.25	.24
10	105	.24	.02	.02	.02	.02	.22	.24	.25	.25	.22	.23	.24	.23
10	106	.22	.02	.02	.02	.02	.2	.22	.23	.23	.21	.21	.22	.21
10	107	.32	.02	.02	.02	.02	.32	.32	.36	.33	.32	.32	.34	.32
10	108	.29	.02	.02	.02	.02	.29	.29	.32	.29	.29	.29	.31	.29
10	109	.26	.02	.02	.02	.02	.26	.25	.28	.25	.26	.25	.27	.25
10	110	.22	.02	.02	.02	.02	.22	.21	.24	.21	.22	.21	.23	.21
10	111	.19	.02	.02	.02	.02	.19	.17	.2	.18	.18	.18	.19	.18
10	112	.16	.02	.02	.02	.02	.15	.14	.17	.14	.15	.14	.16	.14
10	113	.13	.02	.02	.02	.02	.13	.11	.13	.11	.12	.12	.13	.12
10	113.55	.12	.02	.02	.02	.02	.11	.1	.12	.1	.11	.1	.11	.1
10	114	.09	.02	.02	.02	.02	.08	.07	.08	.07	.08	.07	.08	.07
10	115	.1	.02	.02	.02	.02	.08	.07	.08	.07	.08	.08	.08	.08
10	116	.1	.02	.02	.02	.02	.09	.07	.08	.07	.09	.08	.08	.08
10	117	.1	.02	.02	.02	.02	.09	.07	.08	.07	.09	.08	.08	.08
10	118	.09	.02	.02	.02	.02	.09	.07	.08	.07	.09	.08	.08	.08
10	119	.09	.02	.02	.02	.02	.08	.07	.08	.07	.08	.07	.08	.07
10	119.07	.09	.02	.02	.02	.02	.08	.07	.07	.07	.08	.07	.08	.07
10	120	.09	.02	.02	.02	.02	.08	.07	.07	.07	.08	.07	.07	.07
10	121	.08	.02	.02	.02	.02	.08	.07	.07	.07	.08	.07	.07	.07
10	122	.08	.02	.02	.02	.02	.07	.06	.07	.07	.07	.06	.07	.07
10	123	.07	.02	.02	.02	.02	.07	.06	.07	.07	.07	.06	.06	.06
10	124	.06	.02	.02	.02	.02	.06	.06	.06	.07	.06	.06	.06	.06
10	125	.06	.02	.02	.02	.02	.07	.06	.06	.08	.07	.06	.06	.07
10	125.61	.06	.02	.02	.02	.02	.07	.06	.06	.08	.07	.06	.06	.07
10	126	.05	.02	.02	.02	.02	.07	.06	.06	.07	.06	.05	.05	.06
10	127	.05	.02	.02	.02	.02	.06	.05	.05	.07	.06	.05	.05	.06
10	128	.04	.03	.02	.02	.02	.05	.05	.05	.06	.05	.04	.04	.05
10	129	.04	.03	.02	.02	.02	.05	.04	.04	.05	.05	.04	.04	.05
10	130	.04	.03	.02	.02	.02	.05	.04	.04	.05	.05	.04	.04	.04
10	131	.04	.03	.02	.02	.02	.05	.04	.04	.05	.05	.04	.04	.04
10	132	.04	.03	.02	.02	.02	.05	.04	.04	.05	.05	.04	.04	.04
10	133	.04	.03	.02	.02	.02	.05	.04	.04	.05	.05	.04	.04	.05

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
10	134	.06	.03	.02	.02	.02	.08	.06	.07	.07	.07	.06	.06	.07
10	135	.07	.02	.02	.02	.02	.09	.07	.07	.08	.08	.07	.07	.08
10	136	.08	.02	.02	.02	.02	.11	.08	.09	.09	.1	.08	.08	.09
10	136.37	.09	.02	.02	.02	.02	.11	.08	.09	.1	.1	.08	.09	.1
10	137	.09	.02	.02	.02	.02	.12	.09	.1	.1	.11	.09	.1	.1
10	138	.1	.02	.02	.02	.02	.14	.1	.11	.12	.12	.1	.11	.12
10	139	.11	.02	.02	.02	.02	.15	.11	.12	.13	.13	.11	.12	.13
10	140	.12	.02	.02	.02	.03	.17	.12	.13	.15	.14	.13	.13	.15
10	141	.09	.03	.02	.02	.02	.14	.1	.11	.11	.12	.09	.1	.1
10	142	.09	.03	.02	.02	.02	.14	.1	.11	.12	.12	.09	.1	.1
10	143	.1	.03	.02	.02	.02	.15	.1	.11	.12	.12	.09	.1	.1
10	144	.1	.03	.02	.02	.02	.15	.1	.12	.12	.12	.09	.1	.1
10	145	.1	.02	.02	.02	.02	.15	.1	.12	.12	.12	.1	.1	.11
10	146	.11	.02	.02	.02	.02	.15	.1	.12	.13	.13	.1	.1	.11
10	147	.11	.02	.02	.02	.02	.15	.11	.12	.13	.13	.1	.1	.11
10	148	.11	.02	.02	.02	.02	.15	.11	.12	.13	.13	.1	.11	.11
10	148.71	.12	.02	.02	.02	.02	.15	.11	.12	.13	.13	.1	.11	.11
10	149	.12	.02	.02	.02	.02	.16	.11	.12	.13	.13	.1	.11	.11
10	150	.15	.02	.02	.02	.02	.18	.13	.14	.17	.15	.13	.13	.14
10	151	.16	.02	.02	.02	.02	.19	.13	.15	.16	.16	.14	.14	.15
10	152	.17	.02	.02	.02	.02	.19	.13	.15	.15	.16	.14	.14	.14
10	153	.17	.02	.02	.02	.02	.19	.12	.14	.14	.16	.13	.14	.14
10	154	.16	.02	.02	.02	.02	.18	.11	.13	.12	.15	.13	.13	.13
10	155	.15	.02	.02	.02	.02	.16	.1	.12	.1	.14	.12	.12	.12
10	155.86	.14	.02	.02	.02	.02	.15	.09	.11	.09	.13	.1	.11	.11
10	156	.14	.02	.02	.02	.02	.15	.09	.11	.09	.13	.1	.11	.11
10	157	.13	.02	.02	.02	.02	.14	.09	.11	.09	.12	.1	.11	.1
10	158	.12	.02	.02	.02	.02	.13	.09	.1	.09	.12	.1	.1	.1
10	159	.09	.02	.02	.02	.02	.09	.07	.07	.07	.08	.07	.07	.07
10	160	.08	.02	.02	.02	.02	.09	.07	.07	.07	.08	.07	.07	.07
10	161	.08	.02	.02	.02	.02	.09	.07	.08	.07	.08	.07	.07	.07
10	162	.09	.02	.02	.02	.02	.09	.07	.08	.07	.08	.07	.07	.07
10	162.8	.09	.02	.02	.02	.02	.09	.08	.08	.08	.08	.07	.07	.07
10	163	.08	.02	.02	.02	.02	.08	.07	.07	.07	.07	.07	.07	.07
10	164	.07	.02	.02	.02	.02	.07	.06	.06	.06	.06	.06	.06	.06
10	165	.06	.02	.02	.02	.02	.06	.05	.05	.05	.05	.05	.05	.05
10	166	.06	.02	.02	.02	.02	.05	.05	.05	.05	.05	.05	.05	.05
10	167	.06	.02	.02	.02	.02	.05	.05	.05	.05	.05	.05	.05	.05
10	168	.07	.02	.02	.02	.02	.06	.06	.05	.05	.06	.06	.05	.05







		SZ	HET				POOL				Seq Update			
CHR	cM	Phen1	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3	Phen1	Phen2a	Phen2b	Phen3
11	95	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	96	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	97	.01	.03	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	98	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
11	99	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
11	100	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
11	101	.01	.03	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
11	102	.01	.03	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
11	103	.01	.03	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01
11	104	.01	.03	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
11	105	.01	.03	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
11	106	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
11	107	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
11	108	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.01
11	109	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.01
11	109.75	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
11	110	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	111	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	112	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	113	.02	.04	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	113.66	.02	.04	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	114	.02	.04	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	115	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	116	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	117	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	118	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	119	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	120	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	121	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	122	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.02	.03
11	123	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
11	124	.03	.02	.03	.02	.02	.03	.03	.03	.03	.03	.04	.03	.03
11	125	.03	.02	.03	.02	.02	.03	.04	.03	.03	.03	.04	.03	.03
11	126	.03	.02	.03	.02	.02	.03	.04	.03	.03	.03	.04	.03	.03
11	126.54	.03	.02	.03	.02	.02	.03	.04	.03	.03	.03	.04	.03	.03
11	127	.03	.02	.03	.02	.02	.03	.03	.03	.03	.03	.04	.03	.03
11	128	.03	.02	.03	.02	.02	.03	.03	.02	.03	.03	.03	.02	.03
11	129	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	130	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
11	131	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	132	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	133	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	134	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	134.1	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
11	135	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	136	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
11	137	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
11	138	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01
11	139	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
11	140	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	141	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	142	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	142.68	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	143	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	144	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	145	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	146	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	147	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	148	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	149	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	150	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	151	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	152	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	153	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	154	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	155	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	155.98	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	156	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	157	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	158	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	159	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	160	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	161	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	162	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	163	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	164	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
11	165	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01







CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
12	69	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	70	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	71	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
12	72	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
12	73	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
12	74	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.02
12	75	.03	.02	.02	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02
12	76	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	77	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	79.06	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	80.66	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
12	83	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01
12	84	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
12	85	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
12	85.17	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01
12	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01
12	87	.01	.03	.02	.03	.02	.01	.01	.01	.01	.01	.01	.02	.01
12	88	.01	.03	.02	.03	.02	.01	.01	.01	.01	.01	.01	.02	.01
12	89	.01	.03	.02	.04	.02	.01	.01	.01	.01	.02	.01	.02	.01
12	90	.01	.03	.02	.04	.02	.01	.01	.02	.01	.02	.01	.03	.01
12	91	.02	.03	.02	.05	.02	.02	.02	.02	.02	.03	.02	.04	.01
12	92	.02	.04	.03	.06	.02	.02	.02	.02	.02	.03	.02	.04	.02
12	92.22	.02	.04	.03	.06	.02	.02	.02	.02	.02	.03	.02	.05	.02
12	93	.02	.04	.03	.05	.02	.02	.02	.02	.02	.03	.02	.04	.01
12	94	.01	.04	.02	.05	.02	.02	.02	.02	.01	.02	.02	.03	.01
12	95	.01	.04	.02	.05	.02	.01	.01	.02	.01	.02	.01	.03	.01
12	96	.01	.04	.02	.06	.02	.01	.01	.01	.01	.02	.01	.03	.01
12	97	.01	.04	.02	.06	.02	.01	.01	.02	.01	.02	.01	.03	.01
12	98	.01	.04	.02	.05	.02	.02	.01	.02	.01	.02	.01	.03	.01
12	99	.01	.04	.02	.04	.02	.02	.01	.02	.01	.03	.01	.03	.01
12	100	.02	.04	.02	.04	.02	.02	.02	.02	.01	.03	.02	.03	.01
12	101	.02	.04	.02	.04	.02	.02	.02	.02	.02	.03	.02	.03	.01
12	101.94	.02	.04	.02	.03	.02	.03	.02	.03	.02	.04	.02	.03	.02

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
12	102	.02	.04	.02	.03	.02	.03	.02	.03	.02	.04	.02	.03	.02
12	103	.02	.04	.02	.03	.02	.02	.02	.02	.02	.03	.02	.03	.02
12	104	.02	.03	.02	.03	.02	.02	.02	.02	.02	.03	.02	.03	.02
12	104.84	.02	.03	.02	.03	.02	.02	.02	.02	.02	.03	.02	.03	.02
12	105	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
12	106	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
12	107	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
12	108	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
12	109	.02	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02
12	110	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	111	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	112	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	113	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	114	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	115	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	116	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	117	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	118	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	118.58	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	119	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	120	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	121	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	122	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	123	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	124	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	125	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	126	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	127	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	127.06	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	128	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	129	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	130	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	131	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	132	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	133	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
12	134	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
12	135	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	136	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
12	137	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
12	138	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
12	138.98	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
12	139	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
12	140	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	141	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	142	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	143	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	144	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	145	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	146	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	147	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
12	148	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
12	149	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.02	.01
12	150	.01	.02	.03	.02	.02	.01	.02	.02	.02	.01	.02	.02	.02
12	150.48	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
12	151	.01	.02	.03	.02	.02	.01	.02	.02	.02	.01	.02	.02	.02
12	152	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.02	.01
12	152.78	.01	.02	.02	.02	.02	.01	.02	.01	.01	.01	.02	.02	.01
12	153	.01	.02	.02	.02	.02	.01	.02	.01	.01	.01	.02	.02	.01
12	154	.01	.02	.03	.02	.02	.01	.02	.01	.01	.01	.02	.02	.01
12	155	.01	.02	.03	.02	.02	.01	.02	.01	.01	.01	.02	.02	.01
12	156	.01	.02	.03	.02	.02	.01	.02	.01	.02	.01	.02	.02	.01
12	157	.01	.02	.03	.02	.02	.01	.02	.02	.02	.01	.02	.02	.02
12	158	.01	.02	.03	.02	.02	.01	.02	.02	.02	.01	.02	.02	.02
12	159	.02	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
12	160	.02	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
12	161	.02	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
12	162	.02	.02	.03	.02	.02	.02	.02	.02	.02	.01	.02	.02	.02
12	163	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
13	0	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	1	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	2	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	3	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	4	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	5	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	6	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01
13	7	.01	.03	.02	.03	.02	.01	.01	.01	.01	.02	.01	.02	.01



[illegible]

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
13	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02
13	80	.03	.02	.02	.02	.02	.03	.02	.02	.03	.03	.02	.02	.02
13	81	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
13	82	.04	.02	.02	.02	.02	.04	.03	.03	.03	.04	.03	.03	.03
13	83	.05	.02	.02	.02	.02	.05	.04	.04	.04	.05	.04	.04	.04
13	84	.07	.02	.02	.02	.02	.07	.06	.05	.06	.07	.06	.06	.06
13	85	.1	.02	.02	.02	.02	.1	.08	.08	.08	.1	.08	.08	.08
13	85.42	.12	.02	.02	.02	.02	.11	.09	.09	.1	.12	.1	.1	.1
13	86	.11	.02	.02	.02	.02	.11	.09	.09	.1	.11	.09	.09	.09
13	87	.1	.02	.02	.02	.02	.1	.08	.08	.09	.1	.08	.08	.09
13	88	.09	.02	.02	.02	.02	.08	.07	.07	.08	.09	.07	.07	.08
13	89	.08	.02	.02	.02	.02	.07	.06	.06	.07	.08	.06	.07	.07
13	90	.07	.02	.02	.02	.02	.06	.06	.06	.06	.07	.06	.06	.06
13	91	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.04	.04	.04
13	91.35	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.03	.04	.04
13	92	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.03	.04	.03
13	93	.04	.02	.02	.02	.02	.03	.03	.03	.03	.04	.03	.03	.03
13	94	.03	.02	.02	.02	.02	.03	.03	.03	.03	.04	.03	.03	.03
13	95	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
13	96	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
13	97	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
13	98	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
13	99	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
13	100	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
13	101	.01	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
13	102	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
13	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
13	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
13	104.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
13	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
13	106	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
13	107	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
13	108	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
13	108.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01
13	109	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01	.01
13	110	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01	.01	.01
13	111	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01
13	112	.02	.02	.02	.02	.01	.02	.02	.02	.02	.02	.01	.01	.01



[illegible]

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
14	18.79	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	19	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	19.99	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	22	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	23	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	24	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
14	25	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
14	26	.01	.02	.03	.02	.03	.01	.01	.01	.01	.02	.02	.02	.02
14	27	.01	.02	.03	.03	.03	.01	.01	.01	.01	.02	.02	.02	.02
14	28	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	29	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	30	.02	.02	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	30.33	.02	.02	.03	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	31	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	32	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	33	.02	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	34	.02	.03	.04	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02
14	35	.02	.03	.04	.02	.03	.02	.02	.02	.02	.02	.03	.02	.02
14	35.55	.02	.03	.04	.02	.03	.02	.02	.02	.02	.02	.03	.02	.02
14	36	.02	.03	.04	.02	.03	.02	.02	.02	.02	.02	.03	.02	.02
14	37	.02	.03	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02
14	38	.02	.03	.05	.03	.03	.02	.02	.02	.02	.02	.04	.02	.02
14	39	.01	.03	.06	.03	.04	.02	.02	.02	.02	.02	.04	.02	.03
14	40	.01	.03	.07	.03	.04	.02	.02	.02	.02	.02	.05	.02	.03
14	41	.01	.03	.08	.03	.04	.02	.02	.02	.02	.02	.05	.02	.03
14	42	.01	.03	.1	.03	.05	.01	.01	.01	.01	.01	.05	.02	.02
14	43	.01	.03	.1	.03	.05	.01	.01	.01	.01	.01	.05	.02	.03
14	44	.01	.03	.1	.03	.05	.01	.01	.01	.01	.01	.06	.02	.03
14	45	.01	.02	.1	.03	.05	.01	.01	.01	.01	.01	.06	.02	.03
14	46	.01	.02	.1	.03	.05	.01	.01	.01	.01	.02	.06	.02	.03
14	46.84	.01	.02	.09	.03	.05	.01	.02	.01	.02	.02	.07	.02	.03
14	47	.01	.02	.09	.03	.04	.01	.02	.01	.02	.02	.06	.02	.03
14	48	.01	.02	.06	.03	.03	.01	.02	.01	.02	.02	.04	.02	.02
14	49	.01	.02	.05	.02	.03	.01	.01	.01	.01	.01	.03	.02	.02
14	50	.01	.02	.04	.02	.03	.01	.01	.01	.01	.01	.03	.02	.02
14	51	.01	.02	.03	.02	.02	.01	.02	.01	.02	.01	.02	.02	.02



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
14	84.05	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	88	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	89.77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	90	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	91	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	92	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	93	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	94	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	95	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	96	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	97	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
14	98	.01	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
14	99	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
14	100	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
14	101	.01	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
14	102	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
14	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
14	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
14	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
14	105.69	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
14	106	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
14	107	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
14	108	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
14	109	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01
14	110	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	111	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	112	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	113	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	114	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	115	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
14	116	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	0	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01
15	1	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.02	.01
15	2	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01
15	3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.02	.01

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		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
15	74	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	75	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	75.73	.02	.02	.02	.02	.02	.03	.02	.02	.03	.03	.02	.02	.02
15	76	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02
15	77	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	78	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	80	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	80.34	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
15	81	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
15	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
15	83	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01
15	84	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
15	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
15	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
15	86.98	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
15	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
15	88	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
15	89	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.02
15	90	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.02
15	91	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.02	.01	.02
15	92	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.02
15	93	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.02
15	94	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
15	95	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
15	95.25	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
15	96	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
15	97	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
15	98	.01	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
15	99	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01	.01
15	100	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.01
15	101	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.01	.01
15	102	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
15	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
15	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
15	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
15	106	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02
16	0	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01











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		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
17	95.73	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	96	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	97	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	98	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	99	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	100	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	101	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	102	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	105.76	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	106	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
17	107	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02
17	108	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.02	.01
17	109	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	110	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	111	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	112	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	113	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	114	.01	.02	.02	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
17	115	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.02
17	116	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.02	.01	.02
17	117	.01	.02	.03	.03	.03	.01	.01	.01	.01	.01	.02	.01	.02
17	118	.01	.02	.03	.03	.03	.01	.01	.01	.01	.01	.02	.01	.02
17	118.42	.01	.02	.03	.03	.04	.01	.01	.01	.01	.01	.02	.02	.02
17	119	.01	.02	.03	.03	.03	.01	.01	.01	.01	.01	.02	.01	.02
17	120	.01	.02	.06	.03	.05	.01	.01	.01	.01	.01	.02	.01	.02
17	121	.01	.02	.05	.03	.04	.01	.01	.01	.01	.01	.02	.01	.01
17	122	.01	.02	.05	.03	.04	.01	.01	.01	.01	.01	.01	.01	.01
17	123	.01	.02	.04	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
17	124	.01	.02	.04	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
17	125	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
17	126	.01	.02	.03	.02	.03	.01	.01	.01	.01	.01	.01	.01	.01
17	127	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	128	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	128.56	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	129	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
17	130	.01	.02	.03	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01







		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
18	58	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	59	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	60	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	61	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	62	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	62.34	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	63	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	64	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	65	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	66	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	67	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	68	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	69	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	70	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	71	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	72	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	73	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	74	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	74.58	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	75	.01	.02	.01	.02	.01	.01	.01	.01	.01	.01	.01	.01	.01
18	76	.01	.02	.01	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	76.98	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	79	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	80	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	81	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	82	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	83	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	83.31	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	84	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	85	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	86	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	87	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	88	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	88.13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
18	90	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01

[illegible]

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
19	10	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	11	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	12	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	13	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	14	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	15	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	16	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
19	17	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	18	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	18.79	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	19	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	20	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	21	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	22	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	23	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	24	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	25	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02
19	26	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	27	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	28	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	29	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	30	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.02
19	30.39	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.03	.03
19	31	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.03	.02
19	32	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.02
19	33	.03	.02	.02	.02	.02	.03	.02	.03	.02	.02	.02	.02	.02
19	34	.03	.02	.02	.02	.02	.03	.02	.03	.02	.02	.02	.02	.02
19	35	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	36	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.03	.02
19	37	.03	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02	.02
19	38	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	39	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	39.18	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	40	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	41	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	42	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	43	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	44	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
19	45	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
19	46	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
19	47	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
19	48	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
19	49	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.02	.01
19	50	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	51	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	51.53	.02	.02	.02	.02	.02	.01	.02	.02	.01	.01	.01	.01	.01
19	52	.02	.02	.02	.02	.02	.01	.02	.02	.01	.01	.01	.01	.01
19	53	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	54	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	55	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	56	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	57	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	57.46	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	58	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	59	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	60	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
19	61	.02	.02	.02	.02	.02	.01	.02	.02	.02	.01	.01	.02	.01
19	62	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	63	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	64	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
19	65	.04	.02	.02	.02	.02	.04	.04	.05	.04	.04	.04	.04	.04
19	65.01	.04	.02	.02	.02	.02	.04	.04	.05	.04	.04	.04	.04	.04
19	66	.04	.02	.02	.02	.02	.04	.04	.05	.04	.04	.04	.04	.04
19	67	.05	.02	.02	.02	.02	.04	.05	.05	.05	.05	.05	.05	.05
19	68	.07	.02	.02	.02	.02	.06	.07	.08	.07	.06	.07	.07	.07
19	68.82	.12	.02	.02	.02	.02	.11	.13	.12	.15	.11	.12	.11	.13
19	69	.12	.02	.02	.02	.02	.1	.13	.12	.14	.1	.12	.11	.13
19	70	.11	.02	.02	.02	.02	.1	.12	.11	.13	.1	.11	.1	.12
19	71	.09	.02	.02	.02	.02	.09	.11	.1	.12	.09	.1	.09	.1
19	72	.08	.02	.02	.02	.02	.08	.1	.08	.1	.08	.09	.08	.09
19	73	.07	.02	.02	.02	.02	.07	.09	.07	.09	.07	.08	.07	.08
19	74	.06	.02	.02	.02	.02	.06	.08	.06	.08	.06	.07	.06	.07
19	75	.06	.02	.02	.02	.02	.05	.07	.06	.07	.05	.06	.05	.06
19	76	.05	.02	.02	.02	.02	.05	.06	.05	.06	.05	.05	.05	.05
19	77	.05	.02	.02	.02	.02	.04	.05	.04	.05	.04	.05	.04	.05
19	78	.04	.02	.02	.02	.02	.04	.05	.04	.05	.04	.04	.04	.04

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
19	79	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.04	.04	.04
19	79.48	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.04	.03	.04
19	80	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.04	.04	.04
19	81	.04	.02	.02	.02	.02	.04	.04	.04	.04	.04	.04	.03	.04
19	82	.04	.02	.02	.02	.02	.04	.04	.04	.04	.03	.04	.03	.04
19	83	.04	.02	.02	.02	.02	.03	.04	.03	.04	.03	.03	.03	.03
19	84	.04	.02	.02	.02	.02	.03	.03	.03	.04	.03	.03	.03	.03
19	85	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
19	86	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
19	87	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.03	.02	.03
19	88	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02
19	89	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	90	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	91	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	92	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	93	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	94	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	95	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	95.17	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	96	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
19	97	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02
19	98	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	99	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	100	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	101	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	102	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
19	106	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	0	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	1	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
20	2	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
20	3	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
20	4	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
20	5	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
20	6	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
20	7	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
20	8	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
20	9	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01
20	10	.02	.02	.02	.02	.02	.02	.01	.02	.01	.01	.01	.01	.01
20	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	18.89	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	19	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	20	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	21	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	22	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	23	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	24	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	25	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	26	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	27	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.02
20	28	.02	.03	.02	.02	.02	.02	.02	.02	.02	.02	.01	.02	.01
20	29	.01	.03	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01
20	30	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	31	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	31.03	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	32	.01	.03	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	33	.01	.03	.02	.02	.02	.02	.01	.02	.02	.02	.01	.02	.01
20	34	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	35	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	36	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	37	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
20	37.66	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
20	38	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
20	39	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
20	40	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
20	41	.01	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
20	42	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01

[illegible]

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
20	77	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	78	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	79	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	80	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	81	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
20	82	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
20	82.05	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01
20	83	.02	.02	.02	.02	.02	.02	.01	.02	.01	.02	.01	.01	.01
20	84	.02	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
20	85	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01
20	86	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	87	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	88	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	89	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	90	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	91	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	92	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	92.7	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	93	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	94	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	95	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	96	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	97	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	98	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	98.96	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	99	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	100	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	101	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	102	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	103	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	104	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	105	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
20	106	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
20	107	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
20	108	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
20	109	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02
21	0	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02
21	1	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.02



		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
21	2	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.02	.01	.01
21	3	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	4	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	5	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	7	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	9	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	10	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	19.62	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	22	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	23	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	24	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	25	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	26	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	28	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	29	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	29.44	.01	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01	.01
21	30	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	31	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	32	.01	.02	.02	.02	.02	.01	.01	.01	.01	0	0	0	0
21	33	.01	.02	.02	.02	.02	0	0	0	0	0	0	0	0
21	34	0	.02	.02	.02	.02	0	0	0	0	0	0	0	0
21	35	.01	.02	.02	.02	.02	.01	.01	.01	.01	0	0	0	0
21	36	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	37	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
21	38	.02	.02	.02	.02	.02	.02	.02	.02	.02	.01	.01	.01	.01

[illegible]

		SZ	HET				POOL				Seq Update			
CHR	cM	Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
22	5	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	6	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	7	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	8	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	9	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	10	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	11	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	12	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	13	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	14	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	15	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	16	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	17	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	18	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	19	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	20	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	21	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	22	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	23	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	24	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	24.38	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	25	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	26	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	27	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	28	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	29	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	0	.01	0
22	30	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	0	.01	0
22	31	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	0	.01	0
22	32	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	33	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	34	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	35	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	35.57	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
22	36	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	37	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	38	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	39	.01	.02	.02	.02	.02	.01	.01	.01	.01	.01	.01	.01	.01
22	40	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01
22	40.89	.01	.02	.02	.02	.02	.01	.01	.01	.01	.02	.01	.01	.01

CHR	cM	SZ	HET				POOL				Seq Update			
		Pheno1	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3	Pheno1	Pheno2a	Pheno2b	Pheno3
22	41	.01	.02	.02	.02	.02	.02	.01	.01	.01	.02	.01	.01	.01
22	42	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
22	43	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
22	43.49	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
22	44	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02	.02
22	45	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02
22	46	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.03
22	47	.02	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.03
22	47.6	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02
22	48	.03	.02	.02	.02	.02	.02	.02	.02	.03	.02	.02	.02	.02
22	49	.03	.02	.02	.02	.02	.03	.02	.03	.03	.02	.02	.02	.03
22	50	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.03
22	51	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.03
22	52	.03	.02	.02	.02	.02	.03	.03	.03	.03	.02	.02	.02	.03
22	53	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.03
22	54	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.02	.02	.03
22	55	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.02	.03
22	56	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
22	57	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03
22	58	.03	.02	.02	.02	.02	.03	.03	.03	.03	.03	.03	.03	.03

## Appendix 2.NIMH Chinese Sample specific genetic maps

Chr.	Marker	cM	Chr.	Marker	cM	Chr.	Marker	cM
1	D1S2845	10	2	D2S441	91.70	3	D3S1262	182.35
1	D1S2660	10.8	2	D2S1394	98.34	3	D3S2398	189.50
1	D1S1612	15.92	2	D2S1777	103.86	3	D3S2418	195.53
1	D1S1597	24.61	2	D2S1790	110.40	3	D3S1311	204.01
1	D1S3669	34.96	2	D2S2972	116.53	4	D4S2366	10.00
1	D1S552	39.47	2	D2S410	128.35	4	D4S403	24.06
1	D1S1622	47.85	2	D2S1328	134.79	4	D4S2639	30.70
1	D1S255	57.26	2	D2S442	148.85	4	D4S391	41.67
1	D1S3721	61.37	2	D2S1399	156.41	4	D4S2632	48.21
1	D1S2134	66.59	2	D2S1353	163.86	4	D4S1627	57.83
1	D1S3728	80.11	2	D2S1776	170.09	4	D4S3248	66.72
1	D1S1665	92.99	2	D2S1391	186.01	4	D4S2367	71.84
1	D1S1728	99.73	2	D2S1384	197.09	4	D4S3243	82.92
1	D1S551	100.53	2	D2S2944	205.88	4	D4S2361	88.14
1	D1S1588	110.46	2	D2S434	211.30	4	D4S1647	99.64
1	D1S1631	118.43	2	D2S1363	223.22	4	D4S2623	107.50
1	D1S3723	120.13	2	D2S427	230.78	4	D4S2394	122.10
1	D1S534	133.01	2	D2S2968	242.07	4	D4S1644	133.70
1	D1S1653	143.77	2	D2S125	249.73	4	D4S1625	134.00
1	D1S1679	151.94	3	D3S2387	10.00	4	D4S1629	146.13
1	D1S1677	154.64	3	D3S1560	18.07	4	D4S2368	157.63
1	D1S1619	167.84	3	D3S1304	23.49	4	D4S2431	163.46
1	D1S1589	168.74	3	D3S4545	26.69	4	D4S2417	171.53
1	D1S518	178.77	3	D3S1259	34.55	4	D4S408	181.04
1	D1S1660	184.7	3	D3S3038	44.79	4	D4S1652	190.14
1	D1S1647	190.32	3	D3S2432	59.83	5	D5S2488	10.00
1	C1S1248	198.59	3	D3S1768	62.83	5	D5S2849	18.48
1	D1S2141	205.64	3	D3S2409	67.64	5	D5S2505	24.61
1	D1S549	211.06	3	D3S1600	70.49	5	D5S807	29.32
1	D1S3462	221.61	3	D3S4542	74.40	5	D5S817	35.04
1	D1S235	229.17	3	D3S2406	86.43	5	D5S2845	46.75
1	D1S547	242.05	3	D3S4529	92.66	5	D5S2848	51.16
1	D1S1609	246.26	3	D3S2459	98.89	5	D5S1470	58.00
2	D2S2976	10	3	D3S3045	102.70	5	D5S1457	66.79
2	D2S2952	27.48	3	D3S2460	111.08	5	D5S2500	75.89
2	D2S1400	38.03	3	D3S4523	113.08	5	D5S424	88.55
2	D2S1360	46.92	3	D3S1764	129.11	5	D5S641	94.17
2	D2S405	56.43	3	D3S1744	138.00	5	D5S1725	99.69
2	D2S1788	66.36	3	D3S1763	153.92	5	D5S1503	105.31
2	D2S1356	73.92	3	D3S3053	159.24	5	D5S1453	110.23
2	D2S1352	83.12	3	D3S2427	167.31	5	D5S2501	111.93

Chr.	Marker	cM	Chr.	Marker	cM	Chr.	Marker	cM
5	D5S1505	119.49	7	D7S3070	156.10	10	D10S2325	33.92
5	D5S816	134.31	7	D7S3058	165.61	10	D10S1423	47.12
5	D5S1480	140.75	7	D7S559	171.33	10	D10S1426	61.61
5	D5S820	155.57	8	D8S264	10.00	10	D10S1208	67.03
5	D5S1471	169.52	8	D8S1469	24.71	10	D10S1221	79.80
5	D5S1456	174.64	8	D8S1130	29.12	10	D10S1225	83.31
5	D5S211	184.67	8	D8S1106	31.02	10	C10S1218	87.72
5	D5S408	196.27	8	D8S1145	38.07	10	D10S1432	93.85
6	F13A1	10.00	8	D8S560	38.67	10	D10S2327	101.10
6	D6S2434	25.15	8	D8S136	40.40	10	D10S2470	113.55
6	D6S1660	39.53	8	D8S1771	46.63	10	D10S677	119.07
6	D6S2439	40.53	8	D8S1477	57.08	10	D10S1239	125.61
6	D6S2427	49.01	8	D8S1110	66.90	10	D10S1237	136.37
6	D6S1017	53.62	8	D8S1113	72.73	10	D10S1230	148.71
6	D6S2410	61.69	8	D8S1136	77.65	10	D10S1656	155.86
6	D6S1053	66.50	8	D8S2324	88.62	10	D10S217	162.80
6	D6S1031	74.16	8	D8S1119	95.67	10	D10S212	169.24
6	D6S1056	85.55	8	C8S14	105.81	11	D11S1984	10.00
6	D6S1021	93.41	8	D8S1132	113.47	11	D11S2362	16.64
6	D6S474	99.74	8	D8S592	119.60	11	D11S1999	26.26
6	D6S1040	112.08	8	D8S1179	131.20	11	D11S1981	35.15
6	D6S1009	118.62	8	D8S1128	135.21	11	C11S348	49.53
6	C6S1848	130.12	8	D8S256	144.52	11	D11S1392	55.87
6	D6S2436	139.94	8	D8S373	163.13	11	D11S1344	71.23
6	D6S1035	147.19	9	D9S2169	10.00	11	D11S2371	84.97
6	D6S1277	153.52	9	D9S168	18.17	11	D11S2002	89.98
6	D6S1027	164.28	9	D9S925	33.50	11	D11S2000	109.75
7	D7S3056	10.00	9	D9S1121	43.53	11	D11S1391	113.66
7	D7S513	23.52	9	D9S1118	51.39	11	D11S1998	126.54
7	D7S3051	34.49	9	D9S301	62.89	11	D11S4464	134.10
7	D7S1802	37.69	9	D9S1122	72.30	11	D11S912	142.68
7	D7S1808	46.79	9	D9S922	75.60	11	D11S968	155.98
7	D7S817	54.65	9	D9S283	88.37	12	D12S372	10.00
7	D7S2846	61.29	9	D9S1786	95.72	12	C12S4912	21.18
7	D7S1818	72.68	9	D9S938	100.94	12	D12S391	27.92
7	D7S3046	78.81	9	D9S930	111.39	12	D12S373	36.30
7	D7S2204	88.32	9	D9S934	120.59	12	D12S1042	50.25
7	D7S2212	92.63	9	D9S1825	127.74	12	C12S916	59.66
7	D7S821	100.49	9	D9S2157	139.13	12	D12S398	66.61
7	D7S1799	107.03	9	D9S1826	148.75	12	D12S1294	79.06
7	D7S3061	119.80	9	D9S1838	152.76	12	D12S375	80.66
7	D7S1804	127.77	10	D10S1435	10.00	12	D12S1052	85.17
7	D7S1824	138.22	10	D10S189	22.77	12	D12S1064	92.22
7	D7S2195	143.44	10	D10S1412	29.00	12	D12S1300	101.94

Chr.	Marker	cM	Chr.	Marker	cM	Chr.	Marker	cM
12	PAH	104.84	15	D15S655	62.55	18	D18S535	62.34
12	D12S2070	118.58	15	D15S652	68.07	18	D18S851	74.58
12	D12S395	127.06	15	D15S816	75.73	18	D18S858	76.98
12	D12S2078	138.98	15	D15S657	80.34	18	D18S862	83.31
12	D12S1045	150.48	15	D15S966	86.98	18	D18S1364	88.13
12	D12S392	152.78	15	D15S642	95.25	18	C18S822	95.27
13	D13S787	10.00	16	D16S2616	10.00	18	D18S1371	106.46
13	D13S217	21.92	16	D16S748	21.60	19	D19S591	10.00
13	D13S1493	30.92	16	D16S3103	28.34	19	D19S1034	18.79
13	D13S894	37.25	16	D16S403	32.55	19	D19S586	30.39
13	D13S325	42.57	16	D16S769	40.32	19	D19S714	39.18
13	D13S788	53.65	16	D16S540	44.83	19	D19S433	51.53
13	D13S800	68.14	16	D16S3396	47.03	19	D19S245	57.46
13	D13S317	77.97	16	D16S3253	54.69	19	D19S178	65.01
13	D13S793	85.42	16	D16S2624	67.57	19	D19S246	68.82
13	D13S779	91.35	16	D16S3096	75.64	19	D19S589	79.48
13	D13S796	104.01	16	D16S3091	84.53	19	D19S254	95.17
13	D13S1265	108.02	16	D16S539	98.59	20	D20S103	10.00
13	D13S285	119.20	16	D16S2621	102.90	20	D20S482	18.89
14	D14S742	10.00	17	D17S1308	10.00	20	D20S851	31.03
14	D14S1280	18.79	17	D17S1298	16.94	20	D20S604	37.66
14	D14S608	19.99	17	D17S974	42.19	20	D20S470	47.18
14	D14S599	30.33	17	D17S1303	43.19	20	D20S477	54.02
14	D14S306	35.55	17	D17S799	48.31	20	D20S478	62.40
14	D14S587	46.84	17	D17S2196	58.66	20	D20S481	72.33
14	D14S592	52.16	17	D17S975	62.27	20	D20S480	82.05
14	D14S588	59.31	17	D17S1880	66.18	20	D20S451	92.70
14	D14S53	66.15	17	D17S1293	69.93	20	D20S171	98.96
14	D14S606	70.97	17	D17S1299	79.44	21	D21S1432	10.00
14	C14S1937	78.63	17	D17S2180	82.85	21	D21S1437	19.62
14	D14S617	84.05	17	D17S1290	95.73	21	D21S2052	29.44
14	D14S1434	89.77	17	D17S2193	105.76	21	D21S1440	38.13
14	D14S1426	105.69	17	D17S1301	118.42	21	D21S2055	42.54
15	D15S822	10.00	17	D17S784	128.56	21	D21S1446	59.91
15	D15S165	12.20	17	D17S928	132.87	22	D22S420	10.00
15	D15S1012	14.10	18	C18S1781	10.00	22	D22S345	24.38
15	D15S659	21.05	18	D18S976	19.51	22	D22S689	35.57
15	D15S643	34.67	18	D18S843	29.34	22	D22S685	40.89
15	D15S1507	42.33	18	D18S542	39.27	22	D22S683	43.49
15	D15S131	50.10	18	D18S877	53.65	22	D22S445	47.60

## Curriculum Vitae

**Viatcheslav SAVIOUK, MD**

### EDUCATION

Graduate Program in Molecular Biosciences Rutgers, the State University of New Jersey & The University of Medicine and Dentistry of New Jersey. <b>PhD</b> , October 2008	2000-2008
Siberian State Medical University, Tomsk, Russia <b>MD</b> , Summa Cum Laude	1993-1999

### POSITIONS HELD

Research Assistant Rutgers, the State University of New Jersey	2006-present
Clinical Instructor / Pediatric Resident State University of New York, Downstate Medical Center & Kings County Hospital, Brooklyn, NY	2005-2006

### RECENT PUBLICATIONS

**V. Saviouk**, M.P. Moreau, I.V. Tereshchenko, L. Brzustowicz. Association of synapsin 2 with schizophrenia in families of Northern European ancestry. Schizophrenia research, 2007 Nov; 96 (1-3): 100-111

**V. Saviouk**, E. W. C. Chow, A. Bassett, L. Brzustowicz. Tumor necrosis factor promoter haplotype associated with schizophrenia reveals a linked locus on 1q44. Molecular Psychiatry. 2005 Apr; 10 (4): 375-383