# Examination of Genetic Linkage of Chromosome 15 to Schizophrenia in a Large Veterans Affairs Cooperative Study Sample

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Previous studies have reported genetic linkage evidence for a schizophrenia gene on chromosome 15q. Here, chromosome 15 was examined by genetic linkage analysis using 166 schizophrenia families, each with two or more affected subjects. The families, assembled from multiple centers by the Department of Veterans Affairs Cooperative Study Program, consisted of 392 sampled affected subjects and 216 affected sibling pairs. By DSM-III-R criteria, 360 subjects (91.8%) had a diagnosis of schizophrenia and 32 (8.2%) were classified as schizo-affective disorder, depressed. Participating families had diverse ethnic backgrounds. The largest single group were northern European American families (n = 62, 37%), but a substantial proportion was African American kindreds (n = 60, 36%). The chromosome 15 markers tested were spaced at intervals of approximately 10 cM over the entire chromosome and 2–5 cM for the region surrounding the α-7 nicotinic cholinergic receptor subunit gene (CHRNA7). These markers were genotyped and the data analyzed using semiparametric affecteds-only linkage analysis. In the European American families, there was a maximum Z-score of 1.65 between markers D15S165 and D15S1010. These markers are within 1 cM from CHRNA-7, the site previously implicated in schizophrenia. However, there was no evidence for linkage to this region in the African America kindreds. Published 2001 Wiley-Liss, Inc.†

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## INTRODUCTION

The etiology of schizophrenia is unknown. Twin, adoption, and family studies consistently implicate genetic factors in schizophrenia susceptibility [McGue and Gottesman, 1989; Tsuang, 2000]. Genetic linkage analysis has been used extensively in attempts to identify candidate regions for schizophrenia susceptibility loci. One candidate region identified by this approach is chromosome 15q14. Freedman et al. [1997] provided the initial evidence for a schizophrenia locus in this region when they demonstrated linkage using an auditory-evoked response inhibition as the phenotype. Prior work demonstrated that schizophrenia subjects and a subset of nonschizophrenic relatives exhibit a reduced ability to inhibit the P50 response compared to controls [Waldo et al., 1991]. When P50 response inhibition was used as an endophenotype in a genome-wide linkage study, parametric linkage analysis yielded strong evidence for linkage to 15q14 markers ($LOD_{max} = 5.30$, $\theta = 0$, $P < 0.001$, for marker D15S1360). Marker D15S1360 is physically close to the $\alpha$-7 nicotinic cholinergic receptor subunit (CHRNA7) gene.

Several subsequent linkage studies have reported positive results for 15q14 markers using narrow and broadly defined schizophrenia (including schizo-affective depressed) as the phenotype [Kaufmann et al., 1998; Leonard et al., 1998; Riley et al., 2000]. Another positive study used periodic catatonia [Stober et al., 2000] as the phenotype. In contrast, other replication studies of 15q14 have yielded negative results [Neves-Pereira et al., 1998; Curtis et al., 1999]. With two exceptions [Coon et al., 1994; Kaufmann et al., 1998], complete genome-wide studies have not identified 15q14 as a region of interest [Moises et al., 1995; Pulver et al., 1995; Levinson et al., 1998; Hovatta et al., 1999; Ekelund et al., 2000; Gurling et al., 2001].

To address the possibility of a schizophrenia locus at 15q13–14, we examined linkage of chromosome 15 markers to schizophrenia in 166 previously unstudied families ascertained by the Department of Veterans Affairs Cooperative Studies Program [Tsuang et al., 2000]. Each family had two or more affected subjects and DNA from a total of 773 subjects (including 392 affected subjects) was available. This study included families with diverse ethnic backgrounds. Modest evidence for linkage was obtained with 15q14 markers for European American families but not in African American families. These results provide some support for a schizophrenia gene at 15q14, near or at CHRNA7.

## MATERIALS AND METHODS

### Ascertainment

The Department of Veterans Affairs (DVA) Cooperative Studies Program (CSP) collected clinical data and blood samples from 166 families with two or more affected subjects from seven Veteran Affairs Medical Centers [Tsuang et al., 2000]. Pedigrees were ascertained in three stages: two probands (schizophrenia or schizo-affective disorder, depressed) for each family were recruited; all first-degree relatives were subsequently enrolled; pedigrees were extended into branches containing additional affected subjects. Individuals were diagnosed based on the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994; Faraone et al., 1996]. All probands and biological relatives who agreed to participate completed the following standard research protocol: a structured diagnostic interview and family history assessment for Axis-I disorders; an assessment of schizotypal personality disorder; and an assessment for positive and negative symptoms.

### Clinical Characteristics

All diagnoses were independently made according to DSM-III-R by two senior psychiatrists or psychologist investigators with clinical and research experience in the diagnosis of psychosis. When disagreements occurred, the absence of the diagnosis was accepted to avoid false positive classifications. The diagnosis was made based on the content of the interview, the case vignette, information provided by the relatives, and a complete review of medical records. As previously reported, the kappa coefficient for ascertainment diagnosis in a subset of 42 subjects among the seven sites was 0.89 [Tsuang et al., 2000].

Among the 166 families ascertained, 124 had two affected subjects, 30 had three affected subjects, 7 had four affected subjects, 4 had five affected subjects, and 1 had six affected subjects. There are a total of 216 affected sibling pairs in these families. The mean number of individuals sampled was 4.7 per family. Most of the affected subjects (n = 360; 91.8%) met DSM-III-R criteria for schizophrenia. Thirty-two subjects met criteria for schizo-affective disorder, depressed. The mean age of onset was $22.1 \pm 6.2$ years. The probands were 76% male with a mean current age of $43 \pm 10$ years. The relatives were 42% male with a mean current age of $49 \pm 17$ years.

### Genotyping

Genotypes were determined by PCR amplification of polymorphic loci using primers labeled with fluorescent probes. DNA fragments were analyzed using an ABI377 DNA sequencing instrument and GeneScan and Genotyper software. Two different individuals who were blind to subject phenotype independently reviewed each genotype. Technicians performing the genotyping were blind to the diagnosis of the subjects. Approximately 5% of the samples were genotyped twice to check for accuracy. PedCheck was used to identify genotypes incompatible with Mendelian inheritance [O'Connell and Weeks, 1998].

### Linkage Analysis

We performed semiparametric linkage analysis using the exponential model of Genehunter Plus [Kong and Cox, 1997], a modified version of Genehunter [Kruglyak et al., 1996]. We used the $S_{pairs}$ score that assesses identity by descent (IBD) sharing among all pairs of

affected individuals within families. We repeated our analyses using the $S_{all}$ score and obtained very similar results.

Before performing the linkage analysis, we divided the families into ethnic groups based on the probands' parents' races as identified in the DIGS. For the 166 families, 62 (37%) had both parents listed as European American, 60 (36%) had both listed as African American, and 44 (27%) had parents listed as other races or different races. Based on this information, we defined broad and narrow race categories. For the narrow ethnic group, we included only those 122 families in which both parents are of the same ethnic group (both either African American, n = 60, or European American, n = 62). For the broad ethnic group categories, 13 families were added to the European American group. These families had at least one European American parent and the second parent was non–African American. Also, for the broad ethnic category, 31 families were added to the African American group. These families had either one African American parent or two mixed race parents where each parent was part African American.

We used two definitions of affection status. The narrow definition included only schizophrenia and schizo-affective disorder, depressed. The broad definition also included schizotypal personality disorder (n = 19) and psychotic disorder not otherwise specified (n = 6).

Of the 166 families, 30 had repeated genotype incompatibilities at many markers. For 13 families, reported pedigree structures were incorrect but could easily be corrected by using the available genotype information. Correct relationships for the remaining 17 families could not be resolved with our present data, and those families were excluded from the current analysis. Finally, we identified 25 families with three or fewer genotype incompatibilities, but with little evidence of incorrect pedigree structure. For these families, we excluded marker data for the marker with the identified error, but kept all other marker data. Table I lists the numbers of families and affected individuals included in each analysis, after excluding the 17 families with large numbers of unexplained genotype incompatibilities.

## RESULTS

Previous linkage studies have identified 15q as a candidate region for a schizophrenia locus. Thus, as part of an ongoing genetic linkage study of all chromosomes, we initially targeted chromosome 15 for analysis. The sample used was ascertained at seven Veterans Affairs Medical Centers [Tsuang et al., 2000] and consisted of 166 families with two or more affected subjects for a total of 216 sibling pairs. The families were of mixed ethnic background with European Americans (37%) and African Americans (36%) comprising the major groups. The high proportion of African American kindreds reflects the patient population of the Veterans Affairs Medical Centers involved in the study.

Figure 1 shows the results of the linkage analysis with chromosome 15 markers, when race is broadly defined and affection status is narrowly defined. The maximum signal is observed in European American families with the peak $Z_{max}$ of 1.65 (Fig. 1) occurring at 22.5 cM, between markers D15S165 (20.2 cM) and D15S1010 (23.9 cM). This $Z_{max}$ (on a standard normal scale) converts to a maximum LOD score of 0.59 ($P = 0.05$). When the affection status is broadly defined, the location of the peak remains the same but its magnitude decreases ($Z_{max} = 1.53$ at 22.5 cM). The African American families show decreased allele sharing (Z-score = −1.89) at this location. The combined data for all ethnic groups yield Z-scores of −0.41 and −0.45 at 22.5 cM under narrow and broad affection status definitions, respectively.

Strong evidence against linkage is present in the African American families when race is narrowly defined. A nadir located between markers D15S1040 (28.3 cM) and D15S118 (32.6 cM) achieves a Z-score value of −3.68 and −3.54 at 30 cM for narrow and broad definitions of schizophrenia, respectively.

## DISCUSSION

Our work provides some support for the existence of a schizophrenia locus near the centromere of chromosome 15 in European American kindreds. Interestingly, our peak is within 1 cM of D15S1360, the marker that provided the most significant previous evidence for linkage [Freedman et al., 1997]. The study by Freedman et al. [1997] was a linkage study in which P50 response inhibition was used as an endophenotype in nine European American families. Because P50 inhibition is not easily or routinely measured, the study by Freedman et al. [1997] has not been directly replicated. However, the proposed association between the P50 phenotype and schizophrenia and the observed linkage of D15S1360 to the P50 phenotype provides strong evidence for a schizophrenia gene in this

TABLE I. Number of Families and Affected Individuals Included in Each Analysis

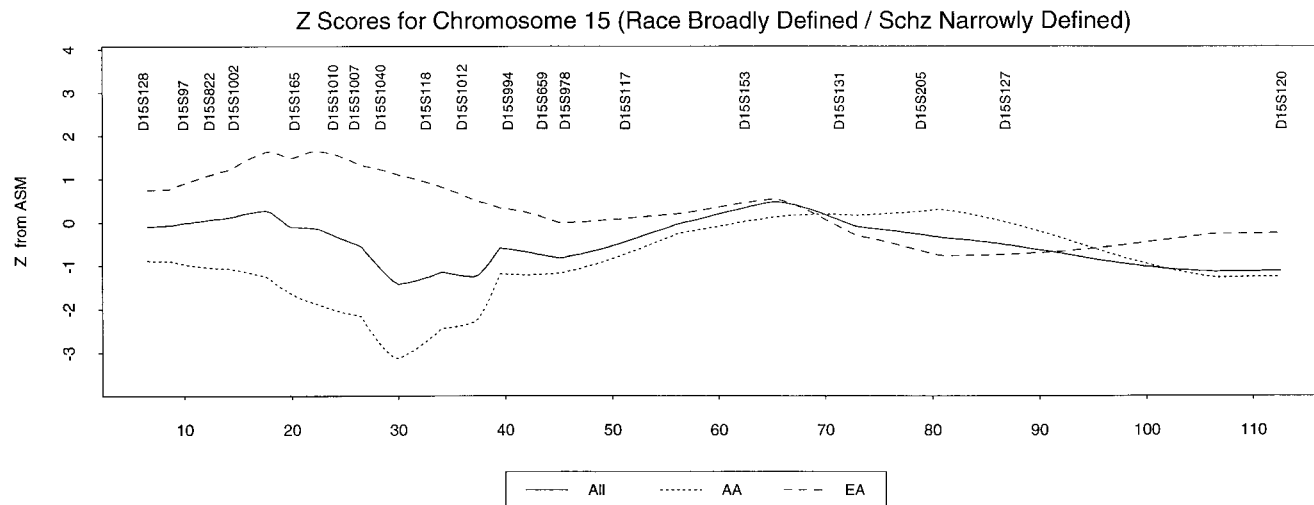| Race | Race broadly defined | | | Race narrowly defined | | |
| | Number of families | Number affected | | Number of families | Number affected | |
| | | Broad | Narrow | | Broad | Narrow |
|---|---|---|---|---|---|---|
| African American | 75 | 186 | 173 | 48 | 118 | 109 |
| European American | 74 | 178 | 172 | 61 | 139 | 135 |

Fig. 1. Plot of Z-scores versus chromosome position (Kosambi cM). Z-scores are plotted versus genetic map position for racial groups broadly defined and schizophrenia narrowly defined. Genetic map positions are from Marshfield map (http://research.marshfieldclinic.org/genetics/Map_Markers/data/Maps). All, all families for all racial groups; AA, African America; and EA, European American. Affectation and race classification descriptions are explained in text.

region. Maximum evidence for P50 trait linkage ($LOD_{max} = 5.30$, $\theta = 0$) was obtained with marker D15S1360, which is located at approximately 23 cM on the genetic map used in Figure 1. In the same families, when the clinical diagnosis of schizophrenia was the phenotype, a lower LOD score was obtained ($LOD = 1.33$, $\theta = 0.07$, D15S1360), which is consistent with fewer subjects being classified as affected in the analysis. Multipoint analysis in the P50 phenotype study yielded a broad peak that substantially overlapped with the multipoint peak obtained in our European American families (Fig. 1).

Other linkage studies have also reported positive findings for the proximal region of chromosome 15. Stober et al. [2000] performed a linkage analysis using periodic catatonia as the phenotype and found that the largest signal generated by a genome-wide screen was on chromosome 15 at 35 cM (nonparametric $LOD = 3.57$, $P = 2.6 \times 10^{-5}$). The National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative study used schizophrenia and schizo-affective depressed as the phenotype and found positive evidence for linkage in this region for African American kindreds (NPL Z-score $= 1.96$, $P = 0.027$) [Kaufmann et al., 1998] but not for European American kindreds [Faraone et al., 1998]. The multipoint peak for the African American analysis was at approximately 6 cM (more centromeric than the peak obtained by Stober et al. [2000]). The NIMH study used the same diagnostic protocols as those applied in the present study. Reanalysis of a subset of the NIMH families, excluding schizo-affective depressed subjects, resulted in a LOD score of 1.46 at $\theta = 0.00$ ($P = 0.002$) for D15S1360 [Leonard et al., 1998].

Other replication studies have yielded negative results. A study that included five multiplex Canadian families found no evidence for linkage to D15S1360 [Neves-Pereira et al., 1998]. Another study that included 54 families also provided no evidence for

linkage to D15S1360 or the flanking markers [Curtis et al., 1999] used in the initial positive report [Freedman et al., 1997]. Genome-wide studies have not typically identified 15q14 as a region of interest [Moises et al., 1995; Pulver et al., 1995; Levinson et al., 1998; Hovatta et al., 1999; Ekelund et al., 2000; Gurling et al., 2001].

There are several reasons why some studies failed to produce a positive chromosome 15 signal. First, considering that schizophrenia may be multigenic and genetically heterogeneous, failure to detect linkage at a specific site does not necessarily exclude the presence of a gene at that site. Rather, some samples may be too small to detect linkage, or the genetic model used may not be appropriate.

Second, different schizophrenia loci or allelic variants may be important in different ethnic groups. In our study, only European American families yielded positive results for 15q14 markers while the African American families did not have evidence for linkage. In contrast, in the NIMH study, results for chromosome 15 were positive for the African American [Kaufmann et al., 1998] but not European American kindreds [Faraone et al., 1998]. These findings are consistent with the hypothesis that schizophrenia is genetically heterogeneous [Tsuang et al., 1999; Gurling et al., 2001] and that schizophrenia loci may differ among various ethnic groups.

Third, diagnostic criteria vary between studies. The current diagnostic criteria for schizophrenia were developed to improve the reliability of the diagnosis. However, this may have resulted in a phenotype that does not reflect the underlying genotype. For genetic studies, it is less important for the diagnosis to correspond to the pure clinical disorder of interest than it is for it to correspond to the underlying genetic entity. Current diagnostic categories may not correctly identify the range of phenotypes associated with varying

combinations of susceptibility genes. In our study, the largest signal was observed when affection status was narrowly defined, which included schizophrenia and schizo-affective disorder, depressed. Similarly, other positive studies used narrowly defined schizophrenia [Leonard et al., 1998; Riley et al., 2000] as well as peripheral phenotypes such as periodic catatonia [Stober et al., 2000]. The diagnostic boundaries of schizophrenia appropriate for genetic studies remain unclear.

Fourth, the chromosome 15-positive signals may be false positive results. This appears less likely given the highly significant results in the P50 inhibition study and the frequency of other replications.

A strong candidate for the chromosome 15 schizophrenia locus is CHRNA7. This gene encodes a subunit of the α-7 nicotinic cholinergic receptor and is within 120 kb of D15S1360 [Gault et al., 1998]. D15S1360 yielded the highest LOD score in the P50 response inhibition linkage study [Freedman et al., 1997] and is within 1 cM from our linkage peak. P50-evoked response potentials can be modulated by cholinergic agonists and antagonists [Leonard et al., 2000]. Nicotine, which binds with high affinity to the CHRNA7 gene, temporarily normalizes the P50 deficits in both schizophrenics and normal controls [Adler et al., 1992]. Other pharmacological data suggest an association between P50 response deficits and the CHRNA7 gene [Luntz-Leybman et al., 1992; Griffith et al., 1998; Stevens et al., 1998]. Thus, it is plausible that CHRNA7 is part of the receptor involved in P50 response inhibition.

Furthermore, twin studies indicate that the inability to inhibit an auditory-evoked response is heritable [Myles-Worsley et al., 1996] and the P50 deficit may be inherited as an autosomal dominant trait [Leonard et al., 1996]. A proportion of schizophrenic patients' clinically unaffected first-degree biological relatives also exhibits poor P50 response suppression [Siegel et al., 1984; Waldo et al., 1991; Clementz et al., 1998]. Overall, these data suggest that this measure may be associated with genetic liability for schizophrenia and that allelic variations in the CHRNA7 gene may be involved in poor P50 suppression.

Direct genetic evaluation of CHRNA7 as a candidate gene has been difficult because the gene is partially duplicated [Gault et al., 1998], making mutation screening problematic. Initial analysis failed to identify a coding region polymorphism with an allele that has an elevated frequency in schizophrenic subjects [Gault et al., 1999; Freedman et al., 2001]. Linkage disequilibrium analysis of markers close to CHRNA7 has yielded mixed results. In the NIMH families, D15S1360, the marker closest to CHRNA7, does not give significant results [Freedman et al., 2001]. However, linkage disequilibrium of D15S165, which is within 1 Mb of CHRNA7, was significant in the combined data set (African American and European American kindreds together) but not for each group separately [Freedman et al., 2001]. Transmission disequilibrium analysis also yielded significant results. In South African Bantu families, haplotype transmis-sion disequilibrium analysis for D15S1360 and flanking marker D15S1043 gave a maximum chi-square of 6.57 ($P = 0.004$) [Riley et al., 2000].

While linkage and linkage disequilibrium are consistent with CHRNA7 being the chromosome 15 schizophrenia gene, the possibility remains that another gene in this region contains the disease-predisposing allele. MEIS2, a homeobox gene involved in neuro-development, is highly active in the subventricular region, the site of neurogenesis [Toresson et al., 2000]. Another gene, CKTSF1B1, the human homologue of DRM/GREMLIN (a DAN/Cerbeus family protein) is highly expressed in subcortical neurons and astrocytes and is thought to be an inhibitory factor during neurodevelopment [Topol et al., 2000]. The ryanodine-3 receptor, found throughout the brain, is an intracellular $Ca^{2+}$ storage modulator and is an important component of the $Ca^{2+}$-modulated spike firing pattern in the thalamocortical systems associated with the waking state [Budde et al., 2000]. Additional studies are needed to determine if any of these genes including CHRNA7 contribute to the pathogenesis of schizophrenia.

## ACKNOWLEDGMENTS

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