Linkage of Chromosome 13q32 to Schizophrenia in a Large Veterans Affairs Cooperative Study Sample

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Several prior reports have suggested that chromosomal region 13q32 may harbor a schizophrenia susceptibility gene. In an attempt to replicate this finding, we assessed linkage between chromosome 13 markers and schizophrenia in 166 families, each with two or more affected members. The families, assembled from multiple centers by the Department of Veterans Affairs Cooperative Studies Program, included 392 sampled affected subjects and 216 affected sib pairs. By DSM-III-R criteria, 360 subjects (91.8%) had a diagnosis of schizophrenia and 32 (8.2%) were classified as schizoaffective disorder, depressed. The families had mixed ethnic backgrounds. The majority were northern European-American families ($n = 62$, 37%), but a substantial proportion were African-American kindreds ($n = 60$, 36%). Chromosome 13 markers, spaced at intervals of approximately 10 cM over the entire chromosome and 2–5 cM for the 13q32 region were genotyped and the data analyzed using semiparametric affected only linkage analysis. For the combined sample (with race broadly defined and schizophrenia narrowly defined) the maximum LOD score was 1.43 (Z-score of 2.57; $P = 0.01$) at 79.0 cM between markers D13S1241 (76.3 cM) and D13S159 (79.5 cM). Both ethnic groups showed a peak in this region. The peak is within 3 cM of the peak reported by Brzustowicz et al. [1999: Am J Hum Genet 65:1096–1103]. Published 2002 Wiley-Liss, Inc.[†]

KEY WORDS: chromosome 13; schizophrenia; linkage; genetics

INTRODUCTION

Twin and adoption studies have consistently implicated genes in the etiology of schizophrenia [Tsuang et al., 1999], and molecular genetic studies have found some consistent support for linkage to 10 regions of the genome(1q21–q22, 5q11.2–q13.3, 6q13–q26, 6p23, 8p21, 11q14–q21, 13q32, 15q15, 18p, 22q11–q13).

Interest in chromosome 13q32 was first generated by Lin et al. [1995] who studied 13 moderate to large families from the United Kingdom and Japan. They reported a maximum LOD score of 1.62 for marker D13S119. In an attempt to replicate these findings, Lin et al. [1997] studied four families from Taiwan and 10 from the United Kingdom. For the UK sample, the maximum LOD score was 1.72 at marker D13S128. The Taiwanese sample showed no evidence of linkage.

Further evidence for linkage to 13q32 came from Blouin et al.'s [1998] genome scan of 54 families. In this region, the maximum LOD score was 4.18 at marker D13S174. A smaller, yet suggestive, LOD score was reported from the genome scan of Shaw et al. [1998]. In a sample of 70 pedigrees, they found a LOD score of 2.85 at marker D13S1293. Subsequently, Brzustowicz et al. [1999], in a study of 21 Canadian families, reported a LOD score of 4.42 at marker D13S793.

Because these positive findings from non-overlapping families cluster within the same region of chromosome 13q, they suggest that this region may harbor one or more schizophrenia predisposing genes. Yet there are also several negative reports [Coon et al., 1994; Faraone et al., 1998; Kaufmann et al., 1998; Riley et al., 1998; DeLisi et al., 2000; Levinson et al., 2000; Mowry et al., 2000; Schwab et al., 2000; Gurling et al., 2001].

The most notable negative report was from Levinson et al. [2000], who studied linkage to 13q in 734 informative multiplex pedigrees containing 824 independent affected sibling pairs. These had been collected in eight centers, including two that had previously reported linkage to the 13q region [Blouin et al., 1998; Shaw et al., 1998]. In this very large sample, the maximum LOD score in the region was 0.09, which argues against the hypothesis that the region contains a schizophrenia susceptibility gene.

In this report, we assess linkage of chromosome 13 markers to schizophrenia in 166 families collected through the Department of Veterans Affairs Cooperative Studies Program [Tsuang et al., 2000]. Our results are consistent with the idea that chromosomal region 13q32 may harbor a schizophrenia susceptibility gene.

MATERIALS AND METHODS

The Department of Veterans Affairs (DVA) Cooperative Studies Program (CSP) collected clinical data and blood samples from 166 families ascertained through a pair of affected siblings. A comprehensive description of the sample and methods of data collection has been published [Tsuang et al., 2000]. Family members were classified as affected if they had a diagnosis of schizophrenia or schizoaffective, depressed, based on the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994; Faraone et al., 1996].

DSM-III-R diagnoses were made 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 based on the content of the DIGS interview, information provided by relatives who had been interviewed with the Family Interview for Genetic Studies (FIGS), and a review of medical records. We achieved high inter-rater agreement on the ascertainment diagnoses as indicated by a kappa coefficient of 0.89 [Tsuang et al., 2000].

Among the 166 families, 124, 30, 7, 4 and 1 had 2, 3, 4, 5 and 6 affected members, respectively. There are a total of 216 affected sibling pairs in these families. The mean number of individuals sampled per family was 4. Most of the affected subjects ($n = 360$; 91.8%) met DSM-III-R criteria for schizophrenia. The remainder ($n = 32$) met criteria for schizoaffective disorder, depressed. The mean age of onset among affected individuals was 22.1 years (SD, 6.2 years). The probands were 76% male with a mean current age of 43 years (SD,10 years). The relatives were 42% male with a current mean age of 49 years (SD,17 years).

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 carried out semi-parametric 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 the linear model and obtained very similar results. The LOD scores reported are those calculated by the allele sharing module of Kong and Cox [1997]. They are not converted NPL scores from Genehunter. The Z-score could be arrived at by: $Z = sign(dhat)*sqrt(2.0)*ln(10.0)*LOD)$, where dhat is the estimate of the excess allele sharing statistic.

Before performing the linkage analysis, we divided the families into racial groups based on the probands' parents' races as identified in the DIGS. For the 166 families, 62 had both parents listed as European American (EA), 60 had both listed as African American (AA), and 44 had parents listed as other races or different races. Based on this information, we defined broad and narrow race categories. For the narrow definition 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.

Two definitions of affection status were used. The narrow definition included only schizophrenia and schizoaffective 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 10 families, reported pedigree structures were incorrect but could easily be corrected by using the available genotype information. Correct relationships for the remaining 20 families could not be resolved with our present data, and those families were excluded from the current analysis. 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 families with large numbers of genotype incompatibilities.

RESULTS

Figure 1 provides multipoint LOD scores for each definition of schizophrenia and race. Table II provides the peak LOD scores and locations. The largest LOD score was attained when both EA and AA families are included in the analysis, which yielded a peak LOD score of 1.43 (Z-score of 2.57, $P = 0.01$) at 79.0 cM between markers D13S1241 (76.3 cM) and D13S159 (79.5 cM). This peak value was achieved using the narrow definition of schizophrenia and broad definition of race. For this definition, the African-American sample had a peak LOD score of 0.30 (Z-score of 1.79, $P = 0.07$) at 70 cM. The European-American sample had a peak LOD score of 1.31 (Z-score of 2.48, $P = 0.01$) at 80 cM.

In the European American families, broadly defining both schizophrenia and race yielded the highest peak value of 1.43 at 80 cM. Using the narrow definition of race substantially decreased the peak LOD to 0.70, but did not change its location. Using the narrow definition

of schizophrenia decreases the peak value slightly to 1.33, but does not change its location.

The peak LOD score attained in the African American families was 0.93 at 104.5 cM and occurred under the broad and narrow definitions of schizophrenia and race, respectively. Similar to the EA families, the peak and location were almost unchanged when the narrow definition of schizophrenia is used (LOD = 0.90 at 104.5 cM). Using the broad definition of race decreased the peak LOD scores modestly and changes the location for both definitions of schizophrenia (LOD = 0.70 at 70 cM).

To accurately assess the significance of our results we need to account for the 12 combinations of definitions for affection status (narrow/broad), race category (narrow/broad) and race (AA/EA/combined) that were used. One hundred simulated data sets were generated under the null hypothesis of no linkage between schizophrenia and any of the markers on chromosome 13. The same family structures and marker allele frequency distributions as our VA sample data were used. We determined that our peak LOD score was exceeded 10% of the time by the peak LOD score of the simulated data. Hence, we found a chromosome 13-wide significance level of 0.10. Although this is not a compelling result, by considering our study as a follow-up study to previous positive finding on chromosome 13 and therefore restricting our attention to the interval between 65 cM and 95 cM (see Table III) we find a significance level of 0.02; that is, only two of the simulated data sets had peak LOD scores that exceeded the one observed in our sample.

DISCUSSION

Our results, when considered in the context of prior literature, provide further support for the hypothesis that chromosome 13q32 harbors a susceptibility gene for schizophrenia. The chromosome 13-wide significance level of our finding ($P = 0.10$ in the total sample) is modest but the region-wide P-value of 0.02 is more compelling in the context of prior research implicating the same region of chromosome 13q. Table III summarizes the positive studies giving the LOD score, the marker nearest the peak, and the marker's location. All of these results cluster in a 30 cM wide region at 13q32. Notably, the location of our overall peak LOD score was less than 3 cM away from the peak reported by Brzustowicz et al. [1999], the study which found the strongest evidence for linkage with a LOD score of 4.4. Although location estimates are approximate and the breadth of our peak is wide, the correspondence of these peaks provides further support

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

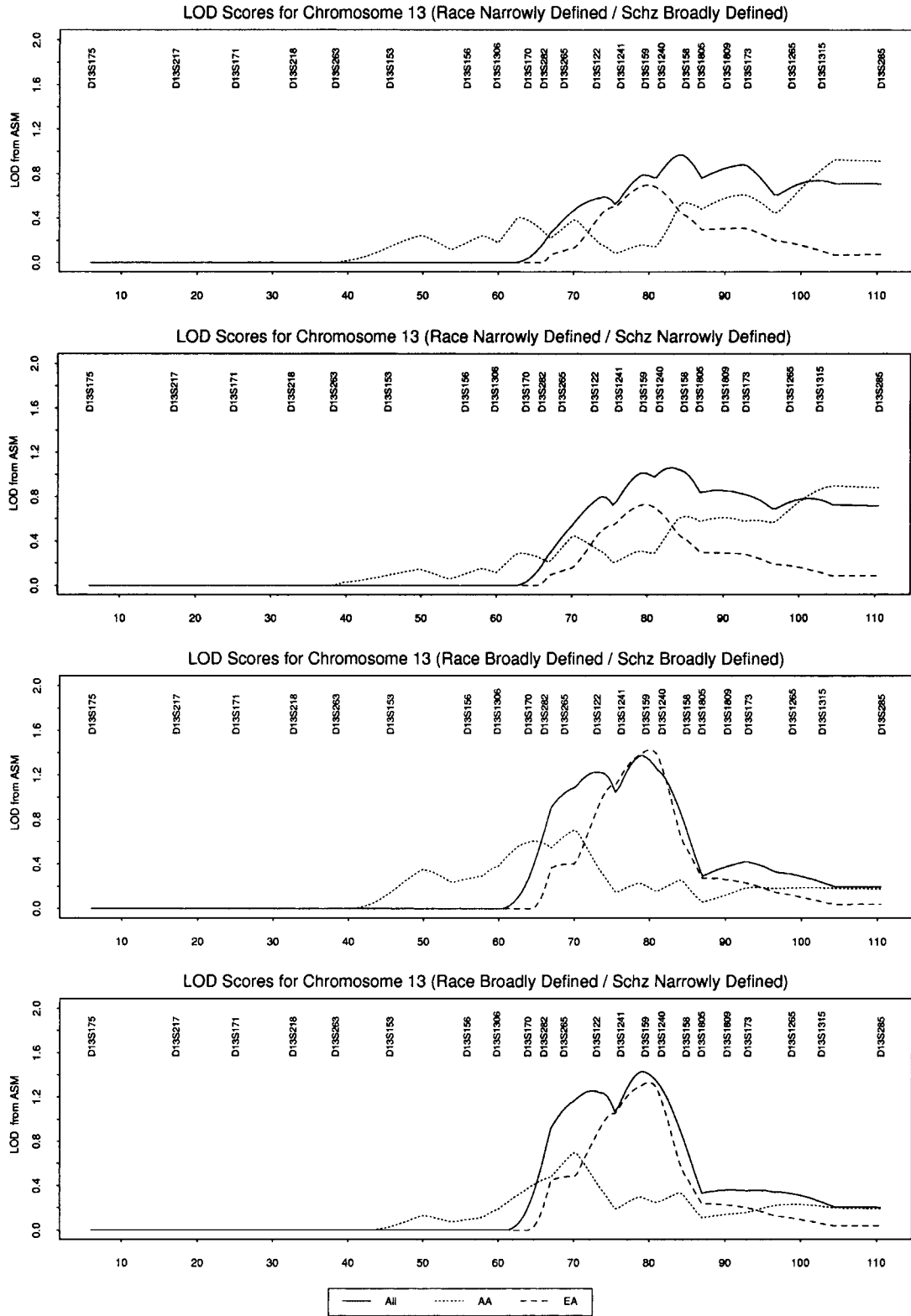|	Race broadly defined			Race narrowly defined		
		Number affected			Number affected	
Race	Number of families	Broad	Narrow	Number of families	Broad	Narrow
African-American	75	186	173	49	118	109
European-American	74	178	172	61	139	135

Fig. 1.   Plots of LOD scores versus chromosome position (Kosambi cM). LOD scores are plotted vs. genetic map position for different racial and diagnostic groups. Genetic map distances 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 in Materials and Methods.

TABLE II. Peak LOD Scores and Locations

Race	Schizophrenia category	Racial category	Peak LOD	Location	LOD at 79cM
AA	Broad	Broad	0.71	70.0	0.23
		Narrow	0.93	104.5	0.16
	Narrow	Broad	0.70	70.0	0.30
		Narrow	0.90	104.5	0.31
EA	Broad	Broad	1.43	80.0	1.40
		Narrow	0.70	80.0	0.69
	Narrow	Broad	1.33	80.0	1.31
		Narrow	0.73	80.0	0.72
Combined	Broad	Broad	1.38	79.0	1.38
		Narrow	0.97	84.0	0.79
	Narrow	Broad	1.43	79.0	1.43
		Narrow	1.06	83.0	1.01

for the presence of a schizophrenia susceptibility gene in this region.

Despite the consistency of the positive findings in Table III, none of these findings meet strict criteria for declaring statistically significant linkage from a genome scan [Lander and Kruglyak, 1995]. Moreover, we cannot ignore the negative report from Levinson et al. [2000], which was based on 734 informative multiplex pedigrees containing 824 independent affected sibling pairs. Their maximum LOD score for chromosome 13q was 0.09. This negative finding is difficult to interpret because only one of their samples had previously indicated the possibility of linkage to the 30cm region of 13q implicated by the studies in Table III [Blouin et al., 1998]. As Lander and Kruglyak [1995] noted, to be interpretable, pooled analyses should include all positive and negative studies. We must also consider that the combination of multiple studies using different methods of ascertainment, assessment and diagnosis introduces sources of heterogeneity that may have obscured some linkage signals.

A visual comparison of the LOD score plots in Figure 1 illustrates the effects of our different definitions of defining race and affection status. There is very little difference between the plots for the broad and narrow definitions of affection status. This makes sense given that the broad group comprised only seven percent of the sample. In contrast, a much larger effect is seen when comparing the narrow definition of race (the first two plots) with the broad definition (the second two plots). The LOD scores are higher and the peak is narrower for the broad definition. This is probably because the

TABLE III. Results From Schizophrenia Studies Showing Some Evidence of Linkage to Chromosome 13q Ordered by Location of Most Significant Finding

Study	Marker	LOD Score	Location[a]
Lin et al. [1997]	D13S128	1.7 (Caucasians) 0.3 (Asians)	50.0 cM
Lin et al. [1995]	D13S119	1.6	71.5 cM
Brzustowicz et al. [1999]	D13S793	4.4	73.0 cM
This report	D13S159	1.4	79.0 cM
Blouin et al. [1998]	D13S174	3.2	84.9 cM

[a]Locations were from each reference and not necessarily on one map.

sample size for the broad definition is 35% greater that the sample for the narrow definition. In contrast, for the broad definition of race, the LOD plots for the combined and European-American samples are almost identical, which suggests that the African-American sample is providing little or no evidence for linkage to 13q32. For the narrow definition of race, the picture is less clear, in part because the LOD peak is less well defined. There is, however, some suggestion that the African-American sample is providing some evidence for linkage to 13q32. But given the sample size, these race comparisons are speculative. Of note is the fact that most of the positive findings have been reported in samples of European ancestry [Lin et al., 1995, 1997; Blouin et al., 1998; Brzustowicz et al., 1999]. The study of Lin et al. [1995] used a mixed sample from the United Kingdom and Japan.

Also of note is the fact that 13q32 is one of four chromosomal regions that have been implicated in both bipolar disorder and schizophrenia [Detera-Wadleigh et al., 1999; Berrettini, 2000; Maziade et al., 2001], which suggests there might be "psychosis susceptibility genes." Berrettini [2000] has argued that bipolar disorder and schizophrenia are related in that they comprise similar multiple disease entities, which may share some genes in common. Although more work is needed to validate this idea, the continuing support for 13q32 in both disorders is consistent with his hypothesis.

What can we conclude from the pattern of positive and negative findings from the linkage studies of chromosome 13q32 in schizophrenia in light of the idea that consistent replication is the acid test for valid discovery in science. Suarez et al. have addressed this issue using statistical simulations. Their simulations assumed that, because psychiatric disorders were likely to be mediated by many genes acting in concert, each of these genes individually would exert only a small effect on the disorder. Although genes of such small effect should be very difficult to detect, because many are involved, the power of an initial study to detect one gene from the set should be reasonably high. The simulations of Suarez showed that a replication study would also have reasonable power to detect one gene from the set but the probability that the same gene would be detected would be low. For the replication study to have sufficient power

to detect the previously detected gene, it must use a much larger sample.

Thus, when considering all studies of chromosome 13q32 together, it seems reasonable to cautiously conclude that this region may harbor a susceptibility gene for schizophrenia, which has a small effect on the risk for the disorder. The current challenge for investigators is to collect very large samples or to find valid methods of pooling samples that will be useful for positional cloning.

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