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Genome Scan of European-American Schizophrenia Pedigrees: Results of the NIMH Genetics Initiative and Millennium Consortium

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The Genetics Initiative of the National Institute of Mental Health (NIMH) was a multisite study that created a national repository of DNA from families informative for genetic linkage studies of schizophrenia, bipolar disorder, and Alzheimer's disease. The schizophrenia families were collected by three sites: Washington University, Harvard University, and Columbia University. This article, one in a series that describes the data collected for linkage analysis by the schizophrenia consortium, presents the results for the European-American sample. The European-American sample comprised 43 nuclear families and 146 subjects. Ninety-six of the family members were considered affected by virtue of having received a DSM-III-R diagnosis of schizophrenia (N = 82) or schizoaffective disorder, depressed (N = 14). The families contained a total of 50 independent sib-pairs. Using the significance threshold criteria suggested by Lander and Kruglyak [(1995): Nat Genet 241–247], no region showed statistically significant evidence for linkage; two markers on chromosome 10p showed statistical evidence suggestive of linkage using the criteria of Lander and Kruglyak [(1995): Nat Genet 241–247]: D10S1423 (nonparametric linkage (NPL) Z = 3.4, *P* = .0004) and its neighbor, D10S582 (NPL Z=3.2, *P* = .0006). Am. J. Med. Genet. (Neuropsychiatr. Genet.) 81:290–295, 1998. © 1998 Wiley-Liss, Inc.

KEY WORDS: schizophrenia; linkage; NIMH Genetics Initiative

INTRODUCTION

This article is one in a series that describes the linkage data collected by the schizophrenia consortium. Cloninger et al. [this issue] describe the background of the project and its strategies for ascertainment, data collection, pedigree extension, diagnosis and data analysis. Kaufmann et al. [this issue] present the results for the African-American sample. We present the results for the European-American sample.

Sample Description

The European-American sample comprised 43 nuclear families and 146 subjects. Ninety-six of the family members were considered affected by virtue of having a DSM-III-R diagnosis of schizophrenia (N = 82) or schizoaffective disorder, depressed (N = 14). The families contained a total of 50 independent affected sib-pairs (calculated as number of affected sibs minus 1). Thirty-six families had 2 affected sibs, and seven

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families had 3 affected sibs. Table I breaks down the sample according to the number of sibs (including the affected sibs) and parents with DNA available. As Table I indicates, 14 of the affected sib-pairs had two parents available for genotyping, 19 had one parent available, and 10 had no parents available. Two of the sib-pairs were half-sibs. One of these had no parental DNA available, while the other had DNA available from the common parent.

Sixty-six percent of the affected subjects were male; they had a mean age of 43 ± 14 years. Their mean age at onset was 20.8 ± 7.5 years, and they had a mean educational level of 11.7 ± 2.6 years. Thirty-one percent of the unaffected subjects were male; they had a mean age of 66 ± 10 years. Their mean educational level of 11.2 ± 3.4 years.

RESULTS

The results are presented in Figure 1, which presents for each chromosome the multipoint nonparametric linkage (NPL) Z-scores computed by GENEHUNTER [Kruglyak et al., 1996] for each marker locus. According to Lander and Kruglyak [1995], highly significant evidence from a genome scan requires $P < 0.0000003$; significant evidence from a genome scan requires $P < 0.00002$; and suggestive evidence requires $P < 0.0007$.

In our analyses, no region showed statistically significant evidence for linkage, but two markers on chromosome 10p showed statistical evidence suggestive of linkage: D10S1423 (NPL Z = 3.4, $P = 0.0004$) and its neighbor, D10S582 (NPL Z = 3.2, $P = 0.0006$).

To facilitate the examination of the remaining small peaks in Figure 1, Table II summarizes the results for all markers with NPL scores >1.5 (these correspond to $P < 0.06$). In creating Table II, our use of a threshold of 1.5 was arbitrary, yet provides a convenient means of summarizing our results.

Table II also shows genetic locations (in megabases from ptr) derived from the Genetic Location Data Base (http://cedar.genetics.soton.ac.uk/public_html/), along with estimates of the mean identity-by-descent sharing of marker alleles estimated by SIBPAL [S.A.G.E., 1994]. For markers not in the Genetic Location Data Base, locations were estimated from flanking markers in the database.

Because we did not have complete parental genotyping information for all families, it was necessary to estimate marker allele frequencies for the linkage analyses. To determine if the choice of allele frequencies had influenced the results, we computed the mean identity-by-descent (IBD) sharing of marker alleles for the two chromosome 10 markers showing suggestive evidence for linkage, using three different estimates of the marker allele frequencies: 1) the estimates, P(i), taken from our sample; 2) P(i) + .10; and 3) 1/(the number of alleles at the marker locus). The results in Table III show that the IBD estimates did not vary much with either the choice of allele frequency estimate or the number of parents with DNA available.

TABLE I. Distribution of Families by Number of Siblings and Parents Genotyped

Number of siblings genotyped	Number of parents genotyped			
	0	1	2	Total
2	3[a]	15[b]	13	31
3	6	4	1	11
4	1	0	0	1
5	0	0	0	0
Total	10	19	14	43

[a]One family consists of a pair of half sibs.
[b]One family constists of a pair of half-sibs plus their common parent. Note: Ninety-six family members were considered affected by virtue of having a DSM-III-R diagnosis of schizophrenia (N = 82) or schizoaffective disorder, depressed (N = 14).

DISCUSSION

Our genome scan of 50 European-American sib-pairs from the schizophrenia consortium of the NIMH Genetics Initiative found suggestive evidence for linkage to one region on chromosome 10p, but no evidence of linkage elsewhere. Notably, we did not find linkage to the three regions that had been implicated by other investigators: 22q11–q13 [Pulver et al., 1994b; Schizophrenia Collaborative Linkage Group (Chromosome 22), 1996], 6p23 [Moises et al., 1995; Schwab et al., 1995; Straub et al., 1995], and 8p22–21 [Pulver et al., 1995; Kendler et al., 1996; Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8, 1996]. We also did not show linkage to 6q13–q26, even though Cao et al. [1997] found linkage to this region using 69 affected sib-pair families from our larger set of pedigrees that included families of European-American, African-American, and other ethnic backgrounds. Notably, the 6q linkage was observed in our genome scan of the African-American families of Kaufmann et al. [this issue].

That we did not confirm prior reports of linkage is consistent with other groups who did not find evidence for linkage to 22q11–q13 [Pulver et al., 1994a; Kalsi et al., 1995; Schizophrenia Collaborative Linkage Group (Chromosome 22), 1996], 6p23 [Wang et al., 1993; Antonarakis et al., 1995; Gurling et al., 1995; Mowry et al., 1995], and 8p22–21 [Kunugi et al., 1996]. As Suarez et al. [1994] reported, consistent replication of linkage findings is not expected under oligogenic inheritance. This fact, the fact that we did not test exactly the same markers used by other groups, and the low power of our sample to detect small effects, emphasize that our negative findings are not conclusive.

There are several reasons to be cautious in interpreting the suggestive linkage to 10p in our schizophrenia pedigrees. Most importantly, the three prior published reports that presented chromosome 10 linkage data did not implicate 10p. Coon et al. [1994b] ascertained nine pedigrees, each containing 3–5 cases of schizophrenia. They found no evidence for linkage to any of four markers in the region 10pter–p13. All of their markers excluded linkage (lod <–2.0) under an autosomal dominant model, and three excluded linkage under a recessive model. Moreover, our results from the African-American sample of the NIMH Genetics Initiative [Kaufmann et al., this issue] and the genome screen of Moises et al. [1995] found no evidence for linkage to

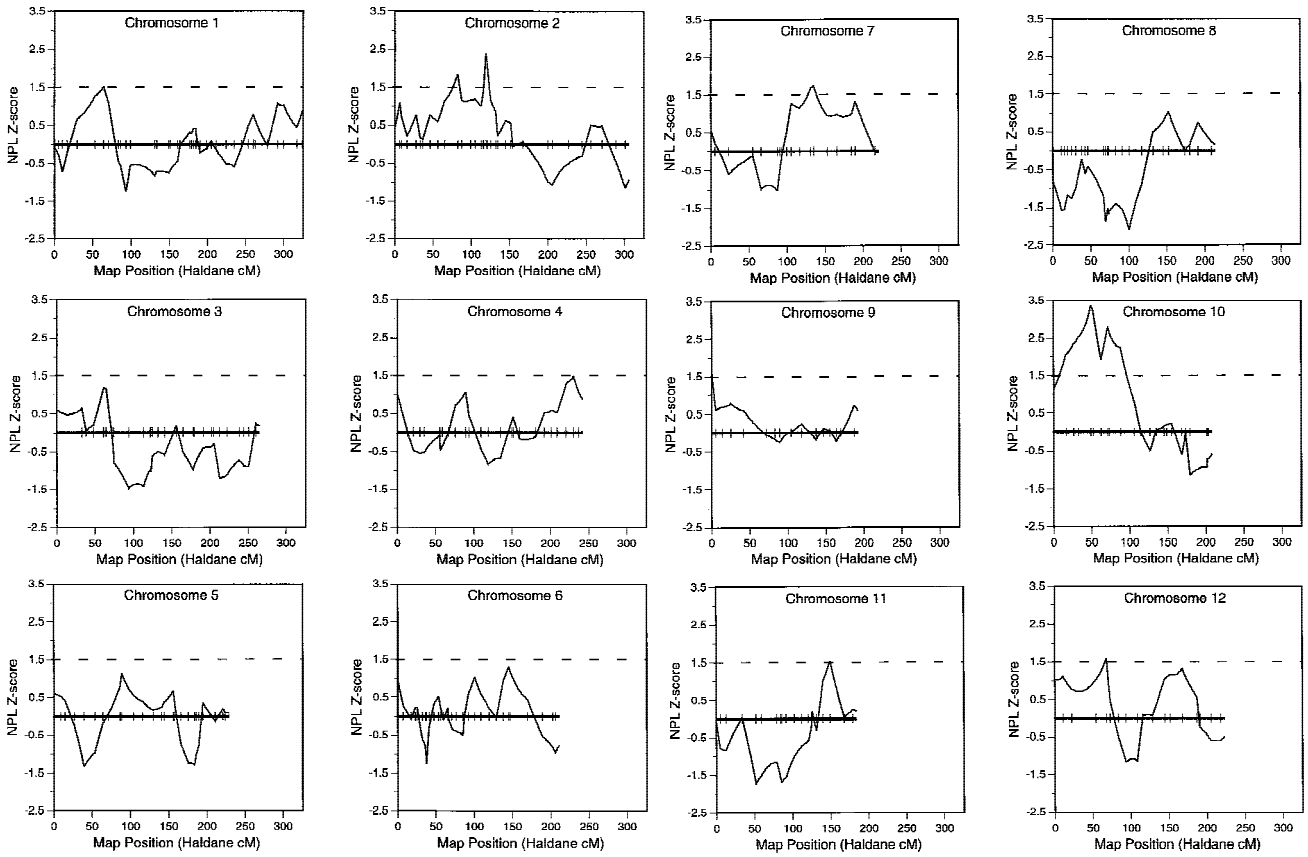

Fig. 1. Multipoint NPL Z-scores for European-American pedigrees.

10p or 10q using 14 markers. Barr et al. [1994] found no evidence of linkage to three markers on chromosome 10q, but did not evaluate linkage to 10p.

In contrast to these negative published findings, in an independent study, Straub et al. [1997] recently presented schizophrenia linkage data from 265 Irish pedigrees which implicate 10p between D10S674 and D10S1426, which overlaps with the region implicated in this report. Their maximum multipoint heterogeneity lod score for this region was 1.91 (P = 0.006), and their maximum multipoint nonparametric (NPL) score was 1.88 (P = 0.03), each occurring at D10S2443. Moreover, Wildenauer (personal communication) has had positive results in this region for D10S582 (P = 0.006) and D10S1423 (P = 0.029). There is also one cytogenetic study that implicates 10p in schizophrenia. Axelsson and Wahlström [1984] screened for chromosome aberrations in 134 consecutive patients with paranoid psychosis. One patient had an inversion on chromosome 10 [inv(10)(p12q21)].

The two 10p markers showing suggestive linkage (D10S1423 and D10S582) have not been precisely located on the cytogenetic map. According to the Genome Data Base (http://gdbwww.gdb.org/gdb/docs/gdbhome.html), D10S1423 is in the region 10p14–p13 and D10S582 is in 10p13–p12. According to the Genetic Location Database (http://cedar.genetics.soton.ac.uk/public_html/) [Collins et al., 1996], the most likely location for D10S582 is 10p13. We consulted Online Mendelian Inheritance in Man (OMIM) (http://www3.ncbi.nlm.nih.gov/Omim/) to determine what genes were in the regions implicated by these two markers.

According to OMIM, Daw et al. [1996] and Lipson et al. [1996] reported that deletions at 10p13–14 were associated with a rare form of velo-cardio-facial syndrome (VCFS). As noted by Pulver et al. [1994b], the more common form of VCFS is caused by microdeletions in the region 22q11, which is in the vicinity of the region they had implicated in their linkage analysis of schizophrenia pedigrees. The relevance of VCFS is that some cases exhibit psychosis and other schizophrenia-like symptoms [Shprintzen et al., 1992]. Moreover, Karayiorgou et al. [1995] found two cases of 22q11 deletions among a series of 100 schizophrenic patients.

The region implicated by our linkage analyses includes the genes for the interleukin-2 receptor alpha chain (IL2RA, {3.8}, 10p15–p14) and interleukin-15 receptor alpha chain (IL15RA, {7.6}, 10p15–p14). Although these genes, which are involved in autoimmunity, have not been directly implicated in schizophrenia, it is of interest that a related gene (interleukin-2 receptor beta chain) on 22q13 showed evidence of linkage to schizophrenia in the study of Pulver et al. [1994b] and that of Coon et al. [1994a]. Although genetic association studies of IL2RB and schizophrenia have been negative [Nimgaonkar et al., 1995; Tatsumi et al., 1997], others have reported abnormalities in in-

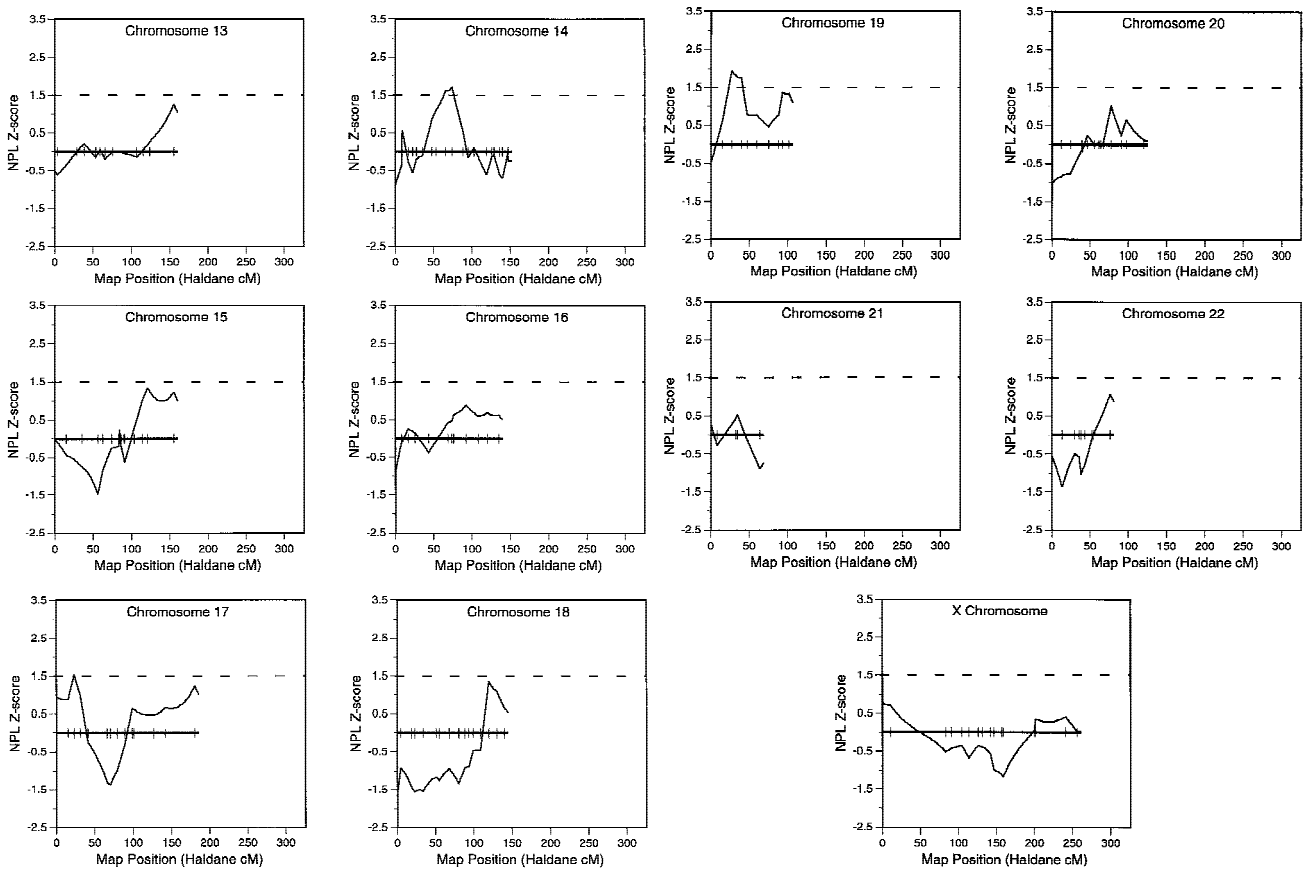

Fig. 1. (*Continued*).

TABLE II. Results for Markers With NPL Z-Scores Greater Than 1.5*

Chromosome	Marker	Marker number	Location	Region	Information content	NPL Z-score	*P*	IBD sharing
1	D1S1622	7	32.5	1p34.3	0.59	1.52	0.07	0.58
2	D2S441	12	69.0	2p14	0.75	1.85	0.03	0.59
2	D2S293	18	105.9	2q12	0.79	2.41	0.008	0.63
2	D2S1893	18	106.6	2q12	0.85	1.99	0.02	0.57
7	D7S821	12	104.5	7q21	0.73	1.66	0.05	0.55
7	D7S1799	13	115.6	7q31	0.69	1.74	0.04	0.55
9	D9S288	1	3.0	9p24	0.71	1.70	0.05	0.54
10	D10S189	2	8.0	10p15	0.57	2.07	0.02	0.57
10	D10S1412	3	11.2[a]	NA	0.68	2.35	0.01	0.56
10	D10S2325	4	13.4[a]	10p14	0.73	2.54	0.006	0.56
10	D10S1423	5	18.5[a]	NA	0.75	3.36	0.0004	0.61
10	D10S582	6	19.5	10p13	0.82	3.24	0.0006	0.63
10	D10S1426	7	34.1[a]	NA	0.77	1.95	0.03	0.55
10	D10S604	8	47.1	10q11.2	0.72	2.79	0.003	0.64
10	D10S1220	9	50.1[a]	10q11.2	0.70	2.65	0.004	0.58
10	D10S1225	10	70.3[a]	10q21	0.64	2.24	0.01	0.56
11	GATA64D0	18	128.4[a]	10q23	0.50	1.54	0.06	0.57
12	D12S1042	5	23.7	12p11.2	0.75	1.58	0.06	0.60
14	D14S592	10	58.1	14q22	0.61	1.60	0.06	0.55
14	D14S588	11	66.5	14q24	0.68	1.70	0.05	0.53
17	D17S796	3	8.4	NA	0.69	1.55	0.06	0.60
19	D19S714	3	29.3[a]	17p12	0.76	1.94	0.03	0.54
19	D19S433	4	34.7	NA	0.73	1.75	0.04	0.53

*NPL Z-scores computed with GENEHUNTER; mean IBD sharing computed with SIBPAIR; locations are in MB from pter (Genetic Location Data Base (http://cedar.genetics.soton.ac.uk/public_html/)) [Collins et al., 1996]; regions were derived from the NCBI Entez Genome Query (http://www.ncbi.nlm.gov/cgi-bin/entrez/); NA, not available.
[a]Estimated location for markers not in database.

TABLE III. Mean Identity-by-Descent Sharing of Marker Alleles for Chromosome 10 Markers*

	D10S1423, number of parents with DNA available				D10S582, number of parents with DNA available			
Marker	Two	One	None	Total	Two	One	None	Total
P(i)	0.60	0.63	0.57	0.61	0.62	0.67	0.57	0.63
P(i) + .10	0.60	0.65	0.60	0.62	0.62	0.70	0.59	0.65
1/no. of alleles	0.60	0.68	0.66	0.66	0.62	0.72	0.63	0.67

*Mean IBD computed by SIBPAL; *P*(i) = marker allele frequencies estimated from the sample.

terleukin-2 production in the lymphocytes of schizophrenic patients [O'Donnell et al., 1996].

We also note that the GAD3 gene, which encodes a form of the enzyme glutamic acid decarboxylase, is located at 22q13 [Edelhoff et al., 1993]. This is another curious correspondence between 22q and 10p, which harbors the GAD2gene {32.9}. GAD catalyzes the conversion of glutamic acid to gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the central nervous system (CNS). The GAD1 gene encodes the 65-kilodalton (kD) form of GAD. In the CNS, GAD65 appears to be localized in nerve terminals, suggesting that it responds to short-term changes in the need for GABA [Martin and Rimvall, 1993]. Postmortem studies have found GAD65 mRNA messages in the suprachiasmatic nucleus [O'Hara et al., 1995; Gao and Moore, 1996a]; the anterior hypothalamic area [Gao and Moore, 1996b]; and in the sexually dimorphic nucleus of the preoptic area [Gao and Moore, 1996b]. Decreased brain levels of glutamic acid decarboxylase have been associated with schizophrenia in some studies [Bird et al., 1977; Akbarian et al., 1995], but not in others [Bennett et al., 1979; Hanada et al., 1987]. It is not known if the positive associations apply to the 65-kD form.

For several reasons, it would be premature to draw any conclusions about candidate genes in the 10p region implicated by our results. Assuredly, our results call for replication by other investigators. Moreover, there are many genes in the broad region implicated by our results. For example, in the interval between D10S1423 and D10S582 (which showed the strongest signal for linkage), there are at least 36 mapped expressed sequence tags, most of which are unidentified transcripts (http://www.ncbi.nlm.nih.gov/SCIENCE96/) [Hudson et al., 1995]. Thus, although our speculations about candidate genes may be useful for generating hypotheses and choosing markers for further studies, they are far from definitive.

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