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# NIMH Genetics Initiative Millennium Schizophrenia Consortium: Linkage Analysis of African-American Pedigrees

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The NIMH Genetics Initiative is a multi-site collaborative study designed to create a national resource for genetic studies of complex neuropsychiatric disorders. Schizophrenia pedigrees have been collected at three sites: Washington University, Columbia University, and Harvard University. This article—one in a series that describes the results of a genome-wide scan with 459 short-tandem repeat (STR) markers for susceptibility loci in the NIMH Genetics Initiative schizophrenia sample—presents results for African-American pedigrees. The African-American sample comprises 30 nuclear families and 98 subjects. Seventy-nine of the family members were considered affected by virtue of having received a DSM-III-R diagnosis of schizophrenia ( $n = 71$ ) or schizoaffective disorder, depressed ( $n = 8$ ). The families contained a total of 42 independent sib pairs. While no region demonstrated evidence of significant linkage using the criteria suggested by Lander and Kruglyak, several regions, including chromosomes 6q16-6q24, 8pter-8q12, 9q32-9q34, and 15p13-15q12, showed evidence consistent with linkage ( $P = 0.01$ – $0.05$ ), providing independent support of findings reported in other studies. Moreover, the fact that different ge-

netic loci were identified in this and in the European-American samples, lends credence to the notion that these genetic differences together with differences in environmental exposures may contribute to the reported differences in disease prevalence, severity, comorbidity, and course that has been observed in different racial groups in the United States and elsewhere. *Am. J. Med. Genet. (Neuropsychiatr. Genet.)* 81: 282–289, 1998. © 1998 Wiley-Liss, Inc.

**KEY WORDS:** schizophrenia; linkage analysis; African-American; NIMH Genetics Initiative

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## INTRODUCTION

This is the third of 3 articles reporting the results of genome-wide nonparametric linkage analyses performed on nuclear families segregating schizophrenia derived from the NIMH Genetics Initiative, a multi-site collaborative study designed to create a national resource for genetic studies of complex neuropsychiatric disorders. In the first article of this series, Cloninger et al. [1998] describe the background of the project and associated strategies for pedigree ascertainment and extension, diagnosis and data acquisition, and data analyses. The companion article by Faraone et al. [1998] presents the results of linkage analyses performed on European-American pedigrees within the NIMH Genetics Initiative sample. Here, we present the results of analyses performed on African-American pedigrees.

Different genes may influence susceptibility to complex disorders in individuals of different racial backgrounds. For example, a recent genome-wide search for

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genetic loci conferring susceptibility to asthma in African-Americans, Caucasians, and Hispanics detected 2, 6, and 2 race-specific loci, respectively; only 1 locus (12q14-24.2) conferred susceptibility in both Caucasian and Hispanic pedigrees [CSGA, 1997].

While cross-cultural similarities in the incidence, manifestations, and course of schizophrenia have been observed [Jablensky et al., 1992], cross-racial differences have received less attention. Nonetheless, racial differences in the prevalence of clinically diagnosed schizophrenia have been recognized [Neighbors et al., 1989; Strakowski et al., 1993]. In addition to its effect on disease prevalence, race may contribute to several clinical characteristics of schizophrenia, including symptomatology [Strakowski et al., 1996], comorbidity [Mueser et al., 1990; Earle et al., 1994], and diagnostic stability [Chen et al., 1996].

Thus—given the presumed differences in genetic architecture between ethnic and racial groups, the observed differences in allele frequencies between such groups [Dean et al., 1994; Hartmann et al., 1994], and the known dependence of linkage results in incompletely genotyped pedigrees on specified allele frequencies [Babron et al., 1993]—we elected to analyze the European-American and African-American samples separately.

### Sample Description

The African-American sample comprised 30 nuclear families and 98 subjects. Seventy-nine of the family members were considered affected by virtue of having received a DSM-III-R diagnosis of schizophrenia ( $n = 71$ ) or schizoaffective disorder, depressed ( $n = 8$ ). The families contained a total of 42 independent sib pairs (calculated as the number of sibs per sibship minus 1). Twenty-one families had 2 affected sibs, 7 families had 3 affected sibs, 1 family had 4 affected sibs, and 1 family had 5 affected sibs. Table I breaks down the sample according to the number of siblings (including the affected siblings) and parents with DNA available. As Table I indicates, 4 of the sib pairs had 2 parents available for genotyping, 17 had 1 parent available, and 9 had no parents available. Five of the sibling pairs contained half-siblings: 1 of these had no parental DNA available; 3 (2 half-sib pairs and a full-sib/full-sib/half-sib trio) had DNA available from the common parent; 1 had DNA from the common father and 1 mother.

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

Sibs genotyped	Parents genotyped			Total
	0	1	2	
2	4 <sup>a</sup>	10 <sup>b</sup>	4 <sup>c</sup>	18
3	5	5 <sup>d</sup>	0	10
4	0	1	0	1
5	0	1	0	1
Total	9	17	4	30

<sup>a</sup>One family consists of a pair of half-siblings.

<sup>b</sup>Two families consist of a pair of half-siblings and their common father.

<sup>c</sup>One family consists of a pair of half-siblings, their common father, and one mother.

<sup>d</sup>One family consists of a full-sib/full-sib/half-sib trio and their common father.

The affected subjects were 44% male and were  $40.9 \pm 11.8$  years of age. Their age at onset was  $20.7 \pm 8.0$  years, and they had an educational level of  $10.2 \pm 3.3$  years. The unaffected subjects were 37% male and were  $62.3 \pm 11.2$  years of age. Their educational level was  $10.9 \pm 3.8$  years.

## RESULTS

The 459 STR markers used in this genome scan provided comprehensive coverage of the autosomes and chromosome X [Cloninger et al., 1998]: chromosome 21 was least covered (with 58%, 23%, and 0% of GENE-HUNTER informativity scores [Kruglyak et al., 1996] exceeding 0.4, 0.6, and 0.8, respectively); chromosome 6 was best covered (with 97%, 82%, and 41% of scores exceeding these values, respectively).

Multipoint results for each chromosome are depicted in Figure 1: NPL Z-scores, computed by GENE-HUNTER [Kruglyak et al., 1996] are shown. In no region did the  $P$  value associated with an NPL Z score result in statistically significant (i.e.,  $P < 0.00002$ ) or even suggestive (i.e.,  $P < 0.0007$ ) evidence for linkage [Lander and Kruglyak, 1995]. Nonetheless, 4 regions previously implicated in genome-wide searches for schizophrenia susceptibility genes (on chromosomes 6q16-6q24, 8pter-8q12, and 9q32-q34), or for genes conferring susceptibility to a neurophysiological phenotype associated with schizophrenia (on chromosome 15p13-15q12), demonstrated  $P$  values approaching 0.01—consistent with replicated linkage (assuming, of course, that the initial studies themselves can be taken to represent significant linkage results). GENE-HUNTER results for these regions included NPL  $Z_{max} = 1.89$ ,  $P = 0.032$ ; NPL  $Z_{max} = 2.27$ ,  $P = 0.013$ ; NPL  $Z_{max} = 2.17$ ,  $P = 0.017$ ; and NPL  $Z_{max} = 1.96$ ,  $P = 0.027$ , respectively.

To facilitate the examination of the remaining peaks in Figure 1, Table II summarizes NPL results for all markers with NPL Z scores  $>1.5$ . Table II also describes the mean identity by descent (IBD) sharing of each of these markers, as computed by SIBPAIR [Satsangi et al., 1996; Terwilliger, 1997], as well as marker map positions, cytogenetic regions, and GENE-HUNTER information contents.

## DISCUSSION

Our genome scan of 30 African-American nuclear families segregating schizophrenia provided evidence supporting linkage in 4 chromosomal regions: 6q16-6q24, 8pter-8q12, 9q32-9q34, and 15p13-15q12, previously suggested to harbor susceptibility loci. In addition, it identified 2 additional regions of some interest: 4q24-q32 and 19p13.2. Although to our knowledge this study represents the first linkage analysis for schizophrenia loci in an exclusively African-American sample, our small sample size and modest statistical results dictate caution in the interpretation of these data.

For ease of exposition, the potential etiologic rôle for each of these chromosomal regions will be discussed in numerical order. In order to facilitate comparison to

other studies, chromosomal locations of various markers were derived from the Genetic Location Database [Collins et al., 1996; internet address: [http://cedar.genetics.soton.ac.uk/public\\_html/](http://cedar.genetics.soton.ac.uk/public_html/)], and are provided in brackets ({}).

#### Chromosome 4

Three markers on chromosome 4q24-q32 (D4S1564, D4S2395, and D4S1644), located from {118.96} to {151.48}, resulted in *P*-values of ~0.05 (Table II). These results are consistent with the report by Palmour et al. [1994] of an association between schizophrenia and a pericentric inversion of chromosome 4 [inv(p15.2;q21.3)]. Two other studies have implicated chromosome 4 as harboring a schizophrenia susceptibility gene: The genome scan of Coon et al. [1994] identified 1 marker, D4S35, suggestive of linkage using the Affected Pedigree Member method [Weeks and Lange, 1988]; the 2-stage genome scan of Moises et al. [1995] implicated 2 markers, D4S405 and D4S400, in the first but not second stage of their study. These 3 markers, however, are quite removed ({44.057}, {34.040}, and {71.470}, respectively) from the region of chromosome 4 suggested by the current study.

#### Chromosome 6

NPL analysis of chromosome 6 produced a broad signal extending from D6S445 {75.529} to D6S310 {143.841}. This chromosome 6 result may be added to a long list of chromosome 6 linkage findings in schizophrenia, which followed initial reports by Wang et al. [1995] and Straub et al. [1995]. The latter analysis of 265 pedigrees collected through the Irish Study of High-Density Schizophrenia Families, identified a maximum heterogeneity lod score at D6S296 {2.958}. This locus appeared to affect susceptibility to schizophrenia in 15–30% of pedigrees. The implicated region was quite broad, with NPL *Z* scores >2 extending over approximately 40 cM from D6S477 {1.314} to D6S291 {35.031} [Straub et al., 1996]. A second study of 43 German and 11 Sephardic Israeli families [Schwab et al., 1995] likewise identified a broad region, extending from D6S470 {4.580} to D6S258 {31.317}, centered on D6S274 {17.943}. An extension of this study, which increased the number of pedigrees to 64 and the marker density to ~1 cM, resulted in a slightly narrower region, peaking at D6S469 {17.060} [Wildenauer et al., 1996]. A third study conducted by the Johns Hopkins University Schizophrenia Collaborative Project which examined 34 chromosome 6 markers again peaked at D6S296 [Antonarakis et al., 1995]. These results were corroborated by the collaborative study of Moises et al. [1995] and by an international collaborative replication study [Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8, 1996] that found suggestive evidence for linkage in the vicinity of D6S274 and D6S429 {13.276}, respectively. Of note, all of these findings have suggested evidence for a schizophrenia susceptibility locus on the short-arm of chromosome 6 (the centromere of chromosome 6 has been mapped to {65.000}). Only a collaborative Australian/American study (B.J. Mowry, personal communication) revealed

positive results on 6q (NPL *Z* score of 1.17 at D6S1021 {119.144}) in the vicinity of our signal, in addition to evidence of equal magnitude on 6p (NPL *Z* score of 1.35 at D6S285 {20.056}).

Thus, several studies have implicated an extraordinarily broad region on chromosome 6, extending from {1.314} to {143.841}, as potentially harboring 1 (or more) schizophrenia susceptibility loci. Such convergent yet divergent results defy easy interpretation. One might posit that the class II MHC loci, HLA-DQ {31.642}, or HLA-DR {31.771} might represent 1 locus, given reports of linkage disequilibrium between such loci and schizophrenia in case/control [Wright et al., 1996; Nimgaonkar et al., 1995] and transmission/disequilibrium (P. Wright, personal communication) tests. Perhaps such a locus at HLA might be in linkage with a second nearby locus on chromosome 6. This appears to be the case in Type I diabetes, in which an extremely broad (~100 cM) linkage signal was decomposed into 2 signals: HLA and a second, theretofore unidentified, linked locus 32 cM away [Delepine et al., 1997].

#### Chromosome 8

Positive evidence for linkage on chromosome 8 extended over a wide region, spanning approximately 50 cM, but appeared to peak at 2 somewhat dispersed peaks: D8S264 {0.870} and D8S1791 {47.430}. It is interesting to note that this same region has been implicated in 2 previous genome scans of schizophrenia—those of Pulver et al. [1995] and of Kendler et al. [1996]. Pulver found evidence approaching significance for linkage [Lander and Kruglyak, 1995] extending from D8S552 {9.480} to D8S133 {23.556}, with IBD sharing ranging from 0.622 to 0.667; Kendler found suggestive evidence for linkage extending from D8S511 {11.767} to D8S1739 {25.820}, with NPL *Z* scores ranging from 2.2 to 2.4. The aforementioned international collaborative replication study likewise found suggestive evidence for linkage in the vicinity of D8S133 [Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8, 1996] and the aforementioned international 2-stage linkage collaboration conducted by Moises et al. [1995] found suggestive evidence for linkage at D8S298 {23.350} and D8S260 {65.900} in the first stage scan, although this was not supported in the second stage of their design. A smaller study, comprising 25 multiplex pedigrees, likewise could not support linkage in this region [Kunugi et al., 1996]. It is worth mentioning that this region harbors a QTL locus accounting for 38% of the variance associated with *harm avoidance* [Cloninger et al., 1998], a quantitative behavioral phenotype that serves as a risk factor for many forms of psychopathology, including psychosis [Cloninger et al., 1994]. The QTL linkage analysis maximized at D8S1106 {10.217}, with lod = 3.2 and *P* = 0.00006.

Of the cloned genes localizable to this region,<sup>1</sup> the

<sup>1</sup>CTSB, DEF1, AAC2, MSR1, LPL, SLC18A1, SFTF2, BMP1, NEFL, GULOP, GSR, LHRH, FGFR1, ADRB3, CHRN3, ANK1, POLB, PLAT, PENK, MOS, CEBPD.

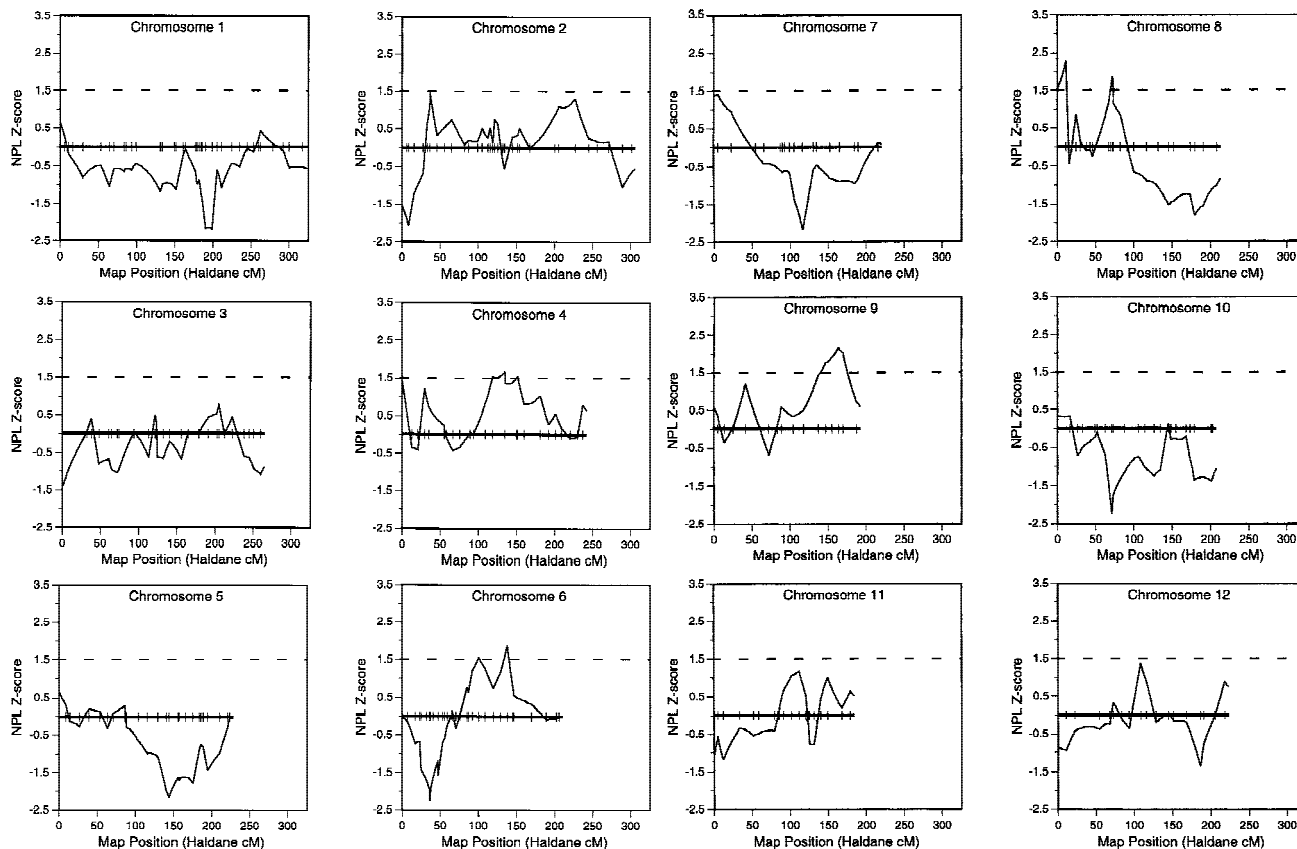


Fig. 1. NPL Z scores from African-American schizophrenia pedigrees. Solid bars denote chromosome lengths (Haldane cM); tick marks denote marker locations. A Z score threshold of 1.5 is shown by the dashed line: Values exceeding this threshold appear on chromosomes 4, 6, 8, 9, 15, and 19. (Figure 1 continued overleaf.)

proenkephalin A gene [55.580] has received special attention. Screening of 150 schizophrenia patients for sequence variations in the 5' promoter region, entire coding sequence, and 3' untranslated region of this gene revealed a single patient, but no controls, with a missense mutation [Mikesell et al., 1996].

### Chromosome 9

Our analysis suggested a broad region of linkage, extending from D9S930 {120.352} through D9S1838 {144.601}, peaking in the vicinity of D9S1818 {140.811}. Of note, Moises et al. [1995] implicated a region extending from D9S175 {74.695} to D9S160 {111.07} in 5 Icelandic pedigrees. D9S175 was again implicated ( $P < 0.01$ ) in an international follow-up study comprising 54 European and European-American families and 11 Asian families [Moises et al., 1995]. In the only other study to examine this portion of chromosome 9 in schizophrenia, Meszaros et al. [1996] found no evidence for linkage between DBH {140.036} and 2 nearby markers in 34 Austrian families, although linkage was not excluded, per se. Given the relatively frequent occurrence of pericentric inversions of chromosome 9 in schizophrenia [Nanko et al., 1993], other studies have excluded linkage elsewhere on this chromosome; although the excluded loci were quite far removed {49.783–57.597} from those implicated in this study [Nanko et al., 1994]. Similarly, our companion study of

European-American pedigrees reports a single marker, D9S288, with an NPL Z score of 1.70 ( $P = 0.0456$ ) [Faraone et al., 1998]—but again, this locus is on the far end of the chromosome {0.00}.

The implicated region of chromosome 9 contains a number of cloned genes<sup>2</sup>. Of all of these, NMDAR1 {144.226} is perhaps most interesting, given reports of glutamatergic dysfunction in schizophrenia [Olney and Farber, 1995].

### Chromosome 15

Our findings on chromosome 15 appear to be localized to the pter-cen region, maximal in the vicinity of D15S128 {19.309} and trailing off toward D15S118 {51.250}. Of considerable interest is the recent report by Freedman et al. [1997] of linkage between the  $\alpha$ -7 nicotinic receptor {41.267} and a neurophysiological abnormality associated with schizophrenia—decreased inhibition of the P50 component of the evoked response. While our results are not inconsistent with this report, we are examining schizophrenia itself as a phe-

<sup>2</sup>ORM, PTGS1, AMBP, PAPP, HXB, CD30LG, FTZF1, GSN, C5, NPS1, PBX3, DAPK1, ENG, GGTA1, PPP2R4, CRAT, ENDOG, RPL7A, ZNF79, SURF5, EPB72, AK1, SPTAN1, ASS, LCN2, RXRA, ABL1, CEL, ABO, SURF, DBH, VAV2, PTGDS, PAEP, GRF2, NOTVH1, COL5A1, NMDAR1.

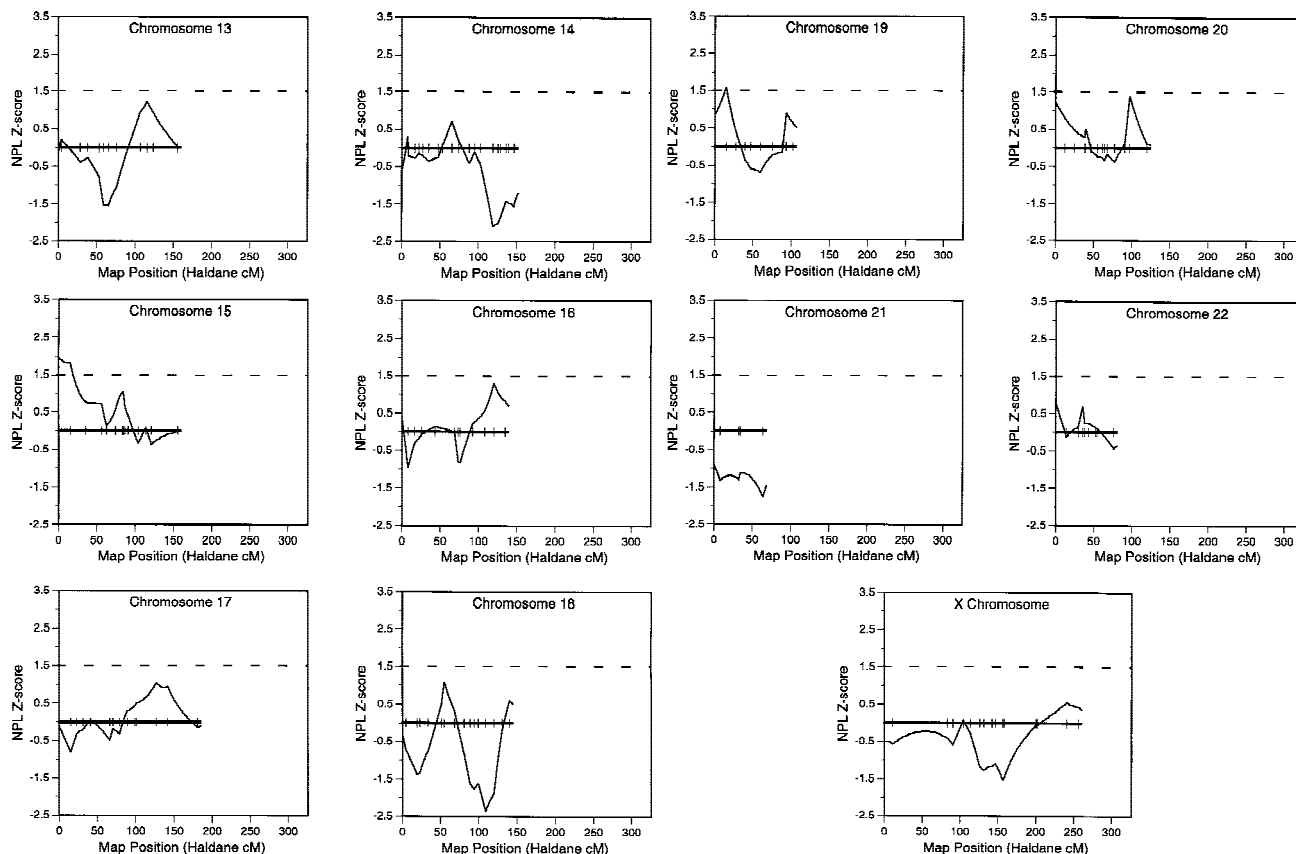


Fig. 1. (Continued).

notype, and our maxima appears somewhat more telomeric than that described by Freedman and associates. Also of interest are the reports of an association between a partial trisomy of chromosome 15 (pter-q13.3) and schizoaffective disorder [Calzolaru et al., 1996] and between Marfan syndrome (15q21.1) and schizophrenia [Sirota et al., 1990], and the observation that the relative risk for

Tay-Sachs disease (associated with low levels of hexosaminidase A [80.367]) is elevated in Askenazi Jewish pedigree segregating schizophrenia [Goodman, 1994]. The fibrillin gene, causative in Marfan syndrome, has itself been excluded as a candidate gene in schizophrenia [Hovatta et al., 1994; Kalsi et al., 1994], but is somewhat distant from our maxima ({55.041} vs.

TABLE II. Results for Markers With NPL Z Scores >1.5

Chromosome	Marker	Marker no.	Position <sup>a</sup>	Region <sup>b</sup>	Info-content	NPL Z score <sup>c</sup>	P value	IBD sharing <sup>d</sup>
4	D4S1564	15	118.96	4q24	0.71	1.54	0.0644	0.56
4	D4S2395	16	134.97	4q26	0.87	1.68	0.0492	0.66
4	D4S1644	19	151.48	4q32	0.77	1.54	0.0637	0.65
6	D6S1056	25	100.69	6q16-21	0.71	1.56	0.0622	0.62
6	D6S1009	29	138.11	6q24	0.77	1.89	0.0316	0.62
8	D8S264	1	0.00	8pter-p23	0.53	1.55	0.0629	0.56
8	D8S1819	2	11.03	8p23	0.81	2.27	0.0133	0.64
8	D8S439	3	11.13	8p23	0.81	2.25	0.0140	0.56
8	D8S532	13	72.44	8p11.2	0.88	1.88	0.0326	0.57
8	ATAG10	14	73.55	8q12	0.86	1.51	0.0674	0.55
9	D9S934	12	146.98	9q32-33	0.60	1.75	0.0422	0.58
9	D9S1825	14	154.88	9q34	0.67	1.91	0.0306	0.50
9	D9S1830	15	163.59	9q33-34	0.80	2.17	0.0167	0.55
9	D9S1818	16	169.53	9q34	0.70	2.04	0.0229	0.61
15	D15S128	1	0.00	15p13	0.66	1.96	0.0272	0.57
15	ATC3C11	2	15.06	15q12	0.63	1.83	0.0358	0.52
19	D19S586	2	14.79	19p13.2	0.68	1.58	0.0596	0.68

<sup>a</sup>Positions derived from the Genetic Location Database ([http://cedar.genetics.soton.ac.uk/public\\_html/](http://cedar.genetics.soton.ac.uk/public_html/)).

<sup>b</sup>Regions derived from the NCBI Entrez Genome Query (<http://www.ncbi.nlm.gov/cgi-bin/entrez/>).

<sup>c</sup>NPL Z scores computed with GENEHUNTER.

<sup>d</sup>Mean IBD sharing computed with SIBPAIR.

{19.309}). Linkage for GABRA5 {17.073} and for GABRB3 {18.710}, however, could not be excluded [Hovatta et al., 1994].

Once again, a number of cloned genes<sup>3</sup> are in the implicated region. Notable among these as candidate genes for schizophrenia are CHRNA7, given the central rôle for nicotinic dysfunction in the aforementioned P50 gating abnormality in both humans and animal models [Luntz-Leybman et al., 1992], and the importance of the  $\alpha$ -7 nicotinic receptor in regulating glutamate release [McGehee et al., 1995]; and GABRA5 or GABRB3, given the growing appreciation for GABAergic abnormalities in schizophrenia [Ereshefsky and Lacombe, 1993].

### Chromosome 19

One marker on chromosome 19, D19S586, located at {14.790}, was associated with an NPL Z score >1.5 (Table II). Likewise, our companion study of European-American pedigrees [Faraone et al., 1997] revealed 2 nearby markers, D19S714 and D19S433, located at {27.08} and {39.63}, respectively, associated with NPL Z scores >1.5. Although these results can at best be considered supportive of linkage and previous parametric genome scans have tentatively excluded much of chromosome 19 [Parfitt et al., 1996], parallel findings in our African-American and European-American samples lend some credence to the notion that this region of chromosome 19 may harbor a schizophrenia susceptibility gene.

### Schizophrenia Susceptibility in African Americans

Although neither our study, nor any of the other studies previously described, provide significant evidence for linkage to schizophrenia according to the guidelines proposed by Lander and Kruglyak [1995], converging support from several independent samples suggest that 1 or several of these regions may contain loci that contribute to schizophrenia susceptibility. It is noteworthy that our African-American sample, and not our European-American sample, demonstrated suggestive evidence for linkage in regions previously reported in mostly European samples. This apparent paradox may have occurred for any of several reasons: 1) it is conceivable that greater informativity of genetic markers among African-Americans resulted in more extreme results; this might seem likely given reports of greater genetic heterogeneity among African-Americans, but becomes less plausible when we consider the roughly equal mean heterozygosity of markers in both racial groups (0.794 vs. 0.758 for the African-American and European-American samples, respectively<sup>4</sup>; 2) it is possible that 1 or several of our

suggestive linkage findings are false positive results and that the racial differences are purely factitious; 3) alternatively, these differences may reflect the fact that only a subset of oligogenes, each of which contributes to a complex disorder, may be relevant in any given dataset [Suarez et al., 1990]; or, finally, 4) it may be that these differences are the result of "phenotype amplification," that is, the increased ability to identify certain phenotypes, and by extension, genotypes, in the setting of (as yet unidentified) environmental factors with which these genotypes interact [Weiss, 1993]. The observation of significantly greater prevalence and sib-sib concordance for schizophrenia among African-Caribbeans in Britain would also be consistent with "phenotype amplification."<sup>5</sup> Similar arguments have been used to account for the higher prevalence of hypertension among African-Americans [Chakraborty et al., 1992].

Despite the fact that the African-American population is itself ethnically diverse, it would appear that our study detected evidence for several genetic loci contributing to schizophrenia susceptibility. Moreover, that different genetic loci were identified in this and in the European-American samples, lends credence to the notion that these genetic differences together with differences in environmental exposures may contribute to the reported differences in disease prevalence, severity, comorbidity, and course that has been observed in different racial groups in the United States and elsewhere.

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<sup>3</sup>RNR3, GABRA5, GABRB3, SNRPN, OCA2, SGNE1, CHRNA7, FMN, RECA, RYR3, EPB42, SORD, ACTC, THBS1.

<sup>4</sup>The observation of similar marker heterozygosities between European-American and African-American samples was somewhat unexpected, insofar as the marker sets we employed were screened for polymorphism primarily in European-American subjects. It is possible that this bias in marker selection was offset by

greater heterogeneity among African-Americans [Bowman and Murray, 1990; Chakraborty et al., 1992; Price, 1996].

<sup>5</sup>Second generation African-Caribbean individuals in Britain appear to be at risk for schizophrenia [Harrison et al., 1988]. This increase in risk does not appear to be confined to nonfamilial cases of psychosis: If anything, siblings of affected African-Caribbean probands may be at 15-fold greater risk for RDC schizophrenia than their white counterparts, suggesting that risk-conferring environmental factors interact with a particularly vulnerable genetic background [Sugarman and Craufurd, 1994; Hutchinson et al., 1996].

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