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Genome Scan of Schizophrenia Families in a Large Veterans Affairs Cooperative Study Sample: Evidence for Linkage to 18p11.32 and for Racial Heterogeneity on Chromosomes 6 and 14

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Genome-wide linkage analyses of schizophrenia have identified several regions that may harbor schizophrenia susceptibility genes but, given the complex etiology of the disorder, it is unlikely that all susceptibility regions have been detected. We report results from a genome scan of 166 schizophrenia families collected through the Department of Veterans Affairs Cooperative Studies Program. Our definition of affection status included schizophrenia and schizoaffective disorder, depressed type and we defined families as European American (EA) and African American (AA) based on the probands' and parents' races based on data collected by interviewing the probands. We also assessed evidence for racial heterogeneity in the regions most suggestive of linkage. The maximum LOD score across the genome was 2.96 for chromosome 18, at 0.5 cM in the combined race sample. Both racial groups showed LOD scores greater than 1.0 for chromosome 18. The empirical *P*-value associated with that LOD score is 0.04 assuming a single genome scan for the combined sample with race narrowly defined, and 0.06 for the combined sample allowing for broad and narrow definitions of race. The empirical *P*-value of observing a LOD score as large as 2.96 in the combined sample, and of at least 1.0 in each racial group, allowing for narrow and broad racial definitions, is 0.04. Evidence for the second and third largest linkage signals come solely from the AA sample on chromosomes 6 (LOD = 2.11 at 33.2 cM) and 14 (LOD = 2.13 at 51.0). The linkage evidence differed between the AA and EA samples (chromosome 6 *P*-value = 0.007 and chromosome 14 *P*-value = 0.004).

KEY WORDS: genome scan; schizophrenia; race; linkage; genetics; chromosome 18; racial heterogeneity

Schizophrenia is a chronic, disabling mental disorder which affects 1% of the population worldwide [Tsuang et al., 1997]. Patients with schizophrenia typically show a deteriorating course of illness during which acute "positive symptoms," such as delusions, hallucinations, looseness of associations, and bizarre behavior occur on a background of chronic, "negative symptoms," such as apathy, impoverished thought, social withdrawal, and blunted affect. The symptoms of schizophrenia cause pervasive impairments in social, occupational, and cognitive functioning and are costly in terms of the personal suffering of patients and families and the burden on the health care system. The symptoms and impairments of schizophrenia

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likely reflect neurodevelopmental deviations that lead to structural and functional anomalies in the frontal–subcortical circuits of the brain [Seidman et al., 1999]. Although the details of schizophrenia's pathophysiology remain to be worked out, current evidence indicates it is a complex disorder influenced by genes, environmental risk factors, and their interaction [Faraone et al., 2004]. For a discussion of the implications complex inheritance has for theories of pathophysiology, see Tsuang and Faraone [1995].

The many family, twin and adoption studies of schizophrenia show that genes influence susceptibility to the disorder and the mode of inheritance is complex [Gottesman and Shields, 1982; Risch, 1990; Faraone et al., 2004]. Among relatives of patients, the risk for psychosis is about 50% to monozygotic twins, 10% to first degree relatives, and 2% to second degree relatives. Sullivan et al. [2003] reviewed 12 twin studies and found that the heritability of liability to schizophrenia was 81%. Adoption studies of schizophrenia have shown that when biological offspring of schizophrenic mothers were raised by adoptive parents, they showed higher rates of schizophrenia as adults, compared to control adoptees [Heston, 1966; Kety et al., 1968; Kendler et al., 1994]. Kety et al. [1968] showed that the paternal half siblings of schizophrenic adoptees had higher rates of schizophrenia than the paternal half siblings of non-schizophrenic adoptees (13% vs. 2%). These latter results cannot be attributed to in utero or post-natal environmental effects, since paternal half siblings have different mothers.

Taken together, the family, twin and adoption studies provide solid evidence that genes influence the susceptibility to schizophrenia. At the same time, they make clear that the concordance rates in monozygotic twins are far from 100%, which also emphasizes the importance of environmental risk factors in the etiology of the disorder. Among the many environmental risk factors studied, the strongest findings have been for events that occur early in neurodevelopment such as anoxic birth complications and maternal infections during pregnancy.

From these data about genes and environmental risk factors, many investigators have concluded that schizophrenia has a complex, multifactorial etiology, and that epistasis among some of the susceptibility genes is likely [Gottesman and Shields, 1967; Risch, 1990; Gottesman, 1997; Faraone et al., 2003]. Although many genome-wide linkage analyses of schizophrenia have suggested potential regions that may harbor schizophrenia susceptibility genes, no region has attained both genome-wide statistical significance and consistent replication. [Coon et al., 1994, 1998; Moises et al., 1995; Pulver et al., 1995; Blouin et al., 1998; Faraone et al., 1998; Kaufmann et al., 1998; Levinson et al., 1998; Shaw et al., 1998; Hovatta et al., 1999; Williams et al., 1999; Bailer et al., 2000; Brzustowicz et al., 2000; Ekelund et al., 2000; Schwab et al., 2000; Gurling et al., 2001; Lindholm et al., 2001; Paunio et al., 2001; DeLisi et al., 2002a,b].

One issue that has not been systematically addressed in genetic linkage studies of schizophrenia is the possibility of genetic heterogeneity due to racial differences, which would be consistent with racial differences in prevalence, clinical features, and treatment response that have been reported [Opolka et al., 2003; Barrio et al., 2003a,b]. Because gene frequencies vary among racial groups, some functional polymorphisms may be more predominant in one group than another. Due to interactions with other genes or environmental risk factors, the same gene variant can have different functional consequences across racial groups.

Several studies have addressed potential racial differences that might be relevant to the genetics of schizophrenia. Candidate gene meta-analyses have found significant associations between schizophrenia and: (a) 5HT2A for Europeans but not Asians [Abdolmaleky et al., 2004], (b) DRD3 for Caucasians but not Asians or Africans [Dubertret et al., 1998], and (c) COMT for Europeans but not Asians [Glatt et al., 2003]. Skol et al. [2003] and Luo et al. [2004] reported associations between markers at the NOTCH4 locus and schizophrenia for African Americans (AA) but not European American (EA)s; Takahashi et al. [2003] reported an association between markers on chromosome 22 and schizophrenia in EAs but not AAs. The latter finding was consistent with Riley et al. [1996a] report of no linkage between schizophrenia and 22q in South African Bantu families. This pattern of findings could be due to genetic heterogeneity between races, but could also reflect a random pattern of false positive or false negative findings.

To date, no schizophrenia linkage study has specifically tested for heterogeneity of linkage results among different racial groups. The NIMH Genetics Initiative schizophrenia linkage study found evidence for linkage to 10p14-p13, and 2p14p12 for EA families [Faraone et al., 1998] and to 6q16-q24, 8pter-q12, 9q32-q34, and 15p13-1q12 for AA families [Kaufmann et al., 1998], but no formal statistical hypothesis for racial heterogeneity was tested.

We previously reported initial results for chromosomes 6, 13, and 15 from a genome scan of 166 schizophrenia families collected through the Department of Veterans Affairs Cooperative Studies Program [Tsuang et al., 2000, 2001; Faraone et al., 2002b; Skol et al., 2003]. A summary and highlights of the completed genome scan are presented herein along with tests for racial heterogeneity at our most interesting linkage signals. The VA data set provides us with a unique opportunity to test for racial heterogeneity due to the substantial numbers of EA and AA families collected.

We found evidence for linkage to chromosome 18p11.32 in each sample and in the combined sample. The second and third largest linkage signals were found on chromosomes 6 and 14 with evidence coming solely from the AA sample. The linkage evidence differed between AA and EA families.

METHODS

Ascertainment, Assessment, and Diagnosis

Tsuang et al. [2000] provide a detailed description of the study methodology and description of the sample. The ascertainment of pedigrees began with the identification of ill probands having at least one biological relative meeting DSM-III-R criteria for the proband selection diagnoses: schizophrenia and schizoaffective disorder, depressed. We included the depressed subtype of schizoaffective disorder as an ascertainment diagnosis because family data suggest it is an alternative expression of the schizophrenia susceptibility genes [Cloninger, 1989]. This research was approved by the Perry Point Coordinating Center Human Rights Committee and by the human studies subcommittees at each participating medical center. All subjects gave informed consent before participating.

We assessed psychiatric diagnoses with the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994; Faraone et al., 1996]. The DIGS is a structured diagnostic interview that makes a detailed assessment of the course of illness, and makes a careful assessment of substance abuse and mood symptoms. The Family Interview for Genetic Studies (FIGS) interview was conducted with all available members of the family. The FIGS questions informants about psychiatric disorders in relatives. For all subjects, available medical records were collected when available. The DIGS and FIGS interviewers had a Masters degree or equivalent experience in a mental health field. All had prior clinical experience with schizophrenic patients and specific training on these instruments prior to the study. DSM-III-R diagnoses were made independently at each site by two senior psychiatrist or psychologist investigators with clinical and research experi-

ence in the diagnosis of psychotic patients. We achieved high inter-rater agreement on the ascertainment diagnoses as indicated by a kappa coefficient of 0.89 [Tsuang et al., 2000].

Genotyping

For the 772 subjects, genotypes were determined by PCR amplification of polymorphic loci using primers labeled with fluorescent probes. The 414 markers used were primarily from the ABI Prism Linkage Mapping set, Version 2.5, HD5 (http://home.appliedbiosystems.com/). Genotypes were determined by PCR amplification of polymorphic loci using primers labeled with fluorescent probes. The mean distance between markers was 8.6 cM, and the largest gap was 22.0 cM. DNA fragments were analyzed using an ABI377 or an ABI3100 DNA sequencing instrument and GeneScan and Genotyper software. Technicians performing the genotyping were blind to the diagnosis of the subjects. Two different individuals who were blind to subject phenotype independently reviewed each genotype. The accuracy of the genotyping methods used was 99.8% as determined by duplicate genotyping of 1,778 genotypes. In the course of the study, three identical twin pairs were identified. The accuracy rate derived from these subjects was 99.6%. Genotyping was 97.4% complete.

Prior to linkage analyses, we identified families with misspecified relationships using RELPAIR [Boehnke and Cox, 1997; Epstein et al., 2000]. Thirty-four of the 166 families included one or more misspecified relationship. In all but one of these 34 families, the correct relationship was easily inferred from the genotype data. The remaining family was not used for linkage analysis. Two putative affected sib pairs were found to be monozygotic twins. Because their families were not informative for linkage, they were excluded from further analysis.

After correcting pedigree structures, we identified genotype errors or mutations which resulted in inconsistencies with Mendelian inheritance using Pedcheck [O'Connell and Weeks, 1998] and Pedstats [Wigginton and Abecasis, 2003]. Twenty-three markers generated four or more genotype incompatibilities and were excluded for all families in the linkage analysis. In addition, we excluded genotypes for 180 markers that generated Mendelian inconsistencies only from those families in which the inconsistencies occurred.

Linkage Analyses

Our definition of affection status included schizophrenia and schizoaffective disorder, depressed type. We defined families as EA and AA based on the probands' and parents' races as identified in the DIGS. For 121 families both parents and the proband were of the same racial group, resulting in 60 families (37%) classified as AA and 61 (37%) classified as EA. There were 42 families (26%) in which the two parents were from different racial groups. They were excluded in the narrow race analyses. We included these families in our analyses using a broad definition of race that classified families as AA if the chance that a randomly chosen allele from an affected family member was of AA origin was greater than 50%. EA families were classified similarly. Using the broad definition, 88 families (54%) were classified as AA, 71 (44%) as EA, and five were excluded (one of the excluded families had also been excluded due to an unresolved, misspecified relationship).

We tested for departures from Hardy–Weinberg equilibrium (HWE) resulting in an excess or deficit of homozygotes separately in the AA and EA groups using a chi-squared goodness-of-fit test. We excluded from further analysis seven markers which showed significant deviation from HWE ($P < 0.005$).

We performed semiparametric linkage analysis using the linear-model-based allele sharing method of Kong and Cox [1997] and the S_{pairs} statistic [Whittemore and Halpern, 1994]. We estimated marker allele frequencies separately for AA and EA samples, and allowed for unequal male and female specific genetic distances based on Marshfield genetic maps [Broman and Weber, 1998]. For linkage calculations we used the computer program Merlin [Abecasis et al., 2002].

To assess the significance of our genome scan results, we used computer simulation. Under the null hypothesis of no disease locus present in the genome, we computed the proportion of simulated genome scans that resulted in a maximum LOD score greater than or equal to the observed maximum LOD score. Rather than carrying out a large number of complete genome scans and assessing significance directly, we simulated and analyzed data for a modest number of genome scans (20 in the analysis reported), and then formed 1,000 pseudo-replicate samples by random selection of each family from one of the 20 simulated scans [Song et al., 2004]. This approach is computationally very efficient, since it replaces most of the linkage statistic calculation with simple summations. As with our original data analysis, we calculated z-scores using the Kong and Cox linear allele sharing method with parameters estimated and corresponding LOD scores calculated every 0.5 cM.

To determine if there was significant heterogeneity in LOD scores between the AA and EA samples, we performed a likelihood ratio test at the position of our three largest peaks in the analyses stratifying families by race. The LR test statistic is $LR_H = 2 \times \ln(10) \times [LOD(AA) + LOD(EA) - LOD(AA + EA)]$. Under the null hypothesis of no heterogeneity, LR_H is asymptotically distributed as a χ_1^2 statistic. The asymptotic P-values were confirmed by simulation.

RESULTS

Among the 166 families ascertained, 124, 30, 7, 4, and 1 families had 2, 3, 4, 5, and 6 affected members, respectively. These families had a total of 772 genotyped members and 216 affected sibling pairs. 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 (affected and unaffected) were 42% male with a current mean age of 49 years (SD, 17 years). Table I lists the numbers of families and affected individuals by race for the families used in the analyses.

TABLE I. Number of Families and Affected Members

	Race broadly defined			Race narrowly defined		
Race	Number of families	Number typed	Number affected	Number of families	Number typed	Number affected
African American	88	378	211	60	263	143
European American	71	354	164	61	297	135

The maximum LOD score across the genome was 2.96 for chromosome 18, at 0.5 cM in the combined sample using race narrowly defined (Fig. 1 & Table II). Using the simulation technique described in the Methods, the empirical *P*-value associated with that LOD score is 0.04 assuming a single genome scan for the combined AA and EA sample with race narrowly defined, 0.06 for the combined sample allowing for broad and narrow definitions of race, and 0.17 if we account for performing analyses on the combined and race stratified sample allowing for broad and narrow race definitions. Our simulations also indicate that, taking into account genome scans for each race and for the combined group using both narrow and broad racial classification, LOD scores greater than 2.2 may be considered suggestive. When considering the race-specific analyses, taking into account both definitions of race, the LOD threshold for suggestive linkage was 1.8 for the AA sample and 1.7 for the EA sample.

Figures 1A and 2A give the genome-wide multipoint LOD scores for the narrow and broad definitions of race for all families, respectively. The chromosome 18 finding was the only LOD score greater than 2.0. For all families, six LOD scores exceeded 1.0 (considering both definitions of race): chromosome 2 had a LOD score of 1.34 at 8.1 cM; chromosome 3 had a LOD score of 1.74 at 103.3 cM; chromosome 6 had a LOD score of 1.44 at 49.2 cM; chromosome 9 had a LOD score of 1.29 at 29.5 cM; chromosome 11 had a LOD score of 1.25 at 4.3 cM; and chromosome 13 had a LOD score of 1.38 at 87.6 cM.

Figures 1B,C, 2B, and C give results stratified by race. On Chromosome 18, both races show a peak LOD score greater than 1.0 at 0.5 cM. We calculated the probability of observing a LOD score as large as 2.96 in the combined sample, and of at least 1.0 in each racial group, again allowing for narrow and broad racial definitions; the empirical *P*-value is 0.04. For AA families, the maximum LOD score was 2.13 at 51.0 cM on chromosome 14. For EA families, the maximum LOD score was 2.09 at 3.0 cM on chromosome 18. The third largest peak in the race-stratified analyses was a LOD score of 2.11 at 33.2 cM on chromosome 6 for AA families.

Given the evidence for linkage to chromosomes 6 and 14 for AAs but not EAs, we tested for heterogeneity of linkage observed between the AA and EA samples at the position of the maximum LOD score. We found differences for chromosome 6 at 33.2 cM ($LR_H = 7.3$; $P = 0.07$) and chromosome 14 at 52.0 cM ($LR_H = 8.2$; $P = 0.004$).

Figure 3A shows, for the narrow definition of race, the detailed plot of LOD scores for chromosome 18, including marker names and genetic map distances from the Marshfield map. The combined sample results are presented with a solid line and analyses by race with dashed (EA) and dotted (AA) lines. Figure 3B provides the same information for the broad definition of race. The racial groups did not differ significantly for the chromosome 18 finding at 0.5 cM ($LR(H) = 0.7$; $P = 0.53$).

For each chromosome having a LOD score greater than 1.0 in any analysis, Table II presents the maximum LOD score (in bold), the location of that LOD score, the racial definition used and the LOD score at that location for the other analyses using the same racial definition.

DISCUSSION

Our genome scan from the Veterans Affairs Cooperative Schizophrenia Linkage Study found some evidence for a schizophrenia susceptibility gene near the tip of chromosome 18p. Evidence for linkage was contributed by both AA and EA families and was somewhat greater when race was narrowly

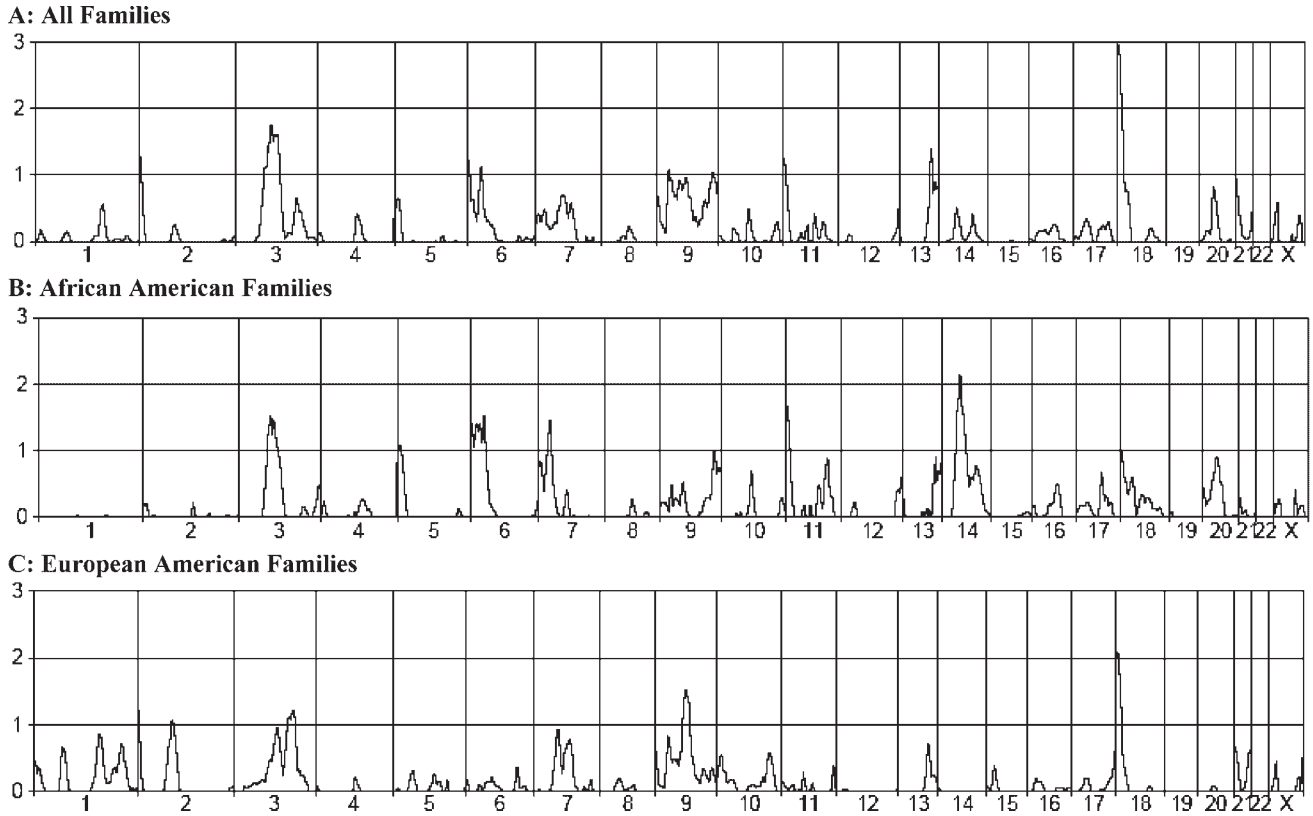

Fig. 1. Genome-wide LOD Scores for Narrow Definition of Race. LOD scores are plotted by chromosome position for each chromosome. Genetic map distances are from Marshfield map (http://research.marshfieldclinic.org /genetics/Map_Markers /data/Maps).

TABLE II. Summary of Maximum LOD Scores Greater Than 1.0

	Max LOD scores				
Chr	AA	EA	All	Position (cM)	Racial definition
2	0.14	1.44	1.33	7.6	Narrow
3	1.43	0.45	1.74	103.3	Narrow
5	1.07	0.00	0.59	8.7	Narrow
6	2.11	0.00	0.64	33.2	Broad
9	0.01	1.51	0.90	78.5	Narrow
11	1.67	0.14	1.24	3.8	Narrow
13	0.71	0.67	1.38	87.0	Narrow
14	2.13	0.00	0.51	52.0	Narrow
17	1.29	0.01	0.80	69.1	Broad
18	1.01	1.99	2.96	0.5	Narrow
X	1.11	0.01	0.72	102.6	Broad

defined. This latter finding is counterintuitive, given that we found no racial heterogeneity at this locus and increasing the sample size would be expected to increase the LOD score. The decrease we observed could be a signal that our finding reflects random variation or is a false positive.

The 18p region implicated by our work is a new region not implicated by prior linkage studies of schizophrenia, as indicated by two meta-analyses [Badner and Gershon, 2002; Lewis et al., 2003]. The second and third largest linkage signals were found on chromosomes 6 and 14, with some evidence for linkage coming solely from the AA sample. We found evidence of racial heterogeneity at the positions of the chromosome 6 and 14 maximum LOD scores, but not evidence for heterogeneity by race for chromosome 18.

Our results implicating 18p11 in schizophrenia are consistent with case reports of chromosomal abnormalities. One study reported a submicroscopic deletion of 18pter, detected by subtelomeric FISH probe in an adult with paranoid schizophrenia and mental retardation [Babovic-Vuksanovic et al., 2004]. Another reported one case of schizophrenia and one case of bipolar disorder associated with an inversion of chromosome 18(p11.3;q21.1) [Mors et al., 1997].

A potential candidate gene for schizophrenia implicated by our 18p11 finding is ADCYAP1 at 1.6 cM on 18p11.32. ADCYAP1 encodes pituitary adenylate cyclase activating polypeptide (PACAP). PACAP regulates three processes relevant to schizophrenia: catecholamine transmission pathways [Isobe et al., 1996; Moser et al., 1999; Park et al., 1999]; neurodevelopment [Koves et al., 1994; Pellegri et al., 1998;

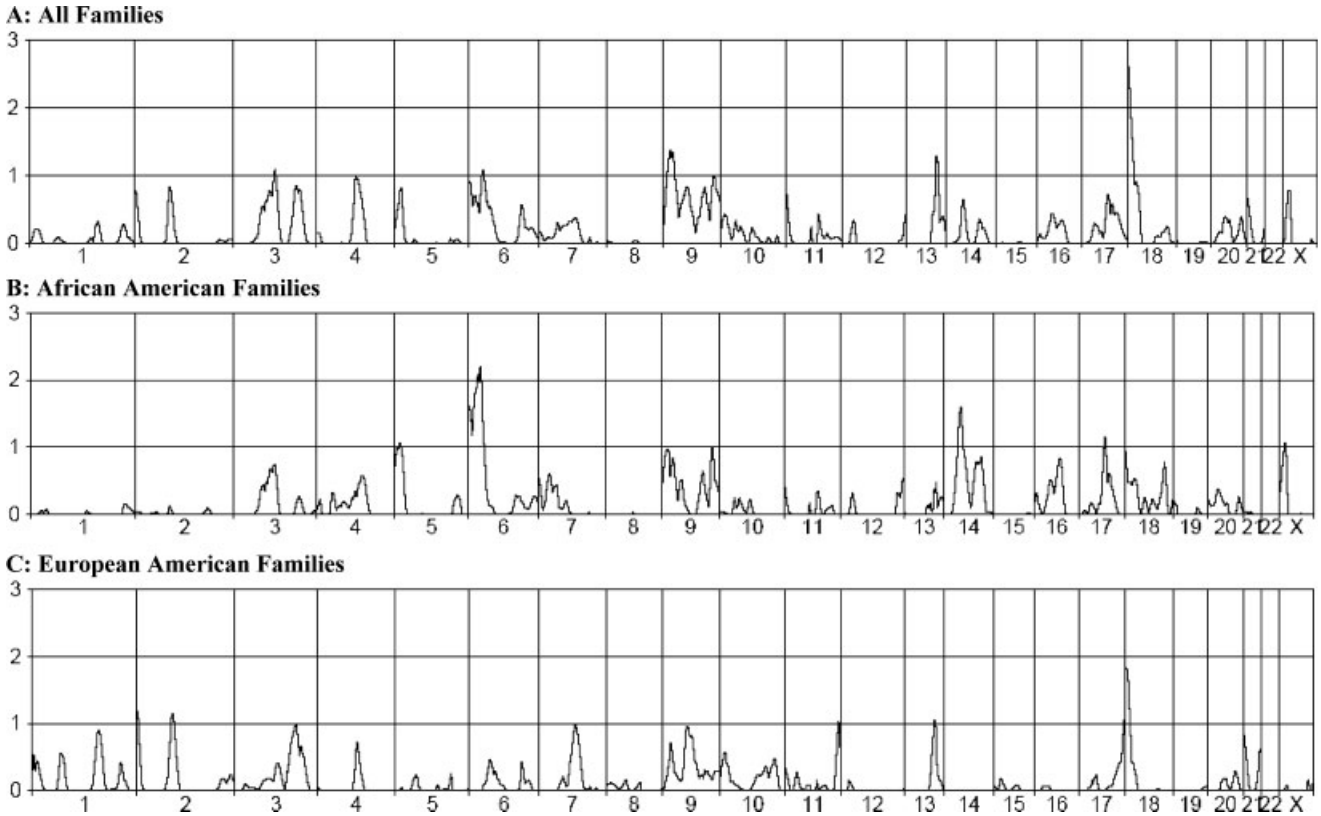

Fig. 2. Genome-wide LOD Scores for Broad Definition of Race. LOD scores are plotted by chromosome position for each chromosome. Genetic map distances are from Marshfield map (http://research.marshfieldclinic.org /genetics/Map_Markers /data/Maps).

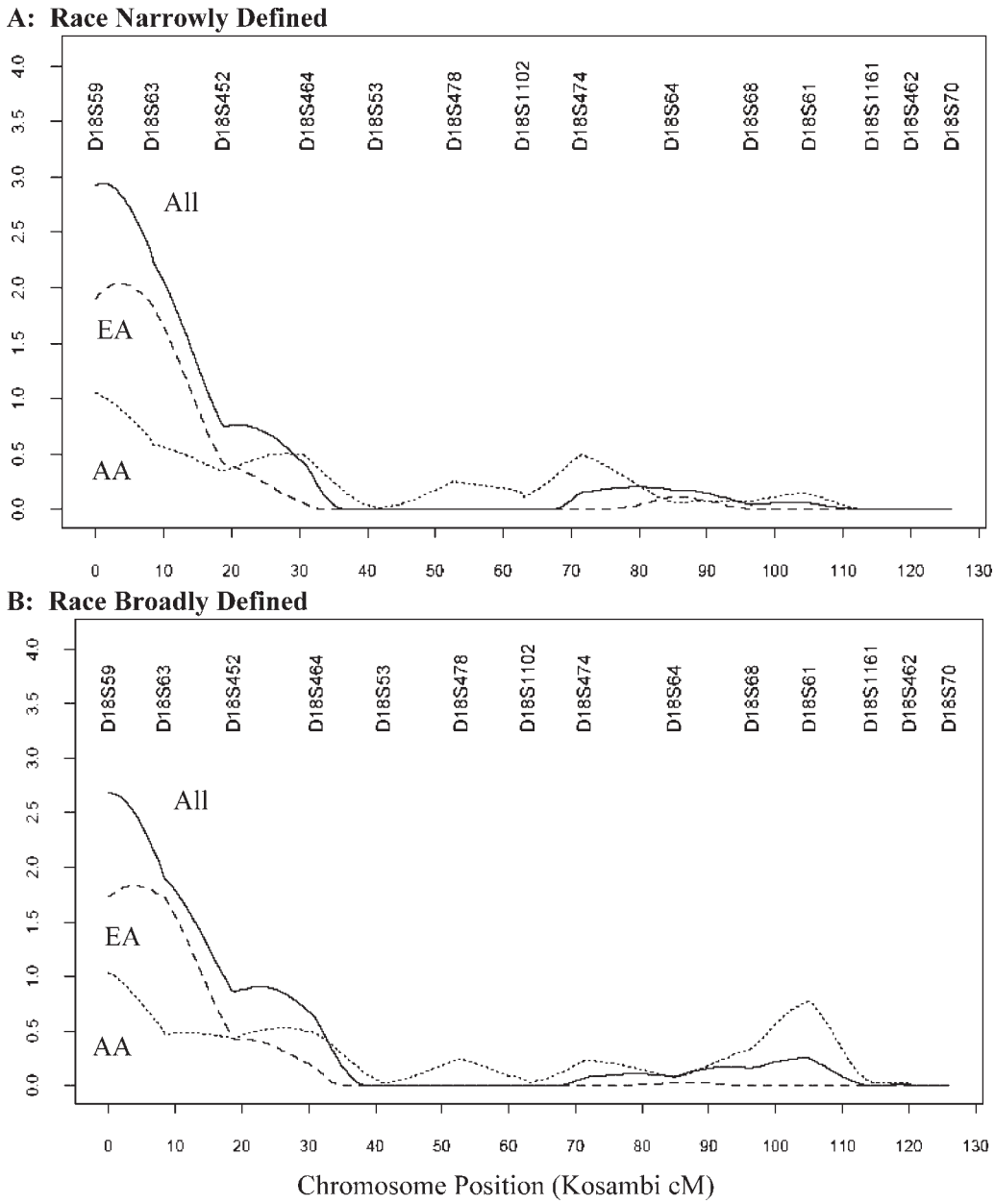

Fig. 3. Plots of LOD scores versus chromosome position (Kosambi cM). Genetic map distances are from Marshfield map (http://research.marshfield-clinic.org /genetics/Map_Markers /data/Maps). Abbreviations are: All, all families for all racial groups; AA, African America; and EA, European American. Affectation and race classification descriptions are in Materials and Methods.

Frechilla et al., 2001]; and glucose regulation [Hamelink et al., 2002; Shintani et al., 2003]. Ishiguro et al. [2001] assessed the potential association between ADCYAP1 and schizophrenia in the Japanese population. They found no difference in the prevalence of a single nucleotide polymorphism between 281 schizophrenic patients and 251 controls.

Other candidate genes at 18p11.32 are THO Complex 1 (THOC1), at 0.5 cM, a component of the transcription/export complex involved in linking transcription of RNA, and its export to the cytoplasm [Strasser et al., 2002], thymidylate synthetase (TYMS) at 1 cM, which is involved in DNA replication and repair [Chu and Dolnick, 2002], and ubiquitin-specific protease 14 (USP14) at 0.5 cM which produces presynaptic dysfunction when deleted in mice [Wilson et al., 2002; Ehlers, 2003].

Because epidemiologic evidence suggests schizophrenia may share some susceptibility genes in common with bipolar disorder, it is also of interest to note that 18p11 has been implicated by studies of that disorder [Crow, 1990; Berrettini, 2000; Bramon and Sham, 2001]. A genome-wide scan of families from Costa Rica reported a LOD score of 1.43 for marker D18S59 [McInnes et al., 1996], which is the marker giving the highest LOD score in our study. Subsequent fine-mapping of this region found a significant association between bipolar disorder and a 331 kb segment that included TYMS and ADCYAP1 [McInnes et al., 2001]. Consistent with this finding, Segurado et al. [2003] meta-analysis of bipolar disorder implicated 18pter-p11 (0 to 24.1 cM).

Our results show no suggestion of racial heterogeneity for our 18p11.32 linkage finding. In contrast, we found evidence

for linkage heterogeneity by race at 33.2 cM on chromosome 6 and 52 cM on chromosome 14, the locations of our second and third largest linkage signals. On chromosome 6p, we found some evidence of linkage for AA families but none for EA families. Our chromosome 6 finding is in a region implicated by several linkage studies [Turecki et al., 1997; Lewis et al., 2003]. This region contains the gene for dystrobrevin-binding protein-1 (DTNBP1) at 29 cM, close to the peak on our AA families (33 cM). Another candidate gene in the 6p linkage region is NOTCH4, at 46 cM, which a meta-analysis suggests is associated with schizophrenia [Glatt et al. (in press)]. NOTCH4 has shown race specific effects in candidate gene association studies. In a prior report from this sample, we found over-transmission of some NOTCH4 alleles in the AA but not the EA group [Skol et al., 2003]. Our finding was confirmed by Luo et al. [2004] in a case-control study of 123 AA patients, 223 EA patients, 85 AA controls, and 211 EA controls. Despite these intriguing findings suggesting that the 6p schizophrenia locus may be over-represented in families of African ancestry, no evidence for linkage of chromosome 6p markers to schizophrenia was reported for 19 African Bantu-speaking families [Riley et al., 1996b] or 30 AA families [Kaufmann et al., 1998]. These contradictory results could be due to low power to detect linkage in these other studies or to false positive findings in our study.

For chromosome 14 we found some evidence for linkage for AAs but not for EAs. No other studies have assessed racial heterogeneity for chromosome 14 loci and none have reported suggestive or significant linkage to the region we implicated in AAs. This highlights the importance of searching for genes in racially homogeneous groups. Although our findings of racial heterogeneity could be due false positive findings, it may also be that by considering the racial groups separately we have revealed linkage evidence that might otherwise have been missed.

The racial differences we and others have found are intriguing. Whereas racial differences found by candidate gene studies could be attributed to differences in the extent of linkage disequilibrium between races, that effect would not explain differences in linkage findings. One explanation for our result is that, although the genetic mechanisms contributing to schizophrenia may be the same for both races, schizophrenia susceptibility alleles may differ in frequency between the two groups. Our results could also reflect systematic differences between the environments of racial groups in events such as obstetric complications which are known to be risk factors for schizophrenia [Zornberg et al., 2000; Faraone et al., 2002a]. If a specific risk factor such as anoxia interacts with a specific susceptibility allele, then we would expect to find greater evidence of linkage for the race that has the greatest prevalence of anoxia. Such effects have been hypothesized to explain the increased prevalence and sibling concordance for schizophrenia among African Caribbeans in the United Kingdom [Hutchinson et al., 1996].

Two other regions yielded modest evidence for linkage in our initial genome-wide scan. The maximum LOD score on chromosome 13q was 1.38 at 88 cM, the same location where Badner and Gershon [2002] meta-analysis found significant evidence for linkage. The individual positive studies are reasonably consistent in implicating this location. Lin et al. [1995] reported a maximum LOD score of 1.62 at 65 cM for a mixed Japanese and British sample and then replicated the finding with a LOD score of 1.7 at 95 cM in another British sample but not in a Taiwanese sample [Lin et al., 1997]. Blouin et al. [1998] reported a LOD score of 4.18 at 85 cM and Brzustowicz et al. [1999] found a LOD score of 4.42 at 76 cM. We also found a modest LOD score of 1.74 at 103 cM on chromosome 3q, a region that has not been implicated by prior linkage studies of schizophrenia.

Our results should be reviewed in the context of several limitations. Although our sample is one of the largest collected with a single methodology, we likely only had sufficient power to detect genes of relatively large effect. This problem is even more acute when considering analyses stratified by race. We also recognize that, although we collected detailed information about race, our racial categories are very broad and cannot be considered genetically homogeneous. Moreover, the racial differences we report must be interpreted cautiously given that no loci showed genome-wide significance in either racial subgroup.

Despite these limitations, we found some evidence of linkage to a new schizophrenia region on the tip of chromosome 18p. Fine mapping studies are needed to clarify this finding, which remains suspect given it had not been implicated by prior linkage studies of schizophrenia, as indicated by two meta-analyses [Badner and Gershon, 2002; Lewis et al., 2003]. We also found evidence of linkage in AAs and racial heterogeneity in the evidence for linkage on chromosomes 6 and 14. These latter findings emphasize the need for molecular genetic studies to consider race when designing ascertainment and analysis schemes and also caution against generalizing findings from one racial group to others.

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