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Genomewide Linkage Scan for Schizophrenia Susceptibility Loci among Ashkenazi Jewish Families Shows Evidence of Linkage on Chromosome 10q22

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Previous linkage studies in schizophrenia have been discouraging due to inconsistent findings and weak signals. Genetic heterogeneity has been cited as one of the primary culprits for such inconsistencies. We have performed a 10-cM autosomal genomewide linkage scan for schizophrenia susceptibility regions, using 29 multiplex families of Ashkenazi Jewish descent. Although there is no evidence that the rate of schizophrenia among the Ashkenazim differs from that in other populations, we have focused on this population in hopes of reducing genetic heterogeneity among families and increasing the detectable effects of any particular locus. We pursued both allele-sharing and parametric linkage analyses as implemented in Genehunter, version 2.0. Our strongest signal was achieved at chromosome 10q22.3 (D10S1686), with a nonparametric linkage score (NPL) of 3.35 (genomewide empirical *P* = .035) and a dominant heterogeneity LOD score (HLOD) of 3.14. Six other regions gave NPL scores >2.00 (on chromosomes 1p32.2, 4q34.3, 6p21.31, 7p15.2, 15q11.2, and 21q21.2). Upon follow-up with an additional 23 markers in the chromosome 10q region, our peak NPL score increased to 4.27 (D10S1774; empirical *P* = .00002), with a 95% confidence interval of 12.2 Mb for the location of the trait locus (D10S1677 to D10S1753). We find these results encouraging for the study of schizophrenia among Ashkenazi families and suggest further linkage and association studies in this chromosome 10q region.

Introduction

Schizophrenia and schizoaffective disorder (MIM 181500), which are hereafter referred to as "SZ," constitute a complex psychiatric disorder that currently affects ~1% of the world populations (Eaton 1985). Although the causes are yet unknown, many lines of evidence, including twin, adoption, and family studies, support a strong genetic component (McGue and Gottesman 1991; Tsuang et al. 1991; Cardno and Gottesman 2000). Such observations have motivated an enormous amount of work toward the discovery of genes involved in SZ, including many genomewide linkage scans and a multitude of candidate gene investigations (Pulver et al. 1994, 1995; Moises et al. 1995; Straub et al. 1995, 1997, 1998, 2002; Wang et al. 1995; Kendler et al. 1996; Schwab et al. 1997, 1998, 2000, 2003; Blouin et al. 1998; Faraone et al. 1998; Brzustowicz et al. 1999, 2000; Levinson et al. 2000; Egan et al. 2001; Gurling et al. 2001; DeLisi et al. 2002; Shifman et al. 2002; Stefansson et al. 2002, 2003).

Although recent data suggest a role for neuregulin 1 (NRG1 [MIM 142445], mapped to chromosome 8p12) in SZ susceptibility in Icelandic and Scottish samples (Stefansson et al. 2002, 2003), the field is generally plagued with inconsistent results across studies. Every human chromosome, in one or another study, has shown some evidence of harboring an SZ gene, but none is consistent across all studies. For example, two meta-analyses of genomewide SZ scans have recently been published, with differing results. Badner and Gershon (2002) conducted meta-analyses based on published SZ scans, using the multiple-scan-probability (MSP) technique to analyze 18 genomewide scans (681 pedigrees), and showed that the strongest evidence for susceptibility loci exists on chromosomes 8p, 13q, and 22q, the three regions previously implicated in our autosomal scan of 54 pedigrees of European descent (Blouin et al. 1998). Lewis et al. (2003) applied a rank-based genome scan meta-analysis to genotype data from 20 genomewide SZ scans and found that, when this method was used,

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Table 1

Structure of 29 Ashkenazi Jewish Families Used in Scan

Relationship Type	No. of Affected Sibs[a]	No. of Founders[b]	Frequency of Families by Type
Siblings (No./Family):			
2	2	2	11
2	2	1	4
2	2	0	1
3	2	2	2
3	2	1	3
3	2	0	2
4	3	1	1
4	2	1	1
Avuncular	NA	2	1
Grandparent-grandchild	NA	2	1
Cousins	NA	4	2
Total			29

[a] NA = not applicable.

[b] No. of genotyped parents for sibships; no. of genotyped founders for other relationship types.

the strongest evidence of linkage was on chromosome 2q.

The reasons for such inconsistencies likely stem from the complex nature of SZ etiology. Several genes, acting additively or in concert, may be responsible for SZ in some families, whereas other genetic combinations may explain the disorder in other subgroups. Thus, linkage studies to date have unwittingly combined families of different genetic etiologies into one test group. Although this approach has proved fruitful for many highly penetrant Mendelian disorders, the heterogeneity problem is a much greater concern when looking for several genes of modest-to-small effects.

One approach to reduce heterogeneity is to pursue families from a relatively genetically isolated population that has emerged from a small number of founders (McKusick 1973; Peltonen et al. 2000; Shifman et al. 2002). This increases the likelihood that the subjects genotyped will have similar underlying genetic predispositions, increasing the ability to detect the effects of a particular gene. This approach has been taken previously for genetic studies of SZ, including focus on Finland (Hovatta et al. 1999; Ekelund et al. 2000; Paunio et al. 2001; Gasperoni et al. 2003), Iceland (Moises et al. 1995; Stefansson et al. 2002; Stefansson et al. 2003), the Central Valley of Costa Rica (DeLisi et al. 2002), the Azores (Pato et al. 1997), and Palau (Micronesia) (Devlin et al. 2002).

We have collected a set of Ashkenazi Jewish families with at least two individuals affected by SZ. The current Ashkenazi Jewish population, living mostly in central and eastern Europe and the United States, descended from a small founder population ~500 years ago (Ostrer 2001). The close genetic relationships among Ashkenazim have been documented through traces of several Mendelian genetic disorders, as well as through Y chromosome and mitochondrial similarities (Tikochinski et al. 1991; Santachiara Benerecetti et al. 1993; Hammer et al. 2000; Nebel et al. 2000, 2001). Because of the reduced genetic variation, genetic studies among the Ashkenazim have been productive in the identification of susceptibility genes for several disorders. Founder mutations have been shown to be important as causes of colorectal cancer (Foulkes et al. 2002), breast cancer (Struewing et al. 1997), and prostate cancer (Rennert et al. 2002) in the Ashkenazim. Even though the rate of SZ does not appear to differ from the rates in other populations, focus on this isolate can reduce heterogeneity in linkage analyses and increase the utility of association analyses.

Subjects and Methods

Ascertainment of Study Subjects

SZ families of Ashkenazi descent were recruited nationally with advertisements in newspapers and Jewish newsletters, talks to community organizations, and the Epidemiology-Genetics Program in Psychiatry Web site). Families were eligible for inclusion in these analyses if the proband met criteria for a diagnosis of schizophrenia, according to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) (American Psychiatric Association 1994), and if a first- or second-degree relative met DSM-IV criteria for schizophrenia or schizoaffective disorder. We recruited 29 multiply affected families of Ashkenazi descent. Probands in these families were recruited from California (34%), the northeastern United States (New York, New Jersey, Pennsylvania, Rhode Island, and Maryland) (31%), the midwestern United States and Canada (Wisconsin, Ohio, Illinois, Minnesota, and Ontario) (21%), and the southern United States (Florida and Mississippi) (10%). Our ascertainment strategy for the multiply affected pedigrees was to directly examine all affected individuals, the parents of those individuals, and any other family members connecting affected pairs. When parents of affected individuals were unavailable, we sought unaffected siblings for DNA samples.

Diagnostic Instruments and Procedures

Affected individuals and their parents were examined in person by a clinical psychologist (hereafter referred to as the "clinical examiner") with the administration of two interviews. In addition, a blood sample was collected. Most of the subjects were seen in their homes. The two interview schedules were as follows: (1) the Diagnostic Interview for Genetic Studies (DIGS, version 2.0; revised for DSM-IV), a semistructured interview

that elicits information about lifetime history of psychiatric symptoms and behaviors; and (2) the Structured Interview for DSM-IV Personality Disorders (SID-P) (Stangl et al. 1985). The SID-P schedule was administered to non-SZ subjects and includes items relevant to the assessment of the following subset of personality disorders: antisocial, borderline, histrionic, compulsive, schizoid, schizotypal, and paranoid. As part of the interview process, a psychiatric treatment history was prepared, and the subjects were asked to sign release forms allowing us to receive copies of their psychiatric treatment records. Interviews were tape-recorded for quality control purposes and for review by members of a consensus diagnosis committee, who assigned final diagnoses for each subject (see paragraph below). In addition to interviewing the subject, the clinical examiner also interviewed an informant about the subject. The clinical examiner completed a written diagnostic formulation for each affected individual, describing prominent features and course of illness.

Final diagnoses were assigned through a consensus procedure. Available information about each subject (i.e., tape recording of the interview, interview booklets, summary of information obtained from informant, clinical examiner's diagnostic formulation, and psychiatric treatment records) was reviewed independently by two members of a consensus diagnosis committee (psychiatrists) who each completed a DSM-IV diagnostic checklist. The checklist contained each necessary criterion for 26 Axis I DSM-IV disorders. Disorders were rated as absent, possibly present, probably present, definitely present, or unknown. Ages at onset of disorders that were rated as present (for any level of certainty) were also recorded. Ratings assigned independently by the two members of the committee were compared. If disagreement existed with respect to (1) the ratings of any of the 26 diagnoses (including certainty levels assigned), (2) age at onset (>4-year discrepancy) for any of the disorders that were rated as positive, or (3) course of illness ratings for individuals with psychotic symptoms, then the two members of the committee met to resolve the discrepancies. Fifty-nine subjects with certainty ratings of probably or definitely present for DSM-IV schizophrenia or schizoaffective disorder were considered to be affected, thereby limiting our analyses to a narrow and conservative definition of the affected phenotype for linkage analyses. Of the 59 affected subjects, 10 were given a consensus diagnosis of DSM-IV schizoaffective disorder.

Demographic and Clinical Characteristics

The family structures in our data set are provided in table 1. The families are generally small, with 26 of the families consisting of affected sibling pairs and 3 families consisting of other affected relative pairs. Affected individuals included those with schizophrenia (83%) or schizoaffective disorder (17%); 66% of these affected individuals were male. The average age at onset for all affected individuals was 20.1 years (range 12–35 years) and was similar for schizophrenia and schizoaffective disorder cases. Individuals who were given a diagnosis of another psychotic disorder or schizophrenia spectrum disorder were classified as "phenotype unknown" in all analyses. Nine subjects in the 29 pedigrees were assigned to the unknown category (five with a psychotic affective illness and four with an schizophrenia spectrum personality disorder).

To reduce the possibility of non-Ashkenazi grandparents or founders in our sample, ancestry questionnaires were completed for each proband to establish country or region of origin of their parents and four grandparents. Eastern Europe (Russia, Poland, Latvia, Lithuania, and Ukraine) and central Europe (Austria, Germany, Hungary, and Romania) account for >98% of the known grandparent countries of origin. Families were excluded if any grandparent of an affected subject was known to be of non-Ashkenazi descent.

Genotyping

All genotyping for this scan was performed at the Australian Genome Research Center (AGRF). The autosomal scan included 382 markers (ABI Prism Linkage Mapping Set, version 2 [MD-10, LMSV2]), with an average spacing of 8.85 cM, covering 3,381 cM, and an average heterozygosity of 0.785. The largest gaps were 24.1 cM on chromosome 8q12.1 and 23.8 cM on 6p21.31. Map order and distances were determined from the Généthon map. Markers were genotyped in 28 multiplexed panels. All PCRs were performed under standard conditions in a total volume of 6 μl, using a PTC-225 DNA Engine Tetrad (MJ Research). Primers were labeled with fluorescent dyes (FAM, HEX, and NED [Applied Biosystems LMSV2]). PCR products were then pooled into multiplex panels of 10–20 markers and electrophoresed for 2.8 h (0.2 mm denaturing polyacrylamide gels, 4.5%) on a 377 DNA Sequencer (Applied Biosystems). Genescan software (Applied Biosystems) assigns tracking for each sample lane. Files are then imported into Genotyper (Applied Biosystems) software that interprets the electropherogram and assigns genotypes.

Follow-up markers for chromosome 10 were chosen from the UCSC genome browser (Kent et al. 2002) (June 2002 assembly) to cover an average spacing of 1 Mb. Priority was given to markers with the highest heterozygosity. Map order and distance were based on the UCSC map, except for two cases in which the DeCode Icelandic map (Kong et al. 2002) was used.

Statistical Analyses

Mendelian inconsistencies and potential relationship errors were evaluated and corrected prior to data analysis using the Pedmanager (v. 0.9) interface at AGRF (Ewen et al. 2000). The AGRF software was also used for binning of alleles, and Genehunter, version 2.0, was used to identify double (flanking) crossovers in haplotypes. Markers were removed from subsequent analyses for the entire family when Mendelian inconsistencies were apparent, and markers were removed for individuals when apparent double crossovers were identified in Genehunter haplotypes. Parametric and model-free allele sharing linkage analyses were performed using the software Genehunter (Kruglyak et al. 1996). Parametric LOD scores and heterogeneity LOD (HLOD) scores were calculated for both dominant and recessive models. Parameters for these models are noted in table 2. Model-free allele sharing was assessed via the NPL_{all} statistic, based on estimated allele sharing for all affected relative pairs in the data set. Marker allele frequencies among the Ashkenazi were estimated on the basis of founders from 60 Ashkenazi pedigrees collected for our psychiatric genetics studies (101 parents from families with DSM-IV bipolar I disorder and SZ). This allowed a more precise estimate of frequencies than relying on founders in the 29 families with SZ. However, parents were available for most of our families (see table 1), so the impact of these allele frequency estimates should not be large. The NPL_{all} method does not directly estimate the location of a susceptibility locus, and one often assumes the best location estimate to be where the NPL_{all} is the highest. However, this is not ideal, and locations estimated in this way can vary greatly (Roberts et al. 1999). For this reason, we employed the method of Liang et al. (2001) to directly estimate location by employing generalized estimating equations. This method is implemented in the software Genefinder and provides estimates of map location (and the 95% CI) for the disease locus (τ).

Empirical *P* values were calculated for the NPL_{all} scores via simulation. The program Merlin (Abecasis et al. 2002) was used to generate 50,000 replicates of families identical to those in our sample. Markers with similar allele sizes and frequencies were also generated under the assumption of no linkage. Linkage analyses were then performed on these unlinked replicates (according to the procedure of Li and Haghighi [1999]), and genomewide empirical *P* values were estimated by extrap-

Table 2

Maximum Linkage Signal for Each Chromosome at Initial Genome Scan

	Model-Free				Dominant[a]			Recessive[b]		
Chromosome	NPL	Peak Marker	cM	P[c]	Maximum HLOD	α (%)[d]	cM	Maximum HLOD	α (%)[d]	cM
1	2.45	D1S2797	68.0	.007	1.23	100	32.9	.90	35	167.3
2	1.40	D22S2259, D22S2368	59.1, 81.7	.081	.25	36	59.1	.27	23	85.0
3	1.62	D3S1263	27.1	.055	.78	60	31.9	1.22	40	117.4
4	2.30	D4S1535	197.7	.011	1.05	75	197.7	1.07	47	192.7
5	1.49	D5S407	66.3	.068	.31	55	40.3	.39	26	68.3
6	2.37	D6S1610	43.6	.009	1.17	78	53.1	2.09	71	57.9
7	2.09	D7S510	56.8	.019	.80	61	56.8	.98	41	53.7
8	1.12	D8S514	123.9	.13	.42	44	123.9	.63	30	123.9
9	1.68	D9S1682	126.4	.048	.80	68	13.7	.63	32	123.0
10	3.35	D10S1686	106.3	.00042	3.14	100	108.6	1.89	64	110.9
11	1.49	D11S905	51.9	.068	1.04	65	54.3	1.00	36	58.0
12	1.89	D12S79	131.3	.03	1.01	77	131.3	.90	34	118.5
13	1.36	D13S263	30.1	.088	.28	36	57.5	.51	26	30.1
14	−.07	D14S65	108.2	.53	.03	13	33.2	.01	4	125.2
15	2.15	D15S128	0	.017	.45	50	0	.84	36	0
16	1.20	D6S3068	41.6	.12	.16	28	41.6	.84	33	41.6
17	.62	D17S938	15.0	.27	.38	45	15.0	.13	14	47.4
18	.91	D18S61	109.8	.181	.20	28	109.8	.08	11	109.8
19	.17	D19S220	49.7	.43	.06	16	49.7	.07	10	46.5
20	.19	D20S117	0	.43	.14	26	0	.15	16	24.8
21	2.04	D21S1914	14.0	.021	1.72	89	14.0	1.19	44	31.2
22	.55	D22S274	49.7	.292	.35	44	49.7	.07	11	49.7

[a] Dominant parametric HLOD scores calculated in Genehunter, version 2.0, assuming disease allele frequency of .005 and penetrances of .65, .65, and .0096 for homozygotes, heterozygotes, and noncarriers, respectively.

[b] Recessive parametric HLOD scores assumed disease allele frequency of .11 and penetrances of .65, .0096, and .0096.

[c] Calculated using Genehunter.

[d] α = estimated proportion of linked families at this location.

olating results for chromosome 1 to the whole-genome level, assuming chromosome 1 represents 0.1 of the genome. For fine mapping, chromosomewide empirical *P* values were calculated as the proportion of replicates showing an equal or more extreme NPL at any point on the chromosome. Although recessive and dominant model parametric analyses were also performed for each chromosome, our inferences were based on NPL results, and we therefore focused on this statistic when estimating *P* values. Furthermore, these additional tests are correlated (on average) with the NPL results and are not likely to increase the overall type I error greatly.

Results

Initial Autosomal Scan Linkage Analyses

NPL plots for model-free analyses, as well as HLOD plots for dominant and recessive parametric models, are shown in figure 1. No initial linkage signal reached "suggestive" or "significant" evidence for linkage according to the criteria of Lander and Kruglyak (1995). Our highest NPL and parametric LOD signals on each chromosome are shown in table 2. The highest signal across the autosomes was observed on chromosome 10, with an NPL = 3.35 and a dominant maximum HLOD = 3.14 (mixing proportion $\alpha = 100\%$). This NPL corresponds to a genomewide *P* value of .035, based on simulations. Genefinder results estimated a susceptibility locus at 110.4 cM (near D10S1686), with a 95% CI around this location of 98.7–122.1 cM.

Other peaks with NPL >2 in this initial scan include chromosomes 1 (NPL = 2.45), 4 (NPL = 2.34), 6 (NPL = 2.37), 7 (NPL = 2.09), 15 (NPL = 2.15), and 21 (NPL = 2.04). The Genehunter locations and parametric results are shown in table 2

Fine Mapping of Chromosome 10q

We chose to focus on our highest signal for immediate follow-up. Twenty-three additional markers were chosen between D10S537 and D10S1693 to attain a spacing of ~1 Mb, and an additional affected aunt was available for analysis at this point. The initial and follow-up linkage plots for this region are shown in figure 2. Evidence of linkage increased to NPL = 4.27, with a chromosomewide *P* value of .00002 at the peak location around D10S1744. The 95% CI for the target region decreased from 23.4 cM to 12.2 Mb (D10S1677–D10S1753 at 97.5–87.7 Mb [UCSC genome browser]). The maximum HLOD under a dominant model also increased to 3.79 ($\alpha = 100\%$).

Discussion

We have performed the first genome scan for SZ susceptibility loci among an Ashkenazi Jewish sample of multiplex pedigrees in hopes of reducing the underlying heterogeneity among SZ linkage samples. Although our strategy restricted recruitment to a relatively small number of families, we have potentially attained a more homogeneous group for detection of linkage. For example, parametric heterogeneity linkage analysis at chromosome 10q implies that 100% of these families show linkage to this locus, thus providing such a strong signal among a small set of families. This chromosome 10 finding was the highest among our results, according to both model-free and parametric analyses. When 23 new markers were added, evidence of linkage to this region of chromosome 10 increased (NPL = 4.27 at D10S1774; *P* = .00002), and a smaller 95% CI was achieved for the gene location. In fact, analysis of the new markers alone replicates evidence of linkage (NPL = 4.35; $P = 5.7 \times 10^{-6}$), even in the absence of the initial scan markers. To determine whether the inclusion of individuals with schizoaffective disorder added genetic heterogeneity to our analyses, we subdivided the families into two groups, those with at least one relative with schizoaffective disorder ($N = 9$) and those without any relatives with schizoaffective disorder ($N = 20$). Both groups of families had excess sharing in this region and had a peak at D10S1774. Beyond this chromosome 10q finding, five additional regions (1p32.2, 4q34.3, 6p21.31, 7p15.2, and 21q21.2) appear promising. We are currently pursuing fine mapping of these regions.

Our linkage signals do not overlap well with the meta-analyses of previous SZ genome scans, consisting mostly of outbred populations (Badner 2002; Lewis et al. 2003). For example, other scans have shown linkage to 10p at ~45 cM from the p-terminus (Faraone et al. 1998; Schwab et al. 1998; Straub et al. 1998; Badner and Gershon 2002). This is at least 50 cM from our signal. However, a few smaller linkage studies have shown some evidence of linkage to SZ and/or bipolar disorder on 10q (Mowry et al. 2000; Cichon et al. 2001; Ewald et al. 2002). These studies show a signal closer to the p-terminus than ours, but the peak areas slightly overlap. Given differences in methods, family numbers, and family structures, these signals could potentially represent the same underlying locus.

Also, our signal on chromosome 1 is on the opposite end of the chromosome from the 1q finding of the SZ meta-analysis. An association between the chromosome 1 hKCa3/KCNN3 gene and SZ has been observed among Ashkenazi Jews (Dror et al. 1999); however, this is located on the opposite arm of the chromosome from our linkage peak. One interesting area is the overlap of

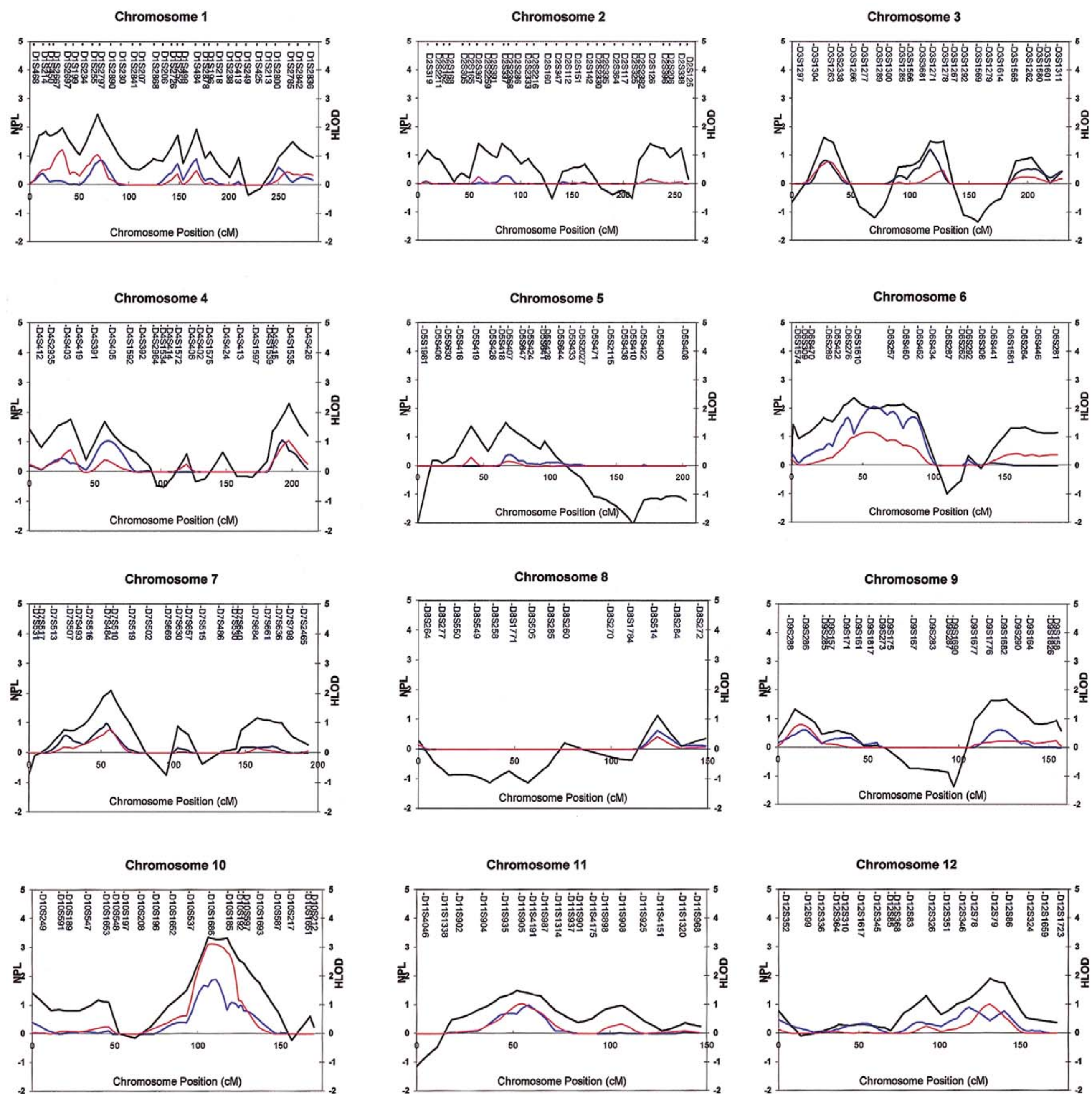
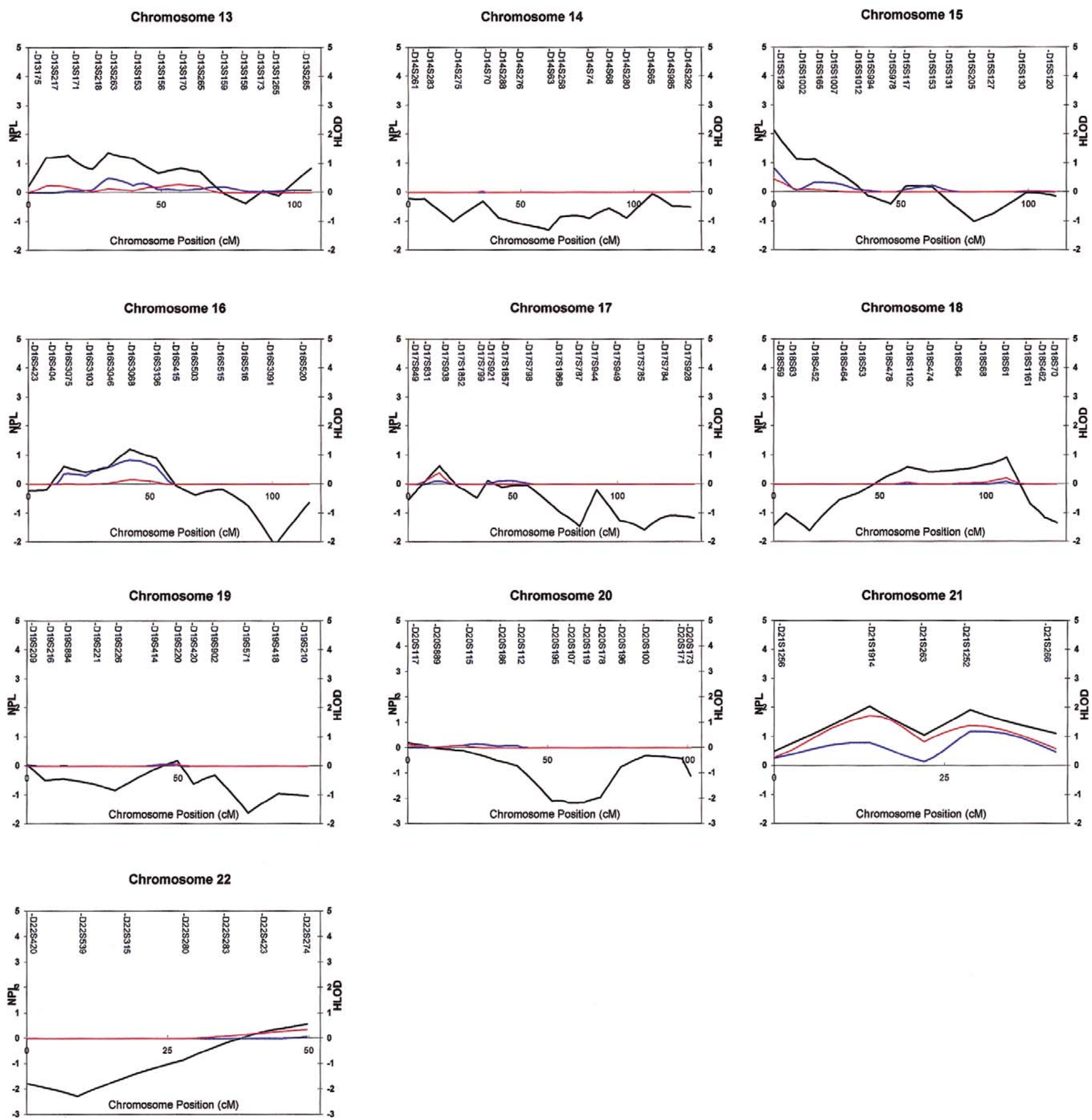


Figure 1 Results of multipoint linkage analysis for the autosomes showing NPL scores (*black*) and HLOD for the dominant (*red*) and recessive (*blue*) parametric models.

our 6p finding with previous linkage to an SZ locus in this region (Straub et al. 1996; Kendler et al. 2000). Several candidate genes have been identified in this region, most notably *dysbindin* (Straub et al. 2002; Schwab et al. 2003). Although our signal does not directly align with the location of this gene, the correspondence is potentially important. Our second peak, on chromosome 21, is ~5–10 Mb from the chromosome 21q11 linkage observed in bipolar families (Curtis 1999), which may support an overlap in susceptibility to both disorders. However, we did not see evidence for linkage to the marker closest to the bipolar region in our families, and the importance of this peak in our data set must be clarified by further follow-up. Interestingly, our Ashkenazi families did not produce a linkage signal on chromosome 22, which contains the COMT gene that



has been associated with SZ among Ashkenazim in Israel (Shifman et al. 2002). Our sample may simply lack the power to detect this gene through linkage analyses, although our chromosome 10 finding implies that linkage can be detected in this small, homogeneous set.

Our strong linkage finding on chromosome 10q is encouraging for a small set of families and may attest to the advantages of studying a relatively homogeneous set of families to first elucidate disease-related genes. The discovery among Ashkenazim does not, however, preclude the importance of genes found in this subgroup among other, more outbred populations. In fact, genetic variation associated with human disease among the Ashkenazim is often found at detectable levels among other populations and shown to have importance for disease susceptibility in general (Schorge et al. 2001).

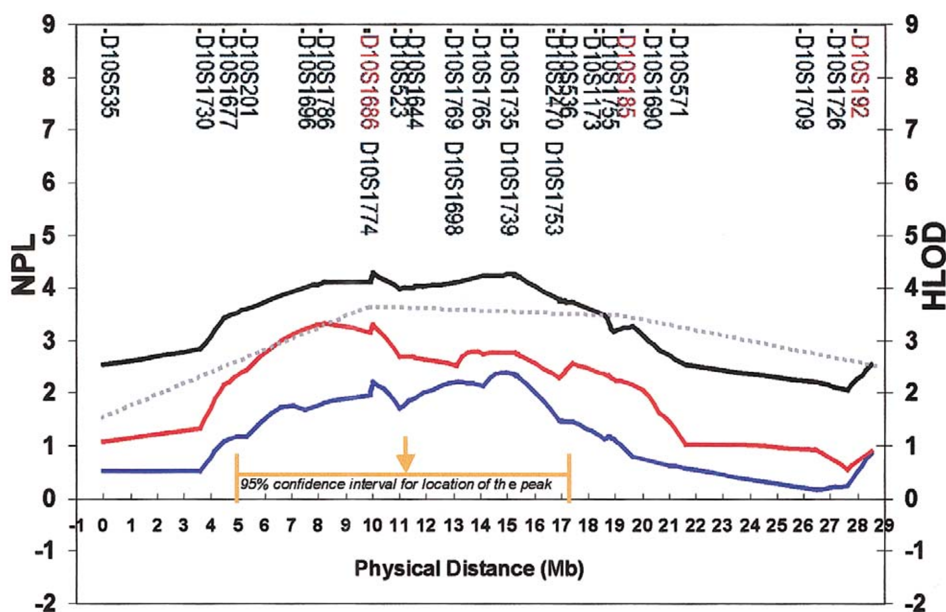


Figure 2 Results of multipoint linkage analysis for the follow-up genotyping in the 10q region, showing NPL (*black*) and HLOD scores for the dominant (*red*) and recessive (*blue*) parametric models. The NPL scores for three markers used in original 10-cM scan (marker names in red) are indicated by the gray dashed line. The map location of polymorphisms was obtained from the November 2002 assembly of the human genome.

Furthermore, identification of any causal variation in SZ, even for rare families, would be highly important for our understanding of the disorder.

In summary, we observe a strong linkage signal for SZ on chromosome 10q. Our evidence for linkage increased upon follow-up and has resulted in a 12-Mb region in which to perform additional linkage and association analyses. Interestingly, several highly plausible candidates lie within this region, including the serotonin 7 receptor, HTR7, and neuregulin 3, which is from the same gene family as the NRG1 recently found to be associated with SZ among Icelandic and Scottish populations (Stefansson et al. 2002, 2003). We are currently pursuing candidate gene studies as well as SNP-based fine mapping of this region.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Australian Genome Research Center, http://www.agrf.org.au

CEPH-Généthon Integrated Map, http://www.cephb.fr/ceph-genethon-map.html

Diagnostic Interview for Genetic Studies, http://zork.wustl.edu/nimh.digs/newpage11.htm

Epidemiology-Genetics Program in Psychiatry, http://www.hopkinsmedicine.org/epigen

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SZ and NRG1)

UCSC Genome Bioinformatics, http://genome.cse.ucsc.edu/

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