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Genomewide Genetic Linkage Analysis Confirms the Presence of Susceptibility Loci for Schizophrenia, on Chromosomes 1q32.2, 5q33.2, and 8p21-22 and Provides Support for Linkage to Schizophrenia, on Chromosomes 11q23.3-24 and 20q12.1-11.23

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We have performed genetic linkage analysis in 13 large multiply affected families, to test the hypothesis that there is extensive heterogeneity of linkage for genetic subtypes of schizophrenia. Our strategy consisted of selecting 13 kindreds containing multiple affected cases in three or more generations, an absence of bipolar affective disorder, and a single progenitor source of schizophrenia with unilineal transmission into the branch of the kindred sampled. DNA samples from these families were genotyped with 365 microsatellite markers spaced at ~10-cM intervals across the whole genome. We observed LOD scores >3.0 at five distinct loci, either in the sample as a whole or within single families, strongly suggesting etiological heterogeneity. Heterogeneity LOD scores >3.0 in the sample as a whole were found at 1q33.2 (LOD score 3.2; $P = .0003$), 5q33.2 (LOD score 3.6; $P = .0001$), 8p22.1-22 (LOD score 3.6; $P = .0001$), and 11q21 (LOD score 3.1; $P = .0004$). LOD scores >3.0 within single pedigrees were found at 4q13-31 (LOD score 3.2; $P = .0003$) and at 11q23.3-24 (LOD score 3.2; $P = .0003$). A LOD score of 2.9 was also found at 20q12.1-11.23 within in a single family. The fact that other studies have also detected LOD scores >3.0 at 1q33.2, 5q33.2, 8p21-22 and 11q21 suggests that these regions do indeed harbor schizophrenia-susceptibility loci. We believe that the weight of evidence for linkage to the chromosome 1q22, 5q33.2, and 8p21-22 loci is now sufficient to justify intensive investigation of these regions by methods based on linkage disequilibrium. Such studies will soon allow the identification of mutations having a direct effect on susceptibility to schizophrenia.

Introduction

Although it is clear that genetic factors have a substantial effect on the risk of development of schizophrenia (Gurling 1996), attempts to use genetic analysis in the determination of a mode of transmission have produced conflicting results (Baron 1986; Risch 1990; Gurling 1996; Pritchard 1996). The high prevalence (.085) of schizophrenia (MIM 181500) in the population makes it certain that heterogeneous factors contribute to the etiology, and, if genetic risk factors differ in their nature and magnitude in different individuals, then such analyses will not produce valid results. It is highly likely that genetic effects within a single family are more homogeneous than are those between families. Recent work supports the view that, unless a polymorphism is very common and has only a minor effect on risk, extended pedigrees have more power for detection of linkage than do smaller structures such as sib pairs (Durner et al. 1999). With these considerations in mind, we chose to study large, densely affected families that appeared to demonstrate only a single source of schizophrenia and that also appeared to demonstrate subsequent unilineal inheritance.

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Previous Linkage Studies of Schizophrenia

Previous linkage studies have been reviewed and summarized in the workshop reports of the 5th International and 6th World Congresses of Psychiatric Genetics (Nurnberger and Gurling 1998; Tsuang 1999). Ten reports of studies in which the whole genome was screened for schizophrenia-susceptibility genes have now been published (Coon et al. 1994; Moises et al. 1995; Straub

et al. 1997*a;* Blouin et al. 1998; Faraone et al. 1998; Levinson et al. 1998; Hovatta et al. 1999; Williams et al. 1999; Paunio et al. 2000). Many other studies have tested for linkage over small genetic distances on many chromosomes, and these are mentioned below in the discussion of our own linkage analyses.

Chromosome 1q

The presence of a susceptibility locus on chromosome 1q (SCZD9 [MIM 604906]) is supported by linkage analysis and by the association of schizophrenia with cytogenetic abnormalities (St. Clair et al. 1990; Kosower et al. 1995; Ekelund et al. 1997; Blackwood 1998; Hovatta et al. 1999; Brzustowicz et al. 2000; Millar et al. 2000). One large Scottish kindred has demonstrated significant linkage between schizophrenia and related disorders and a balanced translocation involving chromosomes 1 and 11, t(1;11)(q42.1;q14.3) (St. Clair et al. 1990; Millar et al. 2000). The Finnish linkage study by Hovatta et al. (1999) supported linkage between a highly (90%) penetrant dominant locus with loci D1S2141 and D1S2891, with two-point admixture LOD scores of 3.73 and 3.82, respectively. This position is slightly telomeric to that implicated by Kosower et al. (1995), who published a combined allelic association, cytogenetic, and family study of heterochromatic C-band variants in the q22.1-23 region of chromosome 1. In one family, they observed cosegregation of a 1qH (C-band) variant and the Duffy blood-group alleles with schizophrenia (Kosower et al. 1995). The region identified by Hovatta et al. (1999) appears to be slightly centromeric to the chromosome 1q42.1 region implicated by Millar et al (2000). The second genome scan of schizophrenia in Finland (Ekelund et al. 1997), using a national sib-pair sample, also provided some evidence of linkage to this region on chromosome 1. However, the strongest support for linkage on 1q22 derives from a schizophrenia-linkage study using large, multiply affected Canadian families (Brzustowicz et al. 2000). The maximum three-point multipoint LOD score was 6.50 ($P = .0002$) on 1q22, between markers D1S1653 and D1S1679, with 75% of families estimated to have schizophrenia linked to this locus.

Chromosome 5p

In our initial genetic linkage analyses, in seven families from Iceland and the United Kingdom, we found positive LOD scores with linkage markers D5S39 and D5S76, which were originally thought to be localized on chromosome 5q11-13 (SCZD1 [MIM 181510]) (Sherrington et al. 1988). Further analyses, with newly created genetic linkage markers and a larger sample of 23 families (Sherrington et al. 1993), showed diminished support for linkage over this region (Kalsi et al. 1999). The original study, as well as replications performed at that time by other research groups, used relatively uninformative low-heterozygosity RFLPs to attempt replication; in addition, these markers were poorly localized. Since then, D5S39 has been placed closer to the centromere, and locus D5S76, which gave us the highest LOD score, has been repositioned, on the short arm of chromosome 5, at 5p14.1-13.1 (Buetow et al. 1994), between The Genome Database locations for D5S419 and D5S395 (Gyapay et al. 1994). A genome scan of schizophrenia by Moises et al. (1995), who studied five Icelandic pedigrees, also screened chromosome 5p and obtained negative results. However, the selection criteria for ascertainment of families were different from our own criteria, and, indeed, the Icelandic study by Moises et al. (1995) included two pedigrees that we had excluded because they were bilineal and because they contained multiple cases of schizophrenia and bipolar affective disorder, in several generations. Silverman et al. (1996) have reported a maximized two-point LOD score of 4.37 between schizophrenia and D5S111 in a single family, with some evidence of linkage to D5S477, D5S651, and D5S674, as well. All of these markers map to chromosome 5p14.1-13.1 and, like D5S76, lie between markers D5S419 and D5S395. One further study of the 5p14.1-13.1 region, by Garver et al. (1998), found nonparametric LOD scores of 2.49 and 2.55 with the markers D5S111 and D5S426, respectively. These loci are closely linked to D5S419. A further study of the 5p14.1-13.1 region in Canadian families with schizophrenia (King et al. 1997) failed to find any evidence for linkage, as have several other genome scans of schizophrenia.

Chromosome 5q

A second region on chromosome 5 has been implicated, in a set of Irish pedigrees (Straub et al. 1997*b*), with heterogeneity LOD scores (HLODs) of 3.04 ($P = .0005$) and 3.35 ($P = .0002$) at D5S393 and D5S804, respectively. A collaborative study of 5q22-31 (Levinson 1999) found that four of eight independent samples gave LOD scores >1.00. Some further degree of support for the involvement of this locus was obtained in a study of a sample of German families, which produced a LOD score of 1.8 at 5q22-31, with marker D5S399 (Schwab et al. 1997). Subsequently, a study of a single large kindred from Palau, Micronesia, gave a LOD score of 3.4 for markers in the 5q22-31 region (Byerley et al. 1999). Finally, a linkage study of Finnish families has also found schizophrenia linkage, with a LOD score >3.00 at 5q22-31 (Paunio et al. 2000).

Chromosome 8p

The 8p22-21 region on chromosome 8 was originally identified as showing possible genetic linkage to schizo-

phrenia (SCZD6 [MIM 603013]), as part of a genome-wide search, with a maximum admixture LOD score, at D8S136, of 2.35, under a dominant model and 2.20 under a recessive model (Pulver et al. 1995). This result was followed up, within the same family sample (Blouin et al. 1998), with new markers, giving a LOD score of 3.64 ($P = .0001$). Another study (Kendler et al. 1996) obtained HLODs of 2.00 with D8S1731, 2.52 with D8S1715, and 2.08 with D8S133. Elsewhere, we have published the results obtained, through use of three markers from this region, from 23 Icelandic and British families (Kalsi et al 1996). Using the MFLINK linkage-analysis program (Curtis and Sham 1995), we found a maximized LOD score of 2.17 with marker D8S136. Further analyses, using multipoint LOD scores and additional markers, also supported linkage. The present report describes the results from a subset of the 13 largest families drawn from this sample of 23 pedigrees. In response to the initial findings on chromosome 8, 14 research groups genotyped 14 microsatellite markers in a collaborative sample of 403–567 pedigrees (Levinson et al. 1996), which included both the pedigrees originally showing evidence of linkage as well as newly typed pedigrees. These yielded HLODs of 2.22 ($P = .0014$) for the new sample and of 3.06 ($P = .00018$) for the combined sample. Recently, study of a Canadian sample has provided further support for linkage to this region, with a LOD score of 3.49 (Brzustowicz et al. 1999). Other studies of 8p21-22 have either offered less-significant statistical support or have been negative (Hovatta et al. 1999; Williams et al. 1999).

Chromosome 11q

As described above, a balanced t(1;11)(q42.1;q14.3) translocation was found to cosegregate with schizophrenia and other psychiatric disorders in a single large Scottish pedigree (St. Clair et al. 1990; Blackwood et al. 1998; Millar et al. 2000). Analysis of linkage between both the chromosome 1q and 11q translocations and the disease locus produced LOD scores that varied between 3.1 and 6.0, according to the disease model applied. Marker D11S931 was found to lie very close to the chromosome 11 translocation breakpoint that cosegregates with both schizophrenia and other, nonpsychotic, psychiatric disorders (Devon et al. 1997; Devon and Porteous 1997). A number of linkage studies of this region have been negative (Gill et al. 1993; Wang et al. 1993; Mulcrone et al. 1995). However a linkage study of a Japanese population (Nanko et al. 1992) discovered LOD scores of 1.00–1.50 with marker D11S35, and, in a separate study, one of four Canadian pedigrees produced a LOD score of 3.41 with D11S35 (SCZD2 [MIM 603342]) (Maziade et al. 1995). Other linkage studies have failed to detect any evidence of linkage on chromosome 11 (Kalsi et al. 1995*c;* Moises et al. 1995; Straub et al. 1997*a;* Faraone et al. 1998; Kaufmann et al. 1998).

Subjects and Methods

Thirteen pedigrees containing individuals with schizophrenia were investigated. These kindreds constituted the most densely affected and largest of the 23 pedigrees used in our previous linkage studies. They consisted of five British and eight Icelandic families, as described elsewhere (Kalsi et al. 1995*b,* 1996; Chen et al. 1997). They were contributed to a large multicenter collaboration organized by the European Science Foundation (ESF), which arranged for the genotyping to be performed. Diagnoses were assigned through use of Research Diagnostic Criteria (RDC) (Spitzer et al. 1978). Subjects were interviewed through use of the Lifetime Version of the Schizophrenia and Affective Disorders Schedule SADS-L (Spitzer and Endicott 1977). This information was supplemented by material from case notes. Subjects were also rated for schizoid personality and schizotypal disorder, through use of Diagnostic and Statistical Manual of Mental Disorders (3d edition, revised) (DSM-IIIR) criteria. Two psychiatrists who were blind to the genotyping assigned consensus diagnoses. Extensive tracing of pedigrees was done, and attempts were made to characterize the diagnoses of other members of the kindreds as accurately as possible. In total, 1,850 individuals were entered into a database, with affection status derived from case records, direct interviews, and diagnostic information. For those individuals who were not interviewed, medical records were used to assign RDC diagnoses. In some cases no medical records were available, but we had been informed by relatives that a person had symptoms of schizophrenia or bipolar affective disorder. In these cases, a "best-guess" diagnosis according to the RDC was entered into the database. In the case of subjects who had been born and had died during the 19th century or who were estranged from their families, we were reliant on family information and record books; in many cases, no accurate information was available. In these cases, subjects were recorded as being of either unaffected or unknown affection status. Unless the DSM-IIIR criteria for a possible schizotypal disorder could be established on the basis of reliable information, we did not record any individual as being affected. Pedigrees were selected on the basis of appearing to demonstrate a single source of schizophrenia or DSM-IIIR schizotypal illness, with unilineal transmission and no cases of bipolar affective disorder. A pedigree was considered unilineal not just on the basis of the interview diagnoses with the SADS-L but also on the basis of all the information available to us from past records and from relatives from the 1,850 individuals in the data-

base. No families were excluded solely on the basis of bilineal inheritance of schizotypal disorder, because in all such families bilineality was also indicated by cases of schizophrenia. Two affection classes were used for the linkage analysis: "core schizophrenia" consists of schizophrenia, unspecified functional psychosis, and schizoaffective psychosis; "schizophrenia spectrum" consists, in addition, of schizoid and schizotypal personality disorder, according to DSM-IIIR criteria. Of the 182 interviewed individuals in these 13 pedigrees, 56 were assigned to the core schizophrenia category and an additional 12 were assigned to the spectrum category. Fifty nanograms of total genomic DNA extracted from venous blood samples was amplified by PCR with oligonucleotide primers, according to the protocols of the Généthon linkage-mapping set (Gyapay et al. 1994). The markers used were those identified by Généthon and were mapped to chromosomes in the CEPH families by least-recombination methods, as described by Gyapay et al (1994). Polyacrylamide gels were used to separate amplified dinucleotide-repeat fragments, with either radioactive or fluorescent labeling. Genotypes were read blind to diagnostic information. Tests for Mendelian inheritance of marker data were performed, and inconsistent genotypes were repeated or omitted.

Linkage analysis was performed by standard LOD-score methods and using "model-free" likelihood-based analysis. For LOD-score analyses, the VITESSE program was used (O'Connell and Weeks 1995), except in the case of markers on the X chromosome, for which the FASTLINK program was used (Cottingham et al. 1993; Schaffer 1996). Separate analyses were performed for the core and spectrum models, with penetrances of .4 and .6 and phenocopy risks of .005 and .01, respectively. Combined analyses were also performed using liability classes, in which subjects falling into the different diagnostic categories were allocated the appropriate individual penetrance probabilities. For each of the core, spectrum, and combined affection models, analyses were performed under the assumption of either dominant or recessive transmission, with the disease-allele frequency set to .008 or .13, respectively. Thus, each set of LOD-score analyses implemented six different transmission models. For the initial screening analyses, a set of two-point analyses was performed with each marker, and a set of three-point analyses was performed with each pair of adjacent markers. Overall LOD scores were calculated under the assumption of admixture, to produce an HLOD.

The "model-free" analyses were performed by the MFLINK program (Curtis and Sham 1995 Curtis et al. 1999) and the accompanying MFMAP utility. With the disease locus at a given map position, MFLINK calculates the likelihood of the data, using a range of different dominant and recessive transmission models, all yielding the same disease prevalence and parameterized with a single variable, the heterozygote penetrance (f_1, which is varied from 0 to 1). The MLOD is the maximum LOD score obtained for any of these transmission models (maximized over f_1). The MALOD is the maximum admixture LOD obtained for any model (maximized over f_1 and the proportion of families linked [α]). The MFLOD is the difference between the log likelihood maximized over both f_1 and α and the log likelihood maximized over f_1 but with α constrained to 0. MFLINK analyses were performed with both the core and spectrum affection models, with the population prevalence being set to .011 and .019 respectively, to match the prevalences used for the LOD-score analyses. Two-point analyses were performed with each marker, with the tested position at a recombination fraction of .05 with the marker, and three-point analyses were performed with each pair of adjacent markers, testing a position midway between them.

An initial screen of all the markers and pairs of markers was performed by the above methods. Each marker and each pair of markers yielded six admixture LOD scores and six LOD scores from the MFLINK analyses (MLOD, MALOD, and MFLOD, for the core and spectrum models). Each type of LOD score was converted to a likelihood-ratio statistic by multiplication by $2ln(10) = 4.6$. The statistic derived from the conventional admixture LOD score was taken to be distributed as a 50:50 mixture of χ^2_2 and χ^2_0. As originally described (Curtis and Sham 1995), the likelihood-ratio statistic from the MFLOD was taken to be distributed as a 50:50 mixture of χ^2_1 and χ^2_0. Subsequently (Curtis et al. 1999), it has been shown that $2ln(10) \times$ MLOD can be taken to be distributed as χ^2_1 and that $2ln(10) \times$ MALOD can conservatively be taken to be distributed as a 50:50 mixture of χ^2_2 and χ^2_0. Using these distributions allows P values to be derived so that the different types of LOD score can be compared more easily. All regions that yielded a result significant at $P < .01$ by any of the methods of analysis were selected for further study.

Additional analyses from regions highlighted by the screening analyses consisted of computation of overlapping five-point linkage scores, with sets of four adjacent markers at a time. Regardless of which method of analysis had produced the significant results, the five-point analyses were performed for each of the six possible combinations of disease definition (core, spectrum, or combined) and mode of transmission (dominant or recessive).

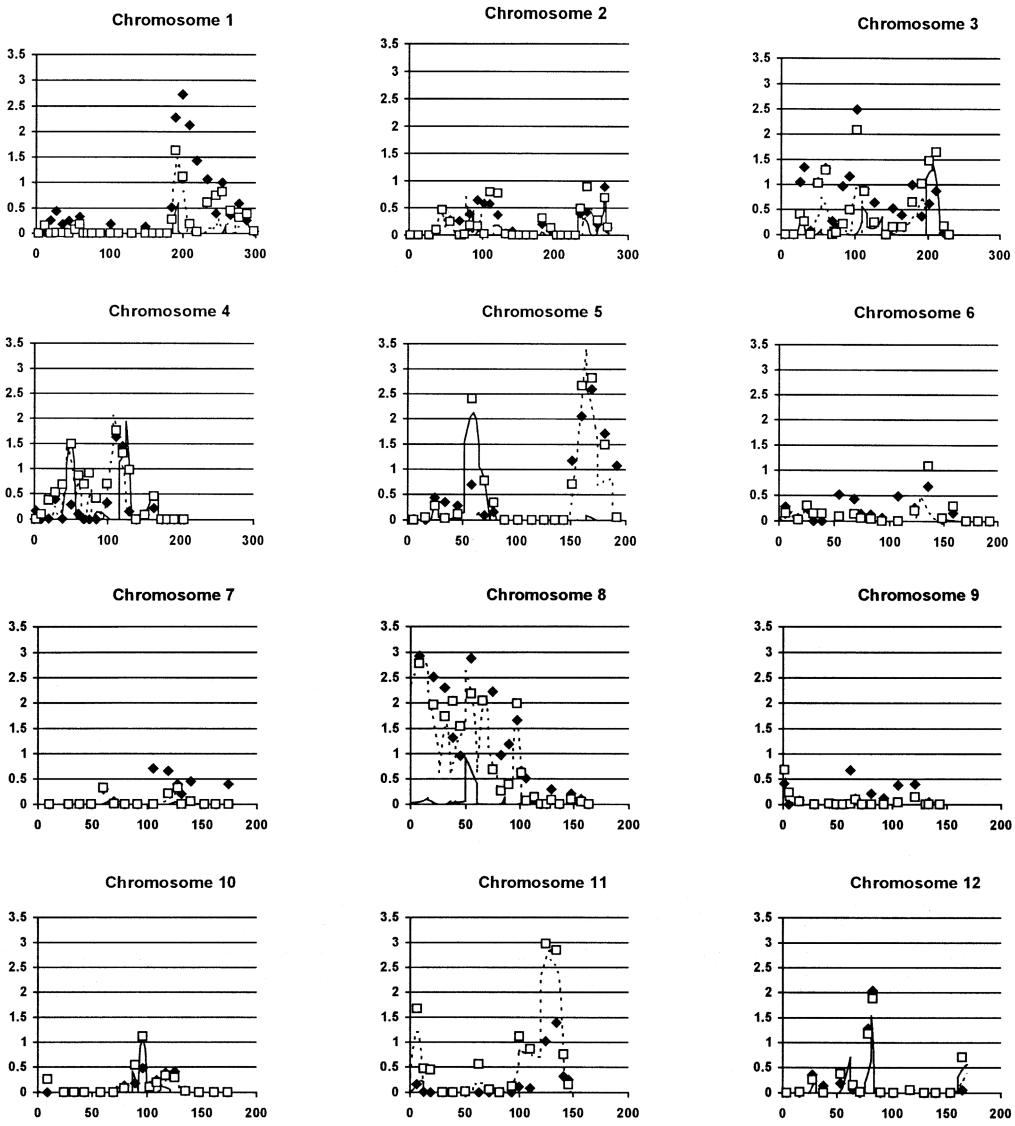
Results

When all of the two-point and three-point HLODs and MFLINK LOD scores were scrutinized, 16 regions con-

Table 1

Results Significant at $P < .01$, from Initial Screen of Two-Point and Three-Point Conventional and Model-Free Linkage Analyses

Marker at or near Peak LOD Score	Map Position (cM)	Cytogenetic Location	Most Significant Result Obtained	Nominal *P*	Comments on LOD Scores
D1S196	186.4	1q22.1-23	Core, recessive, three-point HLOD = 2.9	.0006	Nearby markers also positive
D2S125	267.0	2q23.3-24.2	Spectrum, two-point MLOD = 1.8	.004	Dominant HLODs positive
D3S1263	29.0	3p24.2-22	Spectrum, two-point MALOD = 1.8	.008	
D3S1276	109.0	3p14.2-14.1	Core, three-point MLOD = 2.5	.0007	Dominant and recessive HLODs positive
D3S1262	107.2	3q27	Spectrum, three-point MFLOD = 1.3	.007	Dominant HLODs positive
D4S418	43.9	4q13-31	Spectrum, three-point MFLOD = 1.5	.004	Dominant and recessive HLODs positive
D4S430	125.1	4q13-31	Spectrum, two-point MFLOD = 2.4	.0004	Dominant and recessive HLODs positive, nearby markers positive
D5S407	65.0	5p14.1-13.1	Spectrum, dominant, two-point HLOD = 2.5	.002	
D5S422	163.9	5q32-33	Spectrum, dominant, three-point HLOD = 3.6	.0001	Nearby markers positive
D7S691	64.6	7p13	Core MLOD = 1.4	.01	
D8S503	16.2	8p22	Core, recessive, two-point HLOD = 3.6	.0001	8p markers positive over wide region
D8S503, D8S504	16.2	8p22	Core, three-point HLOD = 3.5	.0001	Recessive HLODs strongly positive, dominant ones less so
D11S922	3.9	11p11.5	Spectrum, three-point MLOD = 1.6	.007	Recessive HLODs positive
D11S934	132.9	11q23.3-24	Spectrum, recessive, two-point HLOD = 3.1	.0004	Nearby markers positive
D12S43	81.5	12q12-24.1	Core, three-point MALOD = 2.0	.005	Dominant HLODs positive
D19S220	61.4	19q13.1	Spectrum, two-point MLOD = 1.5	.009	
D20S112	39.3	20q12.1-11.23	Spectrum, recessive, three-point HLOD = 2.4	.002	Nearby markers positive
D21S1256	8.7	21q11.1-21.1	Spectrum, two-point MALOD = 1.9	.006	Dominant and recessive HLODs positive



taining the following markers produced at least one statistic that was nominally significant at $P < .01$: D1S194-D1S196-D1S2815, D2S125, D3S1263, D3S1261-D3S1276, D4S411-D4S406-D4S430, D5S426-D5S407-D5S2306, D5S410-D5S422-D5S400, D8S504-D8S503-D8S552-D8S261-D8S258-D8S1771-D8S283-D8S285, D8S286-D8S273, D11S922, D11S925-D11S934-D11S4150, D12S85, D12S43-D12S92, D19S220, D20S186-D20S112, and D21S1911-D21S1256. Those markers with the most-positive results in these regions are detailed in table 1. In several of these regions, more than one marker and/or method of analysis yielded positive LOD scores. Figure 1 shows the three-point MALOD scores for the core and spectrum affection models, as well as the three-point HLODs for the combined affection model, under assumptions of dominant and recessive transmission. The full set of results is available from D.C.'s Web site ("Results of genome scan for schizophrenia"). The regions highlighted by the two-point and three-point screening analyses were investigated more intensively by overlapping five-point analyses, and the results are presented in table 2. For some of the regions, evidence for linkage is maintained or enhanced, whereas for others the five-point LOD-score analyses do not support linkage. Admixture LOD scores $\gtrsim 3.0$ were found for the regions D1S194-D1S196-D1S2815-D1S191-D1S412, D5S410-D5S422-D5S400-D5S2111, D8S504-D8S503-D8S552-D8S261-D8S1771, and D11S898-D11S35-D11S925-D11S934-D11S4150. Only one Icelandic pedigree, family 4, individually produces a LOD

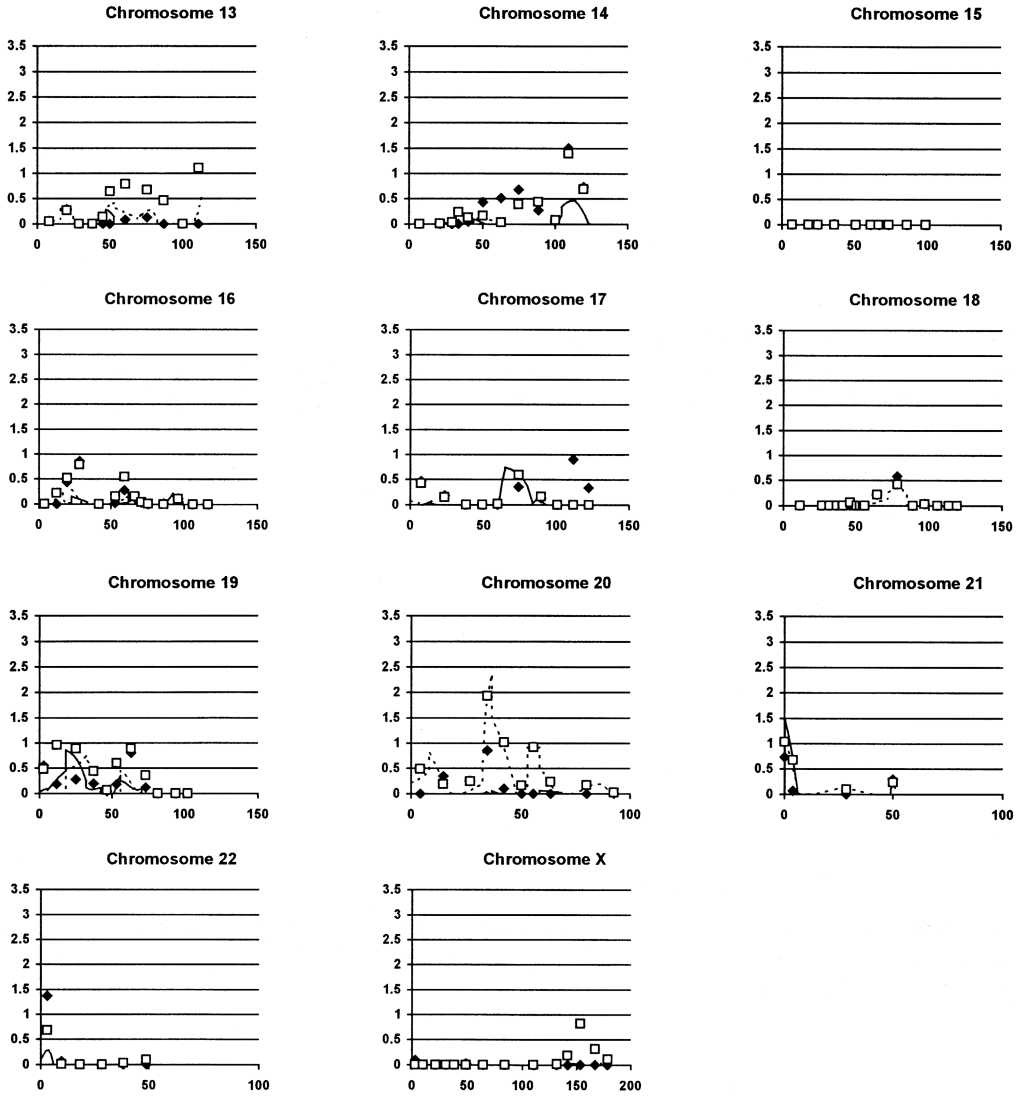


Figure 1 Graphs of three-point LOD scores for schizophrenia against map position (cM), for MALODs with different definitions of affection and for HLODs, under assumptions of dominant and recessive transmission. Blackened diamonds (♦) = MALOD, core affection model; unblackened squares (□) = MALOD, combined (core and spectrum) affection model; solid line (——) = HLOD, combined (core and spectrum) affection model, dominant transmission; dashed line (- - - -) = HLOD, combined (core and spectrum) affection model, recessive transmission.

score ≥3.0, and it does so for three different regions near D4S411-D4S406-D4S430-D4S422, D11S934, and D20S112. The five-point LOD scores in individual pedigrees were examined carefully. Results of this procedure are noted in table 2. By and large, specific families tended to show positive LOD scores for certain loci while showing negative LOD scores in other regions; the exception was family 4, which simultaneously produced LOD scores >3.0 at D4S430, D11S934, and D20S112. These data have not been published before and are part of a wider unpublished collaborative linkage study of schizophrenia, organized by the ESF.

Discussion

The optimal method for analysis of linkage data for a disease with complex inheritance remains uncertain. We have chosen to apply a range of LOD-score analyses that use different disease definitions and either recessive or dominant transmission, along with model-free likelihood-based analyses, all applied, in the first instance, to both two-point and three-point data, which resulted in a substantial number of partially independent results. We did not apply nonparametric sib-pair linkage analysis or the methods implemented in GENEHUNTER

Table 2

Results of Five-Point LOD-Score Analysis of Regions Highlighted by Initial Screening Analyses

Marker at or near Peak LOD Score	Map Position (cM)	Cytogenetic Location	Peak HLOD	Model Used	Nominal P[a]	Comments on LOD Scores
D1S196	186.4	1q33.2	3.2	Core, recessive	.0003	Homogeneity LOD score 2.8; LOD score > 1 in pedigrees 1, 2 and 3
D2S125	267.0	2q23.3-24.2	1.8	Spectrum, recessive	.008	LOD score 1.2 in pedigree 4
D3S1277	56.1	3p24.2-22	.8	Combined, recessive	.07	LOD score > 1 in pedigrees 3 and 5
D3S1285	91.0	3p14.2-14.1	1.0	Core, recessive	.05	LOD score > .7 in pedigrees 3, 4, 11; LOD score 1.2 in pedigree 2, using dominant models
D3S1262	107.2	3q27	1.5	Combined, dominant	.02	LOD score 2.2 in pedigree 6
D4S418	43.9	4q13-31	1.8	Combined, recessive	.007	LOD score > .7 in pedigrees 1, 2, 7, 8, 9
D4S411	107.4	4q13-31	2.1	Core, recessive	.004	LOD score > .7 in pedigree 3, 4, 6, 10
D4S430	125.1	4q13-31	2.0	Combined, dominant	.005	LOD score 3.2 in pedigree 4
D5S426	51.6	5p14.1-13.1	2.2	Combined, dominant	.003	LOD score 2.3 in pedigree 6; LOD score 1.2 in pedigree 3
D5S422	163.9	5q32-33	2.8	Spectrum, dominant	.0008	LOD score 2.5 in pedigree 6; LOD score 1.5 in pedigree 3
D7S691	64.6	7p13	.3	Core, dominant	NS	No support for linkage from five-point analyses
D8S503	16.2	8p21-22	2.8	Core, recessive	.0008	Homogeneity LOD score 2.7; LOD score 1.1 in pedigree 10; otherwise, several small LOD scores
D8S1771	50.3	8p21-22	3.2	Core, recessive	.0005	Homogeneity LOD score is also 3.0; LOD score 1.7 in pedigree 6; LOD score .97 in pedigree 10; otherwise, several small LOD scores; positive LOD scores over large region of 8p
D11S922	3.9	11p11.5	.5	Core, recessive	NS	No support for linkage from five-point analyses
D11S934	132.9	11q23.3-24	2.9	Combined, recessive	.0006	LOD score 3.2 in pedigree 4; LOD score 1.0 in pedigree 5
D12S43	81.5	12q12-24.1	0		NS	No support for linkage from five-point analyses
D19S220	61.4	19q13.1	.4	Spectrum, dominant	NS	No support for linkage from five-point analyses
D20S112	39.3	20q12.1-11.23	2.4	Spectrum, recessive	.002	LOD score 2.9 in pedigree 4; 1.2 in pedigree 7
D21S1256	8.7	21q11.1-21.1	1.7	Spectrum, dominant	.01	LOD score 2.4 in pedigree 1

NOTE.—The highest admixture LOD score obtained from any of the six models tested (for each of the possible combinations of disease definition [core or combined {core and spectrum}] and mode of transmission [dominant or recessive]) is shown, together with information regarding the model that produces this score and the pedigree(s) that appears to make the main contribution to it.

[a] NS = not significant.

(Kruglyak et al. 1996), because such analyses can lose much of the genetic information provided by large multiply affected pedigrees. Each method of analysis that we have used generates a statistic, which can be compared with a standard distribution, to obtain a corresponding *P* value. To obtain an overall significance for each result, one would need to be able to correct for the following facts: (*a*) several prior linkage studies of these loci have been performed, (*b*) our own data consist of several partially independent analyses performed at each map position, and (*c*) multiple partially independent markers are tested. Although, theoretically, one can obtain a genomewide significance if only one method of analysis is applied at each position (Lander and Kruglyak 1995), such a correction is impractical when multiple methods or two-point, rather than multipoint, analyses are performed (Curtis et al. 1995). We therefore provide the LOD scores with their corresponding uncorrected nominal *P* values. It should be noted that the MFLINK analyses do not maximize the likelihood over the recombination fraction but use a single genetic distance; thus, no extra degree of freedom is introduced in this approach, compared with traditional LOD-score analyses, at a fixed set of penetrances. Since similar considerations apply to most, if not all, previous linkage studies of schizophrenia, the uncorrected *P* values we provide at least allow some comparison with other studies.

As described in the abstract, several positive regions were identified by the initial two-point and three-point analyses; however, we regard the five-point analyses as providing the most robust evidence for linkage. When two-point linkage analyses are performed, there may be large differences between the results obtained from adjacent markers, owing to random variation in the subset of meioses for which each marker is informative. By contrast, multipoint analysis can provide almost complete information regarding the inheritance of each chromosomal segment and should be far less sensitive to this random noise. A disadvantage of multipoint analysis may be that model misspecifications are more likely to produce incorrect results—especially, spurious exclusions (Morton 1988; Risch and Giuffra 1992). However, such concerns may be exaggerated (Greenberg et al. 1998), and our own results certainly include a number of strongly positive LOD scores. We have also examined the LOD scores of individual pedigrees in the context of the genome scan, and doing so has illuminated the complex implications of some of our results. Amongst the regions highlighted by positive LOD scores in our initial analyses, two five-point analyses produce overall admixture LOD scores >3.0 and two others produce LOD scores >3.0 in a single pedigree. A number of other regions apparently implicated in the initial two-point scan produce, in five-point analyses, either negligible support for linkage or intermediate results.

The most-promising results obtained are for the 1q32.2, 8p21-22, 11q21, and 5q33.2 regions. The 8p21-22 markers yield a maximum two-point LOD score of 3.6, a three-point LOD score of 3.52, and a five-point LOD score of 3.2, with other markedly positive LOD scores extending over a wide region. We believe that, if these results are considered together with the three other prior independent LOD scores >3.0 for 8p21-22 that have been reported by other research groups, there is now very good evidence for a schizophrenia-susceptibility locus in this region. Although our method for selection of pedigrees might have been expected to enrich the sample for dominant genes, the evidence for linkage, in fact, arises mostly through use of a recessive model. In addition, we find no statistically significant evidence for admixture. However, these ambiguities may be artifacts due to lack of informativeness of certain markers in certain subjects and kindreds. The peaks at D8S503 and D8S1771, which are 30 cM apart, are not clearly distinct from one another and the LOD score between them is not much lower than those at the peaks. We therefore cannot draw from these data any definite conclusions about the precise localization of susceptibility mutations.

The highest overall five-point admixture LOD score (3.2) is obtained in the region around D1S196, again by a recessive model. Under the assumption of homogeneity, the LOD score is 2.8. As described above, independent samples have also provided strong support for linkage to this region, with LOD scores of 3.82 and 6.50 (Hovatta et al. 1999; Brzustowicz et al. 2000). We therefore conclude that, overall, there is also very good evidence for the presence, within this region, of a schizophrenia-susceptibility locus.

Two five-point LOD scores of 3.2 are produced within a single family, near the loci D4S430 and D11S934; the first occurs with a dominant model, the second with a recessive one. It is possible that a 4q31 dominant gene and an 11q recessive gene exert a combined effect to produce disease in this family or that one of the LOD scores is a false positive. Support for linkage at the same 4q31 region has been described in a Finnish study (Hovatta et al. 1999), with a LOD score of 2.74 with marker D4S1586. The overall maximum admixture LOD score at D11S934 is 3.2, and, as has been described above, other researchers have obtained, from other samples, independent support for linkage to this region. The cytogenetic abnormality cosegregating with schizophrenia in a Scottish family (St. Clair et al. 1990) might be interpreted as being a linkage marker for schizophrenia, rather than being a direct etiological factor causing disruption of a susceptibility gene. If this were the case, then our positive results with 11q markers

would confirm this linkage and that reported by Maziade et al. (1995). Interestingly, the same pedigree that produces LOD scores of 3.2 in these two regions also produces a five-point LOD score of 2.9 near D20S112. Once again, this may represent an interactive effect or a situation in which one or more results have occurred by chance.

The other results of note are the admixture LOD scores obtained using dominant-transmission models with markers at 5p14.1-13.1 (two-point LOD score 2.5, three-point LOD score 2.5, and five-point LOD score 2.2) and at 5q32-33 (three-point LOD score 3.6 and five-point LOD score 2.8). The results for the 5p14.1-13.1 markers reflect the schizophrenia linkage that we reported with D5S76 (Sherrington et al. 1988), which is now mapped to this region. This finding supports both that by Silverman et al. (1996), who reported a LOD score of 4.4, and that by Garver et al. (1998), who reported a LOD score of 2.5, both in the same region. On the long arm of chromosome 5, positive LOD scores obtained with 5q32-33 markers replicate the findings by Straub et al. (1997*b*), Byerley et al. (1999), and Paunio et al. (2000), who have all reported LOD scores >3 with markers in this region. Our pedigrees failed to show any suggestion of linkage to a number of regions implicated by other researchers on chromosome 6p22-24 (SCZD3 [MIM 600511]) (Antonarakis et al. 1995; Gurling et al. 1995; Moises et al. 1995; Schwab et al. 1995; Straub et al. 1995; Wang et al. 1996; Brzustowicz et al. 1997; Maziade et al. 1997; Turecki et al. 1997; Levinson et al. 2000), chromosome 6q21-q22.3 (SCZD5 [MIM 603175]) (Cao et al. 1997; Kaufmann et al. 1998), chromosome 7 (Ekelund et al. 1999), chromosome 10 (Faraone et al. 1998; Levinson et al. 1998; Schwab et al. 1998; Straub et al. 1998), chromosome 13 (Lin et al. 1995, 1997; Straub et al. 1997*a;* Blouin et al. 1998; Shaw et al. 1998; Brzustowicz et al. 1999), and chromosome 22 (SCZD4 [MIM 600850]) (Kalsi et al. 1995*a*). These loci are unlikely to have had a major effect on a substantial proportion of the pedigrees considered in the present study. It is possible that the strict selection criteria that we adopted, in which families were rejected if they contained cases of both schizophrenia and bipolar affective disorder, may have biased our positive findings away from detection of linkage on chromosomes 6p and 13q. On the other hand, those families that we rejected because they contained cases of both schizophrenia and bipolar affective disorder clearly had bilineal descent for each type of disorder within a kindred. Such an observation is inconsistent with the idea that these two disorders share any common genetic etiology.

It has become clear that, for a disease with complex inheritance such as schizophrenia, linkage analysis can produce limited inferences as to the nature and localization of any genes that might be exerting an effect on susceptibility. More-definitive results will require a consideration of linkage-study results combined from different data sets, as well as a consideration of evidence for linkage disequilibrium. For now, we conclude that there is strong support, from multiple studies, for schizophrenia-susceptibility loci on 1q33.2, 8p21-22, and 5q32-33. More specifically, we believe that these loci are very unlikely to have been falsely implicated, as a result of multiple testing, in previous and present linkage studies. Further less-well-confirmed linkage evidence also exists for susceptibility loci on 4q13-31, 5p14.1-13.1, 6p24-22, 10p12-13, 11q23.3-24, 20q12.1-11.23, and 22q21. We expect that other, less common susceptibility genes exist and that further linkage analyses will eventually confirm their presence.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

MFLINK Documentation, http://www.hgmp.mrc.ac.uk/Registered/Help/mflink/ (for MFLINK documentation and software-downloading information)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SCZD [MIM 181500], SCZD1 C5p [MIM 181510], SCZD2 C11q24 [MIM 603342], SCZD3 C6p22-24 [MIM 600511], SCZD4 22q12-Q13.1.2 [MIM 600850], SCZD5 C6q21 [MIM 603175], SCZD6 C8p21-22 [MIM 603013], and SCZD9 C1q21-22 [MIM 604906])

Results of genome scan for schizophrenia, http://www.mds.qmw.ac.uk/statgen/dcurtis/szscan.html (Tables of all two-point admixture LOD scores, three-point admixture LOD scores, HLOD scores under dominant and recessive transmission, and MFLINK LOD scores (MLOD, MALOD, MFLOD) for schizophrenia under the core and spectrum models)

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