Article

A Genome-Wide Scan for Linkage to Chromosomal Regions in 382 Sibling Pairs With Schizophrenia or Schizoaffective Disorder

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Objective: Some genome-wide scans and association studies for schizophrenia susceptibility genes have yielded significant positive findings, but there is disagreement between studies on their locations, and no mutation has yet been found in any gene. Since schizophrenia is a complex disorder, a study with sufficient power to detect a locus with a small or moderate gene effect is necessary.

Method: In a genome-wide scan of 382 sibling pairs with a diagnosis of schizophrenia or schizoaffective disorder, 396 highly polymorphic markers spaced approximately 10 centimorgans apart throughout the genome were genotyped in all individuals. Multipoint nonparametric linkage analysis was performed to evaluate regions of the genome demonstrating increased allele sharing, as measured by a lod score.

Results: Two regions with multipoint maximum lod scores suggesting linkage were found. The highest lod scores occurred on chromosome 10p15-p13 (peak lod score of 3.60 at marker D10S189) and the centromeric region of chromosome 2 (peak lod score of 2.99 at marker D2S139). In addition, a maximum lod score of 2.00 was observed with marker D22S283 on chromosome 22q12, which showed evidence of an imprinting effect, whereby an excess sharing of maternal, but not paternal, alleles was present. No evidence of linkage was obtained at several locations identified in previous studies, including chromosomes 1q, 4p, 5p-q, 6p, 8p, 13q, 15p, and 18p.

Conclusions: The findings of this large genome-wide scan emphasize the weakness and fragility of linkage reports on schizophrenia. No linkage appears to be consistently replicable across large studies. Thus, it has to be questioned whether the genetic contribution to this disorder is detectable by these strategies and the possibility raised that it may be epigenetic, i.e., related to gene expression rather than sequence variation. Nevertheless, the positive findings on chromosome 2, 10, and 22 should be pursued further.

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Schizophrenia affects approximately 1% of the general population if considered as a spectrum of genetically related clinical diagnoses (1). Despite numerous biological studies, no underlying inherited mechanism has been found. As polymorphic DNA markers and the laboratory techniques for high throughput linkage analyses have become available over the last 20 years, application of this strategy to finding genes for schizophrenia has been rigorously pursued by several research laboratories. However, numerous reports suggestive of linkage to specific chromosomal regions have contributed to widespread uncertainty concerning the significance of these diverse findings (2–13). Most recently, there have been reports of significant linkages on chromosomes 13q and 1q (5–7, 13–15). Despite all these efforts, at present there have been no convincing reports of any mutation in a schizophrenia susceptibility gene that demonstrate a high degree of statistical significance and/or an alteration in function.

We previously reported a genome-wide scan performed with 70 families having at least two affected siblings, at least one of whom had a diagnosis of schizophrenia (16). No genome-wide significance was observed, but lod scores above 2.0 or a p value of <0.01 were seen for chromosomes 1q22-q23, 2p14-p13, 4pter-cen, 5p15, 10q22-q24, 11pter-p11, 12p13-q24, 13q12-q13, 16q22.1, and 22q11. The present study was an expansion of the previous genome screen with the number of families increased to 309. We previously published negative results for this cohort on chromosomes 8, 13, and X, in response to earlier reports of linkage on these chromosomes (17, 18). The present manuscript summarizes the entire genome-wide scan and reports one significant and one suggestive region of genome-wide significance, according to the criteria for linkage of Lander and Kruglyak (19), but fails to confirm a number of previous reports of linkage. The present findings suggest that a critical reevaluation of the linkage approach is warranted.

TABLE 1. Size of Sibships in Pedigrees With at Least Two Siblings With DSM-III-R Schizophrenia or Schizoaffective Disorder Contributing to a Genome-Wide Linkage Analysis[a]

Sibship Size	Number of Pedigrees	Number of Nonindependent Affected Sibling Pairs
2	262	262
3	27	81
4	4	24
5	0	0
6	1	15
Total	294	382

[a] Families were identified between 1985 and 2001 at research sites in Stony Brook, N.Y.; Oxford, U.K.; Milan, Italy; Santiago, Chile; and Leuven, Belgium.

Method

Subjects and Clinical Procedures

Families with schizophrenia or schizoaffective disorder in at least two siblings (N=309) were identified over a period beginning in 1985 to the present. These originated from five separate geographic collection centers: 213 families from the United States (based at Stony Brook, N.Y.), 50 from the United Kingdom (Oxford), 33 from Italy (Milan), 11 from Chile (Santiago), and two from Belgium (Leuven). The U.S./U.K. families were predominantly of Northern European descent. Details of all clinical procedures for this cohort have been previously published (16, 20, 21), as have pedigree structures (18, 22). Identification of the families and clinical evaluative and diagnostic procedures were similar in all locations. Diagnoses were made by the first author (L.E.D.) and other locally trained diagnosticians. Methods of recruiting included catchment area screening, systematic contact with health professionals at hospital and outpatient facilities, and advertisement through local and national support organizations for families of mentally ill persons (i.e., the National Alliance for the Mentally Ill in the United States and SANE [Schizophrenia A National Emergency] in the United Kingdom.) All individuals participating in this study gave written consent after receiving an explanation of the study procedures and their implications. Identical consent procedures were used in all five countries, and each center was given approval with Single Project Assurance status by the Office of Protection From Research Risks of the U.S. Department of Health and Human Services.

Diagnoses were made by using DSM-III-R criteria on the basis of structured interviews, review of medical records from all hospitalizations or other relevant treatment, and structured information obtained from at least one reliable family member about each individual. From 1985 to 1994 a modified Schedule for Affective Disorder and Schizophrenia (SADS) interview (23) combined with the Structured Interview for Personality Disorders (24) was used. After 1994, these forms were replaced by the newer, comprehensive Diagnostic Interview for Genetic Studies (25), and many of the ill individuals in previously obtained families were reinterviewed with this instrument. The SADS and Diagnostic Interview for Genetic Studies were translated into the appropriate language (i.e., Italian or Spanish) by professional medical translators and back checked. All foreign language interviews were summarized and translated into English before sending them to the Stony Brook site for diagnoses. The physicians and other professionals who performed the clinical evaluations (typically two individuals per site) were trained in these procedures by the first author (L.E.D.), and all underwent periodic diagnostic reliability exercises to maintain consistency between centers. Two independent diagnoses (one made by L.E.D.) were made for each individual in the study. In cases of disagreement between the diagnosing clinicians, a third diagnostician was consulted, and final diagnoses were made by consensus after discussion. Eight families were eliminated from the final analyses because of genetic inconsistencies in at least one crucial member. Thus, 301 families remained. Of these, 294 families had at least two siblings who satisfied the criteria for schizophrenia or schizoaffective disorder (382 nonindependent sibling pairs) (Table 1). The remaining seven families were excluded from the present analyses because one of the affected individuals did not satisfy criteria for these two diagnoses. An initial genome-wide scan involving 70 of these families and using different markers was previously reported (16).

The question of how best to define the affected phenotype from clinical characteristics was considered. Family and adoption studies have shown a genetic relationship between schizophrenia and schizoaffective disorder, and there may not be a scientific basis for the distinction between the two diagnostic categories, since the majority of patients with schizophrenia display depressive symptoms sometime in the course of their illness (reviewed in reference 26). In addition, the diagnostic reliability of the distinction between schizophrenia and schizoaffective disorder is low (25). Thus, these diagnoses were combined into one affected category, with schizoaffective disorder considered as affected.

Genotyping

Three hundred ninety-six highly polymorphic microsatellite markers were genotyped in all families by using standard polymerase chain reaction procedures that incorporated multiplex fluorescent genotyping, as previously described (27). Markers were selected for genotyping on the basis of their heterozygosity and distance from each other in order to cover the entire genome. The markers had an average spacing of 10 centimorgans (cM) (range=0–23 cM) and generated an average genetic information content of 0.75.

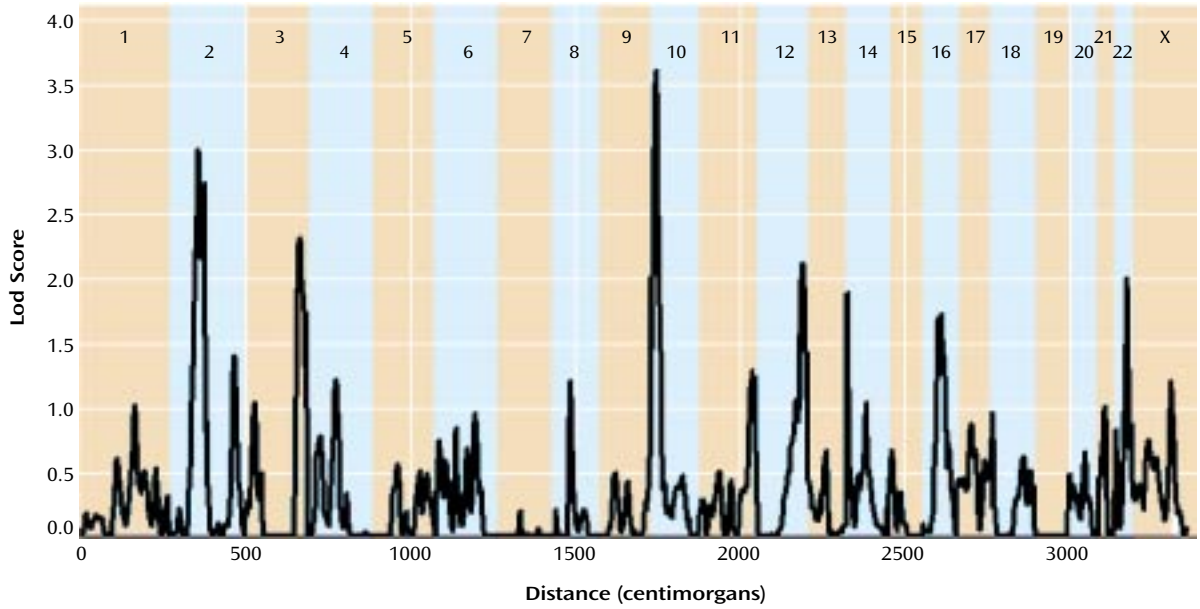
Statistical Analyses

Power analyses were calculated to determine the likelihood of detecting linkage under various gene effect sizes by using study group sizes corresponding to the schizophrenia plus schizoaffective disorder phenotype in the sibships from the total group of families. The methods used to determine the estimated power have been described by Risch (28). Since these power calculations assumed fully informative matings and the average heterozygosity of our markers was approximately 75%, the values represented maximum power. In addition, since the markers were spaced in approximate 10-cM intervals, the power to detect linkage was calculated at a recombination fraction of 0.05 between marker and disease loci (on average, the maximum distance between a potential disease locus and a marker locus). Our study group size had approximately 98% power to detect linkage at a lod score threshold of 2.0 at a relatively small gene effect size as measured by a sibling relative risk (lambda-s) of 2.0 and 89% power to detect linkage at a lod score of 3.0 at the same gene effect size.

Analyses were performed by using a schizophrenia and schizoaffective disorder phenotype, excluding the broader diagnoses of psychosis not otherwise specified or schizophrenia spectrum personality disorder.

For all analyses, allele frequencies for each marker were calculated from the family genotype data. Each of the 396 markers in the genome scan in affected sibling pairs were analyzed by using both the 2-point and the multipoint nonparametric allele sharing tests in MAPMAKER/SIBS (29). Two-point lod scores were computed at each marker by summing the log likelihood ratio of the observed identity-by-descent allele sharing among affected sibling pairs to random Mendelian segregation of 0.25, 0.50, 0.25 for sharing 0, 1, or 2 alleles identity-by-descent, respectively. For multipoint analysis, lod scores were computed in a similar manner at 1-cM intervals along each chromosome. A weighted average (2 divided by the number of affected siblings) was used for

FIGURE 1. Multipoint Nonparametric Maximum Lod Scores in a Genome-Wide Linkage Analysis for 382 Sibling Pairs Affected by DSM-III-R Schizophrenia or Schizoaffective Disorder[a]



[a] The x axis represents distance within the entire genome.

families containing more than two affected siblings. Parent-of-origin allele sharing tests were carried out on chromosome 22 markers by using the sib-ibd module of ASPEX (30).

Parametric analyses were conducted for the two highest regions of significant or suggestive genome-wide linkage by using both recessive and dominant affecteds-only models. Two-point lod scores were calculated with the program MLINK of FASTLINK (31, 32) at increments of theta=0.05, starting at theta=0 and ending at theta=0.5. Z_{max} scores were estimated from the maximum lod score obtained in these iterations. In addition, 2-point lod scores were calculated by assuming heterogeneity, where both alpha (the proportion of linked families) and the lod score were iterated and theta was fixed at 0 by using the program GENEHUNTER (33).

Results

The multipoint maximum lod score between each marker interval is indicated for all markers included in the genome scan (Table 2). There was one region with significant and two with suggestive linkage in this genome scan (lod score greater than 2.2 [19]). The significant peak lod score occurred in 10p14 at marker D10S189 with a Z_{max} of 3.60. The second best linkage result occurred in the centromeric region of chromosome 2 with a peak lod score of 2.99 between markers D2S139 and D2S417. A second peak on chromosome 2 occurred approximately 17 cM distal in 2q12 between markers D2S160 and D2S2254, with a peak lod score of 2.73. Finally, the third best linkage result occurred in 3q27 between markers D3S1602 and D3S1580 with a peak lod score of 2.31. Other peak lod scores ≥2.0 were obtained on chromosome 12q22-q24 at marker D12S324 (Z_{max}=2.10) and on chromosome 22q12-q13 at D22S283 (Z_{max}=2.00). The multipoint maximum lod score curves for all chromosomes are shown in Figure 1. All of the corresponding lod scores and markers used are shown in Table 2.

Parametric lod score analyses were calculated for markers in the chromosome 2 and 10 linkage regions, testing both autosomal dominant and recessive models by using an affecteds-only analysis. The results are shown in Table 3. In the chromosome 10p region, the peak parametric lod scores were obtained by using a recessive model (disease allele frequency=0.0091, phenocopy rate=0.0006). The peak lod score under homogeneity occurred at D10S189, with a Z_{max} of 2.25 (theta=0.30). Under heterogeneity, the lod score increased to 4.07 at D10S189 (theta=0.00, alpha=0.17). In the centromeric region of chromosome 2, the highest lod score assuming homogeneity occurred at D2S286, with a Z_{max} of 2.79 (theta=0.30), also by using a recessive model. When the data were analyzed under heterogeneity, the highest lod score occurred at D2S2229, with a lod score of 3.33 (theta=0.00, alpha=0.12). In addition, under heterogeneity, marker D2S139 located 16 cM proximal to D2S2229 in 2q12 had a peak lod score of 2.52 (theta=0.00, alpha=0.14).

Because of the interest in a possible imprinting effect on chromosome 22q (Vallada and Collier [34]), we investigated both maternal and paternal sharing of alleles among affected sibling pairs. Results of a chi-square test suggested a significant excess sharing of maternal alleles at locus D22S283 (χ^2=16.43, df=1, p=0.00005). The results of the 2-point maternal allele-sharing tests for all markers on chromosome 22 are shown in Table 4.

TABLE 2. Results of Genome-Wide Linkage Analysis for 382 Sibling Pairs Affected by DSM-III-R Schizophrenia or Schizoaffective Disorder[a]

Chromosome and Marker	Distance of the Marker From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score
Chromosome 1								
D1S468	0	0.00	D1S209	87	0.01	D1S218	169	1.02
D1S548	19	0.16	D1S216	100	0.11	D1S238	184	0.38
D1S228	20	0.17	D1S207	113	0.57	D1S413	196	0.50
D1S199	40	0.09	D1S420	114	0.60	D1S245	206	0.34
D1S234	48	0.16	D1S252	135	0.14	D1S213	232	0.50
D1S255	58	0.13	D1S498	152	0.36	D1S235	233	0.53
D1S197	69	0.13	D1S484	162	0.63	D1S2670	240	0.25
D1S220	79	0.00	D1S196	168	1.00	D1S180	258	0.04
						D1S2682	259	0.04
Chromosome 2								
D2S319	8	0.31	D2S2113	91	2.00	D2S347	128	0.45
D2S281	9	0.31	D2S286	92	2.05	D2S368	141	0.01
D2S162	17	0.00	D2S2114	96	2.36	D2S151	154	0.05
D2S168	25	0.01	D2S139	101	**2.99**	D2S142	161	0.08
D2S312	27	0.03	D2S417	102	2.93	D2S2330	162	0.10
D2S220	41	0.17	D2S2216	106	2.48	D2S326	178	0.05
D2S165	42	0.22	D2S2264	109	2.17	D2S364	182	0.09
D2S2298	59	0.00	D2S373	111	2.31	D2S117	193	0.09
D2S2182	62	0.00	D2S2229	112	2.36	D2S325	200	0.41
D2S391	74	0.40	D2S1893	117	2.58	D2S2248	207	1.23
D2S337	78	0.56	D2S160	118	2.73	D2S126	211	1.40
D2S380	82	1.15	D2S2254	126	0.87	D2S396	221	0.58
D2S285	85	1.35	D2S2258	127	0.77	D2S206	224	0.42
						D2S125	243	0.00
Chromosome 3								
D3S1304	8	0.25	D3S1285	66	0.00	D3S1569	124	0.00
D3S1263	9	0.27	D3S1566	73	0.00	D3S1279	132	0.00
D3S3608	26	1.01	D3S3653	82	0.00	D3S1614	150	0.45
D3S1266	27	1.03	D3S1271	88	0.00	D3S1565	163	2.29
D3S3521	49	0.49	D3S1278	98	0.00	D3S1602	165	2.31
D3S1289	50	0.43	D3S1267	106	0.00	D3S1580	171	1.95
D3S1300	58	0.00	D3S1292	114	0.00	D3S1311	189	0.78
Chromosome 4								
D4S412	0	0.00	D4S391	42	0.68	D4S406	117	0.31
D4S394	20	0.20	D4S3001	48	0.18	D4S402	118	0.32
D4S403	21	0.21	D4S428	70	0.48	D4S424	137	0.00
D4S2311	24	0.49	D4S398	74	0.60	D4S413	151	0.01
D4S3048	27	0.66	D4S392	85	1.21	D4S1597	161	0.00
D4S419	36	0.77	D4S1534	90	0.98	D4S415	171	0.03
			D4S1572	109	0.08	D4S1535	183	0.00
Chromosome 5								
D5S1981	0	0.00	D5S428	97	0.04	D5S2117	131	0.24
D5S406	11	0.00	D5S644	102	0.18	D5S393	139	0.40
D5S416	33	0.00	D5S433	103	0.19	D5S436	144	0.49
D5S419	40	0.00	D5S346	111	0.05	D5S434	145	0.51
D5S426	51	0.00	D5S421	112	0.03	D5S673	160	0.39
D5S418	62	0.30	D5S404	116	0.01	D5S422	165	0.48
D5S407	66	0.38	D5S471	118	0.01	D5S400	172	0.28
D5S647	76	0.56	D5S818	120	0.00	D5S429	178	0.21
D5S424	81	0.48	D5S804	128	0.17	D5S408	196	0.01
Chromosome 6								
D6S344	2	0.73	D6S271	61	0.42	D6S1569	136	0.29
D6S1574	12	0.55	D6S257	79	0.12	D6S308	139	0.09
D6S309	19	0.47	D6S493	89	0.63	D6S441	153	0.00
D6S470	22	0.58	D6S462	91	0.68	D6S1655	158	0.00
D6S289	31	0.49	D6S301	115	0.93	D6S1581	162	0.00
D6S276	56	0.77	D6S287	116	0.95	D6S264	177	0.00
D6S426	57	0.84	D6S262	130	0.37	D6S281	183	0.00
Chromosome 7								
D7S517	0	0.00	D7S519	55	0.00	D7S530	121	0.05
D7S513	11	0.00	D7S645	68	0.19	D7S640	122	0.06
D7S507	20	0.00	D7S669	88	0.01	D7S636	145	0.00
D7S493	26	0.00	D7S657	89	0.01	D7S798	154	0.00
D7S2416	32	0.00	D7S515	97	0.00	D7S2546	161	0.00
D7S510	48	0.00	D7S2502	116	0.02	D7S2423	174	0.00

TABLE 2. Results of Genome-Wide Linkage Analysis for 382 Sibling Pairs Affected by DSM-III-R Schizophrenia or Schizoaffective Disorder[a] (continued)

Chromosome and Marker	Distance of the Marker From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score
Chromosome 8								
D8S504	0	0.20	D8S258	42	0.85	D8S270	90	0.18
D8S277	15	0.00	D8S1771	43	1.20	D8S1784	105	0.00
D8S550	20	0.00	D8S283	54	0.35	D8S514	120	0.00
D8S549	37	0.03	D8S260	78	0.15	D8S284	131	0.00
			D8S279	83	0.20	D8S272	139	0.00
Chromosome 9								
D9S288	0	0.00	D9S161	41	0.48	D9S299	97	0.03
D9S286	7	0.00	D9S273	53	0.20	D9S289	107	0.00
D9S285	23	0.08	D9S175	78	0.42	D9S155	124	0.04
D9S157	36	0.41	D9S283	79	0.42	D9S290	133	0.27
D9S171	39	0.48	D9S287	84	0.18	D9S164	145	0.41
						D9S158	146	0.42
Chromosome 10								
D10S249	16	3.55	D10S208	56	0.22	D10S192	117	0.11
D10S189	17	**3.60**	D10S220	70	0.26	D10S597	118	0.13
D10S547	27	1.92	D10S589	79	0.38	D10S190	129	0.00
D10S191	43	0.41	D10S537	82	0.38	D10S587	148	0.13
D10S548	44	0.41	D10S201	96	0.46	D10S217	157	0.28
D10S197	53	0.22	D10S583	105	0.31	D10S169	161	0.27
						D10S212	167	0.20
Chromosome 11								
D11S922	10	0.21	D11S905	59	0.00	D11S898	110	0.36
D11S1338	11	0.24	D11S1313	66	0.29	D11S908	121	0.39
D11S1349	28	0.28	D11S987	77	0.43	D11S1345	142	1.27
D11S902	39	0.49	D11S1314	78	0.43	D11S4150	143	1.28
D11S1324	45	0.46	D11S937	85	0.04	D11S1320	150	0.77
D11S935	54	0.08	D11S1358	102	0.19	D11S968	156	0.43
Chromosome 12								
D12S352	0	0.08	D12S1617	43	0.02	D12S351	103	0.73
D12S99	13	0.00	D12S345	51	0.00	D12S346	109	0.79
D12S336	21	0.00	D12S85	62	0.02	D12S278	118	1.06
D12S364	29	0.00	D12S368	68	0.06	D12S79	137	2.11
D12S310	40	0.01	D12S83	87	0.35	D12S324	139	2.10
			D12S326	94	0.51	D12S1714	151	0.81
Chromosome 13								
D13S175	0	0.43	D13S1297	44	0.36	D13S170	71	0.00
D13S283	12	0.29	D13S153	55	0.65	D13S1283	73	0.01
D13S217	19	0.21	D13S1317	56	0.66	D13S265	74	0.03
D13S171	36	0.28	D13S152	61	0.28	D13S158	94	0.04
D13S263	37	0.24	D13S1306	68	0.00	D13S173	115	0.09
						D13S285	120	0.10
Chromosome 14								
D14S261	0	1.87	D14S288	49	0.53	D14S74	74	0.27
D14S283	9	0.48	D14S276	58	1.03	D14S280	91	0.07
D14S80	32	0.44	D14S63	59	1.03	D14S65	107	0.06
D14S70	35	0.47	D14S258	64	0.55	D14S78	114	0.00
						D14S292	121	0.00
Chromosome 15								
D15S128	11	0.62	D15S119	40	0.42	D15S158	81	0.00
D15S165	14	0.67	D15S153	56	0.13	D15S130	95	0.00
D15S1012	38	0.34	D15S131	65	0.00	D15S1014	102	0.00
			D15S205	73	0.00	D15S120	107	0.00
Chromosome 16								
D16S407	0	0.09	D16S411	39	0.83	D16S421	61	1.47
D16S405	12	0.04	D16S415	44	1.54	D16S3138	69	1.04
D16S3046	23	0.05	D16S3112	46	1.69	D16S3049	73	0.63
D16S401	31	0.19	D16S408	49	1.69	D16S516	74	0.71
D16S409	33	0.33	D16S389	56	1.65	D16S3091	87	0.35
			D16S503	57	1.71	D16S520	101	0.01
Chromosome 17								
D17S849	4	0.43	D17S1857	44	0.87	D17S949	94	0.48
D17S938	17	0.44	D17S798	55	0.67	D17S785	107	0.82
D17S1303	31	0.38	D17S791	62	0.51	D17S802	108	0.94
D17S799	43	0.85	D17S787	78	0.27	D17S784	117	0.12
			D17S948	85	0.59	D17S928	122	0.07

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Chromosome and Marker	Distance of the Marker From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score	Marker	Distance From the Short Arm Telomere (centimorgans)	Maximum Lod Score
Chromosome 18								
D18S59	0	0.01	D18S53	35	0.01	D18S68	84	0.56
D18S63	7	0.01	D18S478	51	0.17	D18S61	97	0.47
D18S452	17	0.00	D18S57	65	0.31	D18S469	99	0.51
D18S464	33	0.01	D18S474	78	0.61	D18S1141	114	0.12
Chromosome 19								
D19S878	0	0.00	D19S226	32	0.00	D19S420	61	0.00
D19S216	9	0.00	D19S433	46	0.00	D19S904	73	0.00
D19S884	20	0.00	D19S225	49	0.00	D19S601	82	0.00
D19S221	29	0.00	D19S220	56	0.00	D19S418	94	0.00
						D19S210	100	0.00
Chromosome 20								
D20S117	3	0.47	D20S189	28	0.32	D20S119	61	0.30
D20S889	12	0.39	D20S186	31	0.21	D20S178	62	0.29
D20S95	15	0.37	D20S118	46	0.47	D20S100	80	0.00
D20S115	23	0.32	D20S195	50	0.63	D20S173	88	0.00
			D20S107	51	0.65	D20S171	92	0.00
Chromosome 21								
D21S1256	11	0.67	D21S1253	17	1.00	D21S1252	28	0.02
			D21S263	20	0.96	D21S266	40	0.00
Chromosome 22								
F8VWFP	0	0.06	D22S431	21	0.06	D22S280	41	1.51
D22S420	10	0.54	D22S421	22	0.10	D22S278	44	1.93
D22S264	11	0.65	D22S258	23	0.11	D22S283	45	2.00
D22S311	12	0.82	D22S315	24	0.11	D22S445	49	1.13
D22S446	13	0.48	D22S310	34	0.67	D22S423	55	0.86
D22S301	17	0.17	D22S275	38	1.23	D22S1140	57	0.80
						D22S274	59	0.68
X Chromosome								
DXS1060	0	0.43	DXS1214	47	0.74	DXS1220	115	1.04
DXS8051	6	0.28	DXS1068	52	0.69	DXS1001	117	1.20
DXS987	20	0.40	DXS1055	71	0.61	DXS1047	133	0.28
DXS1226	29	0.29	DXS986	80	0.42	DXS1227	147	0.16
DXS1202	38	0.39	DXS990	88	0.28	DXS8043	156	0.06
			DXS1106	105	0.24	DXS8091	164	0.06

[a] Lod scores were calculated in multipoint nonparametric allele sharing tests in affected sibling pairs by using the program MAPMAKER/SIBS (29). Markers are shown in sequential map order, followed by the distance in centimorgans to the location within the interval to the next marker where the maximum lod score occurs. The highest lod scores, shown in boldface type, were 2.99 at marker D2S139 and 3.60 at D10S189.

Discussion

Genetic linkage studies of schizophrenia are currently in progress in independent laboratories worldwide. The limiting factor for most investigators has been the lack of availability of a large number of families for analysis. Thus, there have been many reports of suggestive linkage, but very few with significant findings. The present report contributes results from one of the largest complete genome-wide scans of schizophrenia to date. Although our findings when viewed on their own yield some evidence of linkage—for example, significant linkage in chromosome 10p14 and a suggestion of linkage in chromosome 2p14-q12—the most striking feature is the failure to confirm a number of earlier claims of positive findings.

We first consider the apparent evidence for linkage from our own studies. In an initial genome-wide scan (16), chromosome 10p did not show a positive peak. However, others have previously reported 10p findings that suggest linkage to schizophrenia (9, 35, 36), and Schwab et al. (37) have presented data that phosphatidylinositol phosphate kinase on 10p is a candidate gene. However, like our findings for chromosome 2, the chromosome 10p findings are spread over a considerable distance. The finding in our present study (peak lod score of 3.60 at D10S189, 17cM from pter [the short-arm telomere]) is approximately 15–20 cM from the findings of Straub et al. (9) (maximum heterogeneity lod score of 1.95 in a recessive model). It is 25–30 cM from the peak multipoint lod score of 2.13 obtained by Schwab et al. (9), and at the short-arm end of the 60-cM band of positive nonparametric linkage scores of 1.70 to 3.36 from 10p13 to 10q23 reported by Faraone et al. (36) in the European-American pedigrees of the National Institute of Mental Health (NIMH) data set. These scores are thus modest in magnitude and variable in location. Moreover, other systematic genome scans give no support to linkage on chromosome 10. Moises et al. (38) in a two-stage approach in 70 pedigrees, Coon et al. (39) in a large Palaoan pedigree, Brzustowicz et al. (7) in 22 extended Canadian pedigrees, Williams et al. (40) in their two-stage

TABLE 3. Parametric 2-Point Lod Score Analyses for Chromosomes 2p12-q12 and 10p15-p13 in 382 Sibling Pairs Affected by DSM-III-R Schizophrenia or Schizoaffective Disorder[a]

Marker	Distance of the Marker From the Short Arm Telomere (centimorgans)	Dominant Model				Recessive Model			
		Homogeneity		Heterogeneity		Homogeneity		Heterogeneity	
		Z_{max}	Theta	Lod Score	Alpha	Z_{max}	Theta	Lod Score	Alpha
D2S285	81.6	1.20	0.30	1.29	0.19	0.58	0.35	0.33	0.05
D2S2113	85.0	0.45	0.35	0.92	0.15	1.07	0.35	0.48	0.06
D2S286	90.9	1.98	0.25	2.22	0.30	**2.79**	0.30	1.89	0.15
D2S2114	91.8	1.16	0.30	1.12	0.18	1.16	0.35	1.11	0.09
D2S139	95.3	1.88	0.25	2.05	0.25	2.37	0.30	**2.52**	0.14
D2S417	100.9	2.27	0.25	2.73	0.29	2.33	0.30	1.72	0.13
D2S2216	102.8	0.39	0.35	0.44	0.11	0.62	0.35	1.09	0.09
D2S2264	107.6	1.42	0.25	1.54	0.23	1.74	0.30	0.58	0.08
D2S373	108.2	0.81	0.30	0.94	0.17	0.99	0.35	0.48	0.06
D2S2229	111.1	2.03	0.25	2.99	0.26	2.56	0.30	**3.33**	0.12
D2S1893	114.4	0.98	0.30	1.42	0.19	1.49	0.30	2.47	0.10
D2S160	116.7	1.31	0.25	1.82	0.26	1.18	0.30	1.94	0.13
D2S2254	122.8	0.56	0.35	0.89	0.14	1.27	0.35	1.89	0.07
D2S2258	125.8	0.42	0.35	0.85	0.16	1.63	0.30	1.60	0.12
D10S249	0.0	0.39	0.35	0.20	0.10	0.04	0.40	0.00	0.01
D10S1435	3.1	1.02	0.30	0.90	0.19	0.75	0.35	0.75	0.09
D10S1729	11.8	0.89	0.30	1.01	0.21	1.20	0.30	0.59	0.09
D10S189	16.5	1.52	0.25	1.76	0.23	**2.25**	0.30	**4.07**	0.17
D10S1728	23.0	2.09	0.25	2.51	0.27	1.53	0.30	2.37	0.13
D10S1159	25.8	0.97	0.25	0.79	0.20	0.40	0.35	0.65	0.11
D10S547	27.6	0.94	0.30	0.68	0.15	0.63	0.35	0.59	0.08

[a] Parametric lod score analyses were calculated by testing both autosomal dominant models (disease allele frequeny=0.0049, phenocopy rate=0.0006) assuming homogeneity and heterogeneity and recessive models (disease allele frequency=0.0091, phenocopy rate=0.0006) assuming homogeneity and heterogeneity in affected siblings. Additional markers were added in regions close to the peak linkage in the nonparametric analyses. Peak scores in each region are shown in boldface type.

analysis of 196 affected sibling pairs, and Kaufmann et al. (41) in African American pedigrees in the NIMH data all used markers with a resolution of 10 cM or less and failed to observe any positive peaks on 10p. Thus, there is little support in the literature for a conclusion that our multipoint lod score of 3.60 at D10S189 is evidence of a gene for schizophrenia on chromosome 10p14.

In our initial genome scan, we reported a peak lod score of 2.13 on chromosome 2p16.1 at D2S1337. In the current study, the expanded cohort had a peak lod score exceeding criteria for suggestive linkage as suggested by Lander and Kruglyak (19) in the centromeric region of chromosome 2 near the marker D2S417 (102 cM from pter) and second peak in 2q12 at D2S160 (118 cM from pter). Other studies of families with schizophrenia have reported suggestive linkage for this region, although the associations have not reached a high level of statistical significance (36, 38, 39, 42). Coon et al. (39) reported a peak positive score on chromosome 2 at D2S441, which is approximately 98 cM from pter, and Faraone et al. (36) reported a peak nonparametric linkage score of 2.41 on chromosome 2q12 at 104.5 cM from pter in a cohort of 43 nuclear families. Similarly, Levinson et al. (42) reported a peak nonparametric linkage score of 2.01 at D2S410 located in 2q14.1 approximately 115 cM from pter in 45 pedigrees. In one of the earliest reported genome-wide scans for schizophrenia susceptibility genes, Moises et al. (38) reported a nonparametric p value of 0.0001 at D2S135 located approximately 115 cM from pter in 2q12-2q14 in a group of Icelandic and international families. Brzustowicz et al. (6, 7), while noting genome-wide evidence of significant linkage on chromosomes 1q and 13q, found a peak score of 2.42 at D2S1400, approximately 28 cM from pter. In a study of 198 affected sibling pairs, Williams et al. (40) reported a wide peak on 2q at approximately 181 cM from pter, considerably distal to the peak in the present study. Kaufmann et al. (41) reported modest peaks (nonparametric linkage scores <1.5) at 40 cM and 220 cM in African American pedigrees from the NIMH genetics consortium, with no evidence of linkage around the centromere. Thus, although all of these studies have reported findings on chromosome 2, the peaks are of modest magnitude and are widely dispersed along the chromosome. Only one of these findings (39) comes within 4 cM of the present finding.

Chromosome 22q became a focus of attention after the report of Pulver et al. (3) suggesting linkage to this chromosome in schizophrenia and descriptions of schizophrenia-like symptoms in patients with velocardiofacial syndrome, which arises from a deletion in chromosome 22q11 (43). This syndrome and its relationship to schizophrenia have been extensively studied (44, 45). Some positive findings have been reported of linkage more distal to this region on 22q12 (3, 46, 47), and one report of a possible imprinting effect on this putative locus (linkage to maternally but not paternally transmitted alleles) in schizophrenia (48) is consistent with our findings. Nevertheless, our weakly positive lod score for this region in our initial scan of 70 families did not increase further when the cohort was substantially enlarged. In addition, no evidence of linkage in this region was reported by Kaufmann et al. (41), Faraone et al. (36), Williams et al. (40), or Brzustowicz et al. (7). Similarly, the chromosome 3 and 12 suggestive linkages in the present

TABLE 4. Results of 2-Point Maternal Allele-Sharing Tests for Markers on Chromosome 22 in Sibling Pairs Affected by DSM-III-R Schizophrenia or Schizoaffective Disorder[a]

Marker	Distance of Marker From the Short Arm Telomere (centimorgans)	Maternal Allele Sharing[b]			Analysis	
		Yes	No	% Sharing	χ (df=1)	p
D22S278	42.1	100	70	58.8	5.29	<0.02
D22S1173	43.5	43	33	56.6	1.32	<0.25
D22S283	44.9	148	86	63.2	16.43	<0.00005
D22S1177	47.6	118	82	59.0	6.48	<0.01
D22S1045	48.5	88	59	59.9	5.72	<0.02
D22S450	49.7	99	68	59.3	5.75	<0.02
D22S445	50.6	92	55	62.6	9.31	<0.002
D22S423	54.1	71	72	49.7	0.01	<0.92
D22S418	56.7	105	90	53.8	1.15	<0.28

[a] Parent-of-origin allele sharing tests were carried out by using the sib-ibd module of ASPEX (30).
[b] Analysis included only sibling pairs where both parents were genotyped and the mother was heterozygous for the marker.

study have not been reported to be of significance in any previous publications on schizophrenia.

Other regions of potential interest in our initial screen (chromosomes 1q, 4p, 5p, 11p, 16q) were not supported by further evidence of linkage in the fourfold larger cohort in the present scan. Moreover, a number of regions within which specific claims for linkage have been made by other investigators on 5q (2), 6p 24-22 (e.g., reference 8), 13q (5, 6), and 1q (7, 14, 15) with small numbers of families have not shown linkage in the present group of 294 families. Two recent claims are of particular note. In 22 extended families, Brzustowicz et al. (7) reported a heterogeneity lod score of 6.5 with an alpha (proportion of linked families) of 75% for a region in chromosome 1q211-q22 and claimed that the linkage result "should provide sufficient power to allow the positional cloning of the underlying susceptibility gene." Leonard and colleagues (48) reanalyzed data from the relatively small number of families from the NIMH consortium and obtained a lod score of 4.43 at 45.7 cM from the 15p telomere in a heterogeneity analysis with an alpha of 85%. If either of these claims were generalizable to a group of 294 families, we would expect to see lod scores substantially in excess of those reported in references 7 and 48. In fact, in our present study, we found no evidence of linkage to either of these regions. Although it is possible that some unusual skewness in the heterogeneity of our sample and those of others may explain our failure to replicate some previously reported findings, it is also possible that some of the reported linkages (or most) are false positive findings that will not lead to the location of a susceptibility gene.

Alternatively, it may be that the numbers of families with schizophrenia in all existing studies, including our own, are too small to replicate findings consistently. This argument has been supported by the simulated calculations of Goring and colleagues (49) suggesting that if several genes of small effect are involved, as many as 3,000 sibling pairs would be needed to replicate results consistently. Thus, many positive regions with susceptibility genes could be missed even in a group of families as large as our current study group, and unusually large effects may be falsely seen with a much smaller number of families and may be falsely interpreted as evidence for the presence of susceptibility genes.

It is likely that the scope and complexity of linkage analysis combined with the idiosyncrasy of small study group sizes and a natural enthusiasm for positive findings has led investigators to conclusions that cannot be generalized to schizophrenia as a whole. We and others have not yet found a gene for susceptibility to schizophrenia or any other psychosis, although there is hope for the future, given the continued advances in technology. A candidate gene approach that takes into account the key underlying pathology present in patients with long-term schizophrenia (including brain structural, cognitive, and other physiological defects) may be a more fruitful direction. The possibility that linkage or association to a candidate gene may not be present owing to a lack of sequence variation needs to be considered, and the alternative possibility that the anomaly is epigenetic and related to variability in gene expression should be considered. Although the present results on chromosomes 2, 10, and 22 are intriguing and worth further pursuit, we acknowledge that they may be only chance findings awaiting replication and the detection of candidate genes within these regions.

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