

Multicenter Linkage Study of Schizophrenia Candidate Regions on Chromosomes 5q, 6q, 10p, and 13q: Schizophrenia Linkage Collaborative Group III*

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Schizophrenia candidate regions 33–51 cM in length on chromosomes 5q, 6q, 10p, and 13q were investigated for genetic linkage with mapped markers with an average spacing of 5.64 cM. We studied 734 informative multiplex pedigrees (824 independent affected sibling pairs [ASPs], or 1,003 ASPs when all possible pairs are counted), which were collected in eight centers. Cases with diagnoses of schizophrenia or schizoaffective disorder (DSM-III-R criteria) were considered affected ($n = 1,937$). Data were analyzed with multipoint methods, including nonparametric linkage (NPL), ASP analysis using the possible-triangle method, and logistic-regression analysis of identity-by-descent (IBD) sharing in ASPs with sample as a covariate, in a test for intersample heterogeneity and for linkage with allowance for intersample heterogeneity. The data most supportive for linkage to schizophrenia were from chromosome 6q; logistic-regression analysis of linkage allowing for intersample heterogeneity produced an empirical P value $< .0002$ with, or $P = .0004$ without, inclusion of the sample that produced the first positive report in this region; the maximum NPL score in this region was 2.47 ($P = .0046$), the maximum LOD score (MLS) from ASP analysis was 3.10 (empirical $P = .0036$), and there was significant evidence for intersample heterogeneity (empirical $P = .0038$). More-modest support for linkage was observed for chromosome 10p, with logistic-regression analysis of linkage producing an empirical $P = .045$ and with significant evidence for intersample heterogeneity (empirical $P = .0096$).

Introduction

The present investigators have formed a consortium for the purpose of combining a set of eight clinical samples into a large sample of >800 pedigrees multiply affected with schizophrenia (MIM 18150, 603175, 603176), for genetic linkage studies of chromosomal regions in which positive evidence for linkage has been reported. This consortium has grown out of three previous efforts. A report of modestly positive evidence for linkage on chromosome 22q (Pulver et al. 1994b) led to two collaborative studies (Pulver et al. 1994a; Gill et al. 1996) in-

volving 4 and 11 samples, respectively. The second of these studies analyzed a combined sample of 436 ASPs and reported modest support for linkage, with $P = .004$ at D22S278 using likelihood-based ASP analysis. Subsequently, 14 research groups studied 15 markers in regions of chromosomes 3p, 6p, and 8p, in a total of 567 pedigrees (687 independent affected sib pairs) (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996). Suggestive evidence for linkage was observed for chromosomes 6p ($P = .0004$ for

* The Schizophrenia Linkage Collaborative Group III includes all authors, who are listed in the following order: study coordinators (Levinson, Holmans), principal investigators of each research group (Straub, Owen, Wildenauer, Gejman, Pulver, Laurent), and additional authors from each group, with groups listed according to the number of pedigrees contributed. Participating research groups are identified in the paper as “MCV/Ireland” (Straub, Kendler, Walsh), “U Wales” (Owen, Norton, Williams), “U Bonn” (Wildenauer, Schwab, Lerer); “US/Aust” (Levinson, Mowry), “U Chicago” (Gejman, Sanders), “JHU” (Pulver, Antonarakis, Blouin), and “CNRS” (Laurent, DeLeuze, Mallet).

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Table 1**Previous Results in Regions Selected for Study**

GROUP	REFERENCE(S)	NO. OF PEDIGREES	CHROMOSOME ^a			
			5q	6q	10p	13q
Utah	Coon et al. (1994)	9				
Kiel	Moises et al. (1995)	5				
US/Aust	Levinson et al. (1998), Martinez et al. (1999)	43		+		
NIMH SGI:						
White	Faraone et al. (1998)	43			++	
Black	Kaufman et al. (1998)	30		+		
White and black	Cao et al. (1997), Martinez et al. (1999)	63		++		
JHU	Blouin et al. (1998)	54				+++
SUNY/AxyS	Shaw et al. (1998)	70				+
Utah/Palau	Coon et al. (1998)	(Isolate)				
U Wales	Williams et al. (1999)	100				
MCV/Ireland	Straub et al. (1997a)	265	++		++	
U Bonn	Wildenauer et al. (1997)	72	+		++	
U Chicago	Cao et al. (1997), Martinez et al. (1999)	53		++		

^a + = one of the most positive results in genome scan; ++ = nominal $P < .001$; +++ = nominal $P < .00002$.

the combined sample, $P = .001$ after removing the sample in which the finding was first reported) and 8p ($P = .00018$ for the entire sample, $P = .0014$ with the original sample removed), but not for chromosome 3p. These studies may be useful in focusing further attention on regions that demonstrate evidence for linkage across multiple data sets. Therefore, further studies of candidate regions seem justified.

We report here the results of the first effort of the Schizophrenia Linkage Collaborative Group III (SLCG III), which plans to complete at least three further studies with the same data set. SLCG III studies include the seven multiplex schizophrenia samples collected by the participating groups and an eighth data set collected by the National Institute of Mental Health (NIMH) Schizophrenia Genetics Initiative (SGI) (Cloninger et al. 1998), which is available through a NIMH-sponsored repository. Because of expansions of some of the participating samples, a larger data set (>800 ASPs) is available than was available for earlier collaborations, with a smaller number of participating groups, which facilitates coordination of the studies. It is hoped that maintaining a consistent data set will permit valid comparison of multicenter linkage results in various candidate regions, without the selection bias that could emerge if groups participated in some studies and not others. The genetic analysis strategy has also been modified to include both analyses of the combined sample and logistic regression analyses, which take heterogeneity among samples into account.

Material and Methods

Selection of Regions for Study

The investigators selected the four regions for study on the basis of published and reported genetic linkage

studies of schizophrenia, attempting to identify the regions for which there was significant evidence for linkage in at least one study (i.e., chromosome 13q) or for which at least two studies reported that the region was either associated with suggestive evidence for linkage or produced one of the most significant results in a genome scan (i.e., chromosomes 5q, 6q, and 10p). Previous studies of these four regions are summarized in table 1.

Chromosome 5q

The MCV/Ireland group reported a maximum heterogeneity LOD score of 3.35 ($P = .0002$) on chromosome 5q22-q31 at D5S804, under a narrow diagnostic model and a recessive genetic model, with an NPL score of 2.84 ($P = .002$) (Straub et al. 1997b). In the same region, the U Bonn group simultaneously reported maximum LOD scores of 1.8 at marker IL9 in 14 pedigrees and 1.27 at D5S399 in an additional 40 pedigrees (Schwab et al. 1997).

Chromosome 6q

The U Chicago group reported a P value of .00018 by ASP analysis at D6S474 in 53 pedigrees containing 61 independent ASPs (Cao et al. 1997). The same group then typed 87 independent ASPs from the NIMH SGI sample and observed a P value of .00095 at D6S424, ~14 cM proximal to the Chicago peak (Cao et al. 1997). The US/Aust group subsequently studied 43 pedigrees containing 54 independent ASPs and observed a P value of .013, also at D6S424 (Martinez et al. 1999).

Chromosome 10p

The most positive result in the NIMH SGI genome scan of 43 European-American pedigrees was an NPL score of 3.36 ($P = .0004$) at D10S1423 (Faraone et al.

1998). In precisely the same region, the MCV/Ireland group (Straub et al. 1998) observed a maximum NPL score of 1.88 ($P = .03$) and a maximum multipoint heterogeneity LOD score of 1.91 ($P = .006$), the fourth-most-positive region in their genome scan, and the U Bonn group (Schwab et al. 1998) reported an MLS of 2.13 by multipoint ASP analysis and an NPL score of 3.2 ($P = .0007$).

Chromosome 13q

Lin et al. (1995) reported a heterogeneity LOD score of 1.61 at D13S144 and later reported (Lin et al. 1997) a maximum multipoint LOD score of 2.58 near D13S122 and D13S128 in an expanded European sample, although the region was negative in East Asian families. Pulver's group (JHU sample) subsequently reported a maximum NPL score of 4.18 ($P = .00002$) in 54 pedigrees, near D13S174, 8–10 cM centromeric from the results of the studies by Lin et al. (Blouin et al. 1998). Likelihood-based analyses demonstrated a maximum LOD score of 4.54 with a dominant model. In a replication data set of 51 families, these authors observed an NPL score of 2.36 ($P = .007$) in the same region. The SUNY/Oxford/AxyS study (Shaw et al. 1998) observed a maximum NPL score of 1.83 at D13S170, 11 cM centromeric to the JHU peak. Brzustowicz et al. (1999) reported a maximum heterogeneity LOD score of 4.42 at D13S793 (about 10 cM distal to the JHU peak) in 21 extended Canadian families.

Clinical Samples

The characteristics of the eight clinical samples are summarized in table 2. The table also lists references summarizing the clinical methods of each study. In brief, only family members with DSM-III-R diagnoses of schizophrenia or schizoaffective disorder were considered affected for this analysis and are counted in table 2. Schizoaffective disorders have been included because there is substantial evidence that, as they are currently defined, schizoaffective and schizophrenic disorders cosegregate in the same families and are quite difficult to differentiate reliably even by clinicians in the same research program (Faraone et al. 1996) (reviewed by Levinson et al. [1999] and Levinson and Mowry [2000]). Each data set included pedigrees with two or more cases of schizophrenia or related disorders, in constellations that are informative for linkage analysis. All subjects gave informed consent and were evaluated by trained research clinicians using a semistructured research diagnostic interview schedule and best-estimate diagnosis on the basis of interviews, available records, and informant reports. A total of 3,815 individuals were genotyped, including 1,937 individuals affected with schizophrenia or schizoaffective disorder and unaffected

Table 2

SLCG III Samples

CENTER	NO. OF PEDIGREES	NO. OF ASPs		NO. OF INDIVIDUALS	
		Unweighted	Weighted	Affected (Scz/SA)	Typed
U Bonn	71	108	88	165	306
U Chicago	63	95	75	159	305
CNRS	48	95	69	144	290
JHU	53	65	51	145	363
MCV/Ireland	216	273	226	618	1,408
US/Aust	65	73	64	202	359
U Wales	148	188	166	327	465
NIMH SGI	70	106	85	177	319
Total	734	1,003	824	1,937	3,815

NOTE.—Shown are the number of informative pedigrees in which subjects were considered affected with DSM-III-R schizophrenia and schizoaffective disorder; the number of ASPs (unweighted) counting all $N \times (N-1)/2$ possible pairs in each sibship, where N = the number of affected sibs; the number of ASPs weighted to be equivalent to $N-1$ pairs; the number of individual typed subjects affected with DSM-III-R schizophrenia or schizoaffective disorder; and the total number of typed individuals. References for sample descriptions and ascertainment and for laboratory methods are: U Bonn, Schwab et al. (1998); U Chicago, Cao et al. (1997); CNRS, Campion et al. (1994) and Bonnet-Brilhault et al. (1999); JHU, Blouin et al. (1998); MCV/Ireland, Straub et al. (1995, 1998); US/Aust, Levinson et al. (1998); U Wales, Williams et al. (1999); and NIMH SGI, Cloninger et al. (1998) and Kaufmann et al. (1998). The NIMH SGI sample was genotyped for this study by the US/Aust group.

relatives such as parents or siblings of probands, from 734 pedigrees containing 824 “independent” ASPs (number of affected siblings – 1) and 1,003 ASPs when all possible pairs are counted.

Predominant ethnic origins of subjects were: U Bonn, German (white) and Israeli (Sephardic); U Chicago and US/Aust, white or black; CNRS, French, and mixed French-black-Indian-East Asian; JHU, white; MCV/Ireland, Irish (all white); U Wales, British (all white). Details are provided in the papers referenced in table 2.

Selection of DNA Markers

Polymorphic markers that had produced high-quality genotypes in previous studies by participating groups were selected where possible, supplemented by additional markers to create maps with a mean spacing of 5.64 cM (SD = 1.73). A total of 32 markers were selected, including 21 dinucleotide repeats and the remainder tri- or tetranucleotide repeats, with mean heterozygosity of 0.77. The maps are shown in table 3, with distances from Marshfield maps.

Genotyping

Each participating group genotyped the selected markers in its own sample; the NIMH SGI sample was genotyped at these markers for this study by the US/Aust

Table 3
Markers Selected for Study of Candidate Regions

Marker	Heterozygosity	Location ^a (cM)
D5S2027	.78	119.5
D5S2055	.84	125.91
D5S818	.78	130.94
D5S2057	.80	135.25
D5S393	.83	140.72
D5S210	.80	147.49
D5S640	.79	152.62
D10S189	.73	19.00
D10S1412	.73	28.31
D10S2325	.85	32.80
D10S191	.82	37.90
D10S1423	.74	46.23
D10S197	.75	52.10
D10S1426	.74	59.03
D10S604	.66	66.50
D10S1220	.62	70.23
D6S445	.69	91.34
D6S1613	.91	97.11
D6S424	.56	104.08
D6S301	.76	111.17
D6S268	.74	114.93
D6S474	.80	118.64
D6S267	.76	121.97
D6S262	.83	130.00
D13S170	.90	63.9
D13S795	.60	71.06
D13S1241	.82	76.26
D13S779	.66	82.93
D13S174	.87	84.87
D13S797	.71	90.27
D13S173	.82	93.52
D13S895	.88	98.82

^a On the Marshfield genetic map, except for D5S818, D10S1423, and D13S797, whose locations have been extrapolated from the Southampton maps and from available data.

group. All laboratories determined marker genotypes with semiautomated methods using fluorescinated primers. Allele numbering was standardized by typing of two CEPH controls in each laboratory. Details of methods are available in the publications by each group referenced in table 2.

Statistical Analysis

Two types of analyses were utilized (summarized in Appendix A). One set of analyses was performed after all pedigrees were combined into a single sample (with each analysis repeated without the sample in which a positive finding in a given region was first reported). These included multipoint ASP analysis using the possible triangle algorithm (Holmans 1993) and multipoint NPL analysis (Kruglyak et al. 1996) (Z_{all} or NPL scores),

both by means of the GENEHUNTER 2.0 package. NPL analysis was used in addition to ASP analysis because affected relatives other than siblings of probands were included in most samples, and NPL analysis considers the entire constellation of affected relatives. Each analysis was repeated after omitting the sample in which a positive result was first reported in each region (the MCV/Ireland sample for chromosome 5q, the U Chicago sample for chromosome 6q, the NIMH SGI sample for chromosome 10p, and the JHU sample for chromosome 13q). The analysis of all samples was the planned (primary) analysis, as the investigators have planned a series of studies using a consistent data set. Analyses were repeated without the first positive data set as a way to examine possible selection bias, a complex issue which is discussed further below. Note that while a small number of unaffected individuals were "trimmed" from pedigrees by GENEHUNTER, genotypes from all affected individuals were retained in analyses.

The second set of analyses utilized logistic regression of IBD allele sharing in ASPs using site as a covariate, as proposed by Rice (Rice 1997; Dorr et al. 1997). Details of the method are provided in Appendix B. Two tests were applied to the present data. The first tested the significance of the difference in sharing proportions among centers, treating center (site) as a covariate (i.e., a test for intersite heterogeneity). The second tested the overall significance of linkage while allowing for intersite heterogeneity, by setting the sharing proportion at .50 (the lowest biologically meaningful proportion), for every sample with an observed proportion <.50, and then testing for overall deviation from 50% sharing with site as a covariate.

As an additional secondary analysis, dominant and recessive multipoint heterogeneity LOD scores were computed using GENEHUNTER 2.0, with all unaffected individuals coded as "diagnosis unknown," for two models, each with maximum penetrance of 0.50 and no phenocopies, with disease allele frequencies of .005 for the dominant and .10 for the recessive model. Peak scores were compared with two-point LOD scores for the flanking markers which were substantially less positive than the multipoint results (data not shown). These analyses are provided only to permit consideration of possible modes of inheritance and to provide readers with a comparison with the primary "nonparametric" analyses; therefore no *P* values have been computed.

P values reported for NPL tests are pointwise values computed by GENEHUNTER. For the ASP and logistic regression analyses, *P* values were determined by creating 5,000 and 20,000 simulated replicates of the data set, respectively (using the actual pedigree structures and maps of each region), under the assumption of random segregation, and determining the probability of observ-

ing each result by chance. Note that these P values are therefore segment-wise rather than point-wise.

All analyses of IBD sharing in affected sibling pairs (MLS analyses using combining samples and logistic regression) were carried out first with all possible pairs or $[N \times (N-1)]/2$ pairs per sibship, where N equals the number of affected siblings, and then with larger sibships downweighted so that each sibship contributed the equivalent of $N-1$ "independent" pairs. Downweighting can be excessively conservative (Meunier et al. 1997; Sham et al. 1997; Holmans 1998), and using all possible pairs both in analyses and in simulation of P values can result in increased power; thus, the unweighted analyses were considered primary, and the analyses with weighting were carried out for comparison. Here, empirical P values with and without weighting were quite similar. For most analyses, results are shown using all possible pairs (tables 4-7). Results in table 7 (logistic regression analysis of linkage allowing for intersample heterogeneity) are shown both weighted and unweighted, to illustrate the similarity.

Power analyses were carried out for samples of 800 independent ASPs, 34% with missing parents and 66% with two genotyped parents. One-hundred replicates were generated and analyzed for a 200-cM chromosome containing a disease locus under a range of dominant and recessive generating models, with maximum penetrance ranging from .08 to .35, disease allele frequency from .04 to .70, population phenocopy rate from .10 to

.60, and predicted locus-specific relative risk to sibs (λ_{sibs}) from 1.2 to 3.5, and with either 30% or 100% of families linked. With 30% of families linked, the expected proportion of pairs sharing 0 alleles by descent (z_0) in linked families is $0.25/\lambda_{\text{sibs}}$, the expected z_0 in unlinked families is 0.25, the expected z_0 in all families is the weighted average of the two, and the expected populationwide λ_{sibs} is $0.25/z_0(\text{population})$ (Risch 1990a, 1990b). Each replicate was analyzed using multipoint affected sib-pair analysis with GENEHUNTER 2.0, as described above, and it was determined how frequently a maximum LOD score was observed which exceeded an empirically derived threshold for 5% genomewide significance (3.3).

Results

Affected Sibling Pair Analyses (Combined Sample)

MLS values are shown in table 4 from ASP analyses of the combined sample of 1,003 possible ASPs (824 ASPs after downweighting) from 734 pedigrees. The value given for each sample is the maximum value observed throughout the region for that sample analyzed separately; when the maximum LOD score for a sample was >1.0 , the location, in cM, of the result for that sample is shown in parentheses. The total MLS shown is the maximum observed for all samples combined. The only region with a significant segmentwise P value was

Table 4

ASP MLS Results (Unweighted—All Possible Pairs)

GROUP	A. Overall Results			
	MAXIMUM LOD (LOCATION) FOR CHROMOSOMAL REGION			
	5q	6q	10p	13q
U Bonn	.52	1.72 (97.1 cM)	1.54 (46.2 cM)	.33
U Chicago	.19	4.10 (117.1 cM)	2.98 (19.0 cM)	.04
CNRS	.22	0	1.02 (49.7 cM)	.32
JHU	1.41 (150.6 cM)	.04	0	2.46 (80.3 cM)
MCV/Ireland	2.48 (140.7 cM)	.67	.30	.03
NIMH SGI	0	3.94 (102.7 cM)	1.52 (46.2 cM)	.11
US/Aust	.03	1.44 (106.9 cM)	.08	0
U Wales	.60	1.29 (114.9 cM)	0	.21
COMBINED MLS	.58 (140.7 cM)	3.10 (106.9 cM)	.34	.09
Empirical P		.0036		
B. Results When the Sample with the First Positive Report Is Omitted				
Result	MCV/Ireland	U Chicago	NIMH SGI	JHU
Combined maximum LOD	.11	2.47 (106.9 cM)	.12	.026
Empirical P		.01		

NOTE.—Shown are maximum LOD scores from multipoint affected sibling pair analyses of each chromosomal region using the possible triangle method (GENEHUNTER 2.0) using all possible pairs in a sibship for each sample, for all samples combined, and for all samples omitting the sample in which positive findings in a region were first reported. For MLS values >1 , the peak location is shown underlined. P values are the probability of observing a value at least as large anywhere in the region (segmentwise values) in 5,000 simulated replicates of the actual sample and map assuming no linkage.

chromosome 6q, with MLS of 3.10 and $P = .0036$, slightly distal to D6S424. Removal of the first reported positive data set for each region did not change the pattern of results, but the P value for chromosome 6q without the U Chicago data set was more modest (.01). Results of ASP analyses for the combined sample and for each sample separately are shown in figure 1.

NPL Analyses

Results of NPL analyses of the combined sample of 734 pedigrees are shown in table 5. As for ASP analyses, the maximum value for each sample analyzed separately is shown, and when the pointwise P value for a sample was $<.05$, the location is shown in parentheses. The only region with a significant pointwise P value was chromosome 6q ($Z = 2.47$, $P = .0046$). For chromosome 6q, the maximum evidence for linkage in various samples was observed in a region ~20 cM wide, and without the U Chicago data set, the maximum NPL score shifted slightly toward the centromere. The NPL score was essentially identical with and without the U Chicago data set, unlike the MLS, which was reduced without the U Chicago data set. One possible explanation for this is that some of the more-positive samples included pedigrees with affected individuals other than the affected sibship, and these individuals would contribute to the NPL score but not to the MLS.

Logistic Regression Analyses

Table 6 shows the IBD sharing probabilities for the sample from each site and the results of the logistic regression analysis for heterogeneity among samples. Significant heterogeneity was observed for chromosome 6q and for chromosome 10p. Table 7 shows the results of logistic regression analyses of the significance of linkage, taking heterogeneity among samples into account. The results are expressed as LOD scores that are larger than are customarily observed for a given level of significance because of the number degrees of freedom (7 for the primary analysis, 6 with one sample omitted). Chromosome 6q produced evidence for linkage both with and without weighting of larger sibships and with or without the U Chicago sample. Chromosome 10p produced evidence for linkage when all possible pairs were considered (unweighted analysis); this evidence was slightly reduced without the NIMH SGI sample.

Dominant and Recessive LOD Scores

Dominant and recessive LOD scores for the entire sample are shown in table 8. A maximum LOD score of 2.47 was observed for chromosome 6q using a recessive model. No other region produced a LOD score >2.0 .

Power of Affected Sib-Pair Analyses

Details of power analyses are available on request. Power was generally well-predicted by the observed z_0 which is related to populationwide λ_{sibs} as described above. Power was excellent (≥ 0.85) for values of λ_{sibs} of ≥ 1.35 , and adequate (0.65–0.70) for λ_{sibs} equal to 1.3. Thus the present sample has adequate power to detect significant linkage of schizophrenia to a locus contributing to a 30%–35% increase in risk to siblings of affected individuals in the population as a whole. Rybicki and Elston (2000) have recently demonstrated that for multiplicative two-locus models, power may depend also on susceptibility-allele frequency and genotype relative risk (ratio of penetrances of the susceptibility and normal genotypes), and can be less than that predicted by λ_{sibs} alone.

Discussion

In a large collaborative sample, suggestive evidence in support of linkage to schizophrenia was observed on chromosome 6q. This evidence was consistent across a series of planned analyses (NPL and ASP analyses and logistic regression analysis of allele sharing in ASPs allowing for intersample heterogeneity), with or without the sample in which positive evidence for this region was first reported. This region is separated by ≥ 50 cM from the region on chromosome 6p in which evidence for linkage to schizophrenia has also been reported (Straub et al. 1995; Schwab et al. 1995; Moises et al. 1995; Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996), and all available evidence suggests that there is no overlap between these two candidate regions. The maximum evidence for linkage in different samples is distributed across a 20-cM region, with the U Chicago and U Wales data sets producing peaks at 115–117 cM and the other positive data sets clustering at 97–106 cM. The reason for this discrepancy is not known, but simulation studies suggest that, for complex disorders, the location estimates can vary by 10–30 cM across samples if each sample is not very large (Hauser and Boehnke 1997; Roberts et al. 1999). In secondary analyses, the most-positive evidence for linkage was observed under a recessive model; however, we would suggest caution in drawing conclusions about mode of inheritance from single-locus analyses of genetically complex disorders.

More modest support for linkage was observed on chromosome 10p, which was limited to evidence from the logistic regression analyses of significant intersample heterogeneity ($P < .001$) and excess allele sharing in ASPs allowing for intersample heterogeneity (segment-wise $P < .05$).

No statistically significant support for linkage was

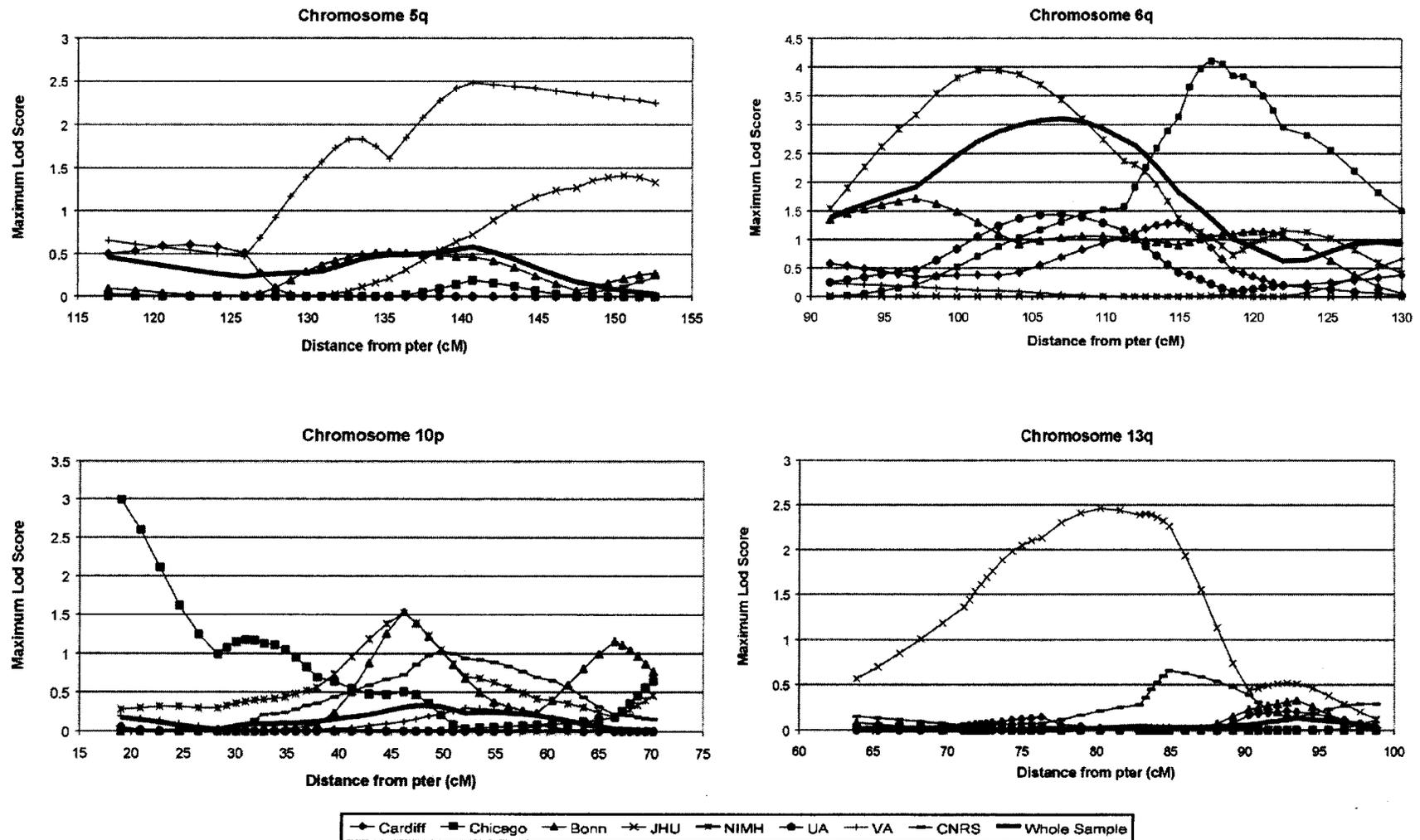


Figure 1 For each chromosomal region, maximum LOD score values are shown for each sample and for the combined sample, for multipoint ASP analysis using the possible-triangle method (GENEHUNTER 2.0).

Table 5**NPL Analysis**

A. Overall Results				
GROUP	NPL SCORE (LOCATION) FOR CHROMOSOMAL REGION			
	5q	6q	10p	13q
U Bonn	.09	2.11 (97.1 cM)	2.13 (46.2 cM)	.82
U Chicago	1.36	1.92 (118.6 cM)	2.24 (19.0 cM)	-.30
CNRS	.64	-.21	1.41 (37.9 cM)	.90
JHU	1.60	.14	-.34	3.18 (82.9 cM)
MCV/Ireland	2.44 (130.9 cM)	.67	1.09	-.06
NIMH SGI	.01	3.67 (104.1 cM)	2.39 (46.2 cM)	.32
US/Aust	-.43	1.32	.20	.01
U Wales	1.03	1.11	-1.11	.59
TOT NPL	.96	2.47 (104.1 cM)	1.01	.19
<i>P</i>	.152	.0046	.138	.408

B. Results When the Sample with the First Positive Report Is Omitted				
Result	MCV/Ireland	U Chicago	NIMH SGI	JHU
Total NPL Score	-.30	2.51 (104.1 cM)	.41	-.27
<i>P</i>		.0047		

NOTE.—Shown are NPL (Z_{all}) scores from multipoint nonparametric linkage analyses of each chromosomal region (GENEHUNTER 2.0) using all typed individuals in each pedigree, for each sample, for all samples combined, and for all samples omitting the sample in which positive findings in a region were first reported. *P* values are pointwise values as reported by GENEHUNTER. For NPL values with $P < .05$, the peak location is shown underlined.

observed in the other two regions studied. For a genetically complex disorder like schizophrenia, the a priori probability of detecting linkage cannot be determined, because the magnitude of the genetic effect at any one locus is unknown, and there may be undetected differences among samples—in diagnostic methods, ascertainment, or other factors—that could obscure evidence for linkage in a collaborative analysis. Thus, linkage cannot be disproved, and we can only conclude that the current analyses fail to add to the existing evidence for linkage on chromosomes 5q and 13q.

The most difficult methodological issue here is possible selection bias (the inclination of investigators to study regions in which they already have positive findings). For example, the largest schizophrenia multicenter analysis of marker D22S278 (Gill et al. 1996) was initiated by several groups with positive evidence at this marker. While suggestive evidence for linkage ($P \gg .001$ in some analyses) was observed in the entire data set, more modest evidence for linkage ($P \gg .05$) was observed in those samples in which this region had not been previously genotyped. The next large multicenter study (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6, and 8 1996) included all 11 groups from the earlier study, specifically to avoid selection bias, along with 3 new groups. Because positive evidence for linkage had initially been observed for each region in a single sample, the primary analyses could be repeated without that sample.

The issue of selection bias in the current study is more

complex. The major safeguard against bias here is that the investigators agreed to work together to study as many schizophrenia candidate regions as funding will permit, without prior knowledge of genome scan data for most of the samples and without first deciding which regions to study. Thus, over time, our studies should accurately reflect the evidence for linkage across a series of candidate regions in this particular large sample (although not necessarily reflecting other available samples). We are currently funded for three further studies of several regions each. Although a new genome scan of the entire sample would give the most complete information, the expense would be quite large, and such a study is not immediately feasible. As an alternative, and to supplement our direct studies of candidate regions, we are currently participating in an effort to apply a novel metaanalysis technique (Wise et al. 1999) to investigate evidence for linkage across all available schizophrenia genome scans.

One could question whether there is a bias inherent in selecting these regions *ahead* of others, in part on the basis of our own previous data. This could result in a premature enthusiasm for certain regions, when, in fact, our future candidate region or metaanalysis studies could produce more-positive results in other chromosomal regions. This issue is illustrated by the history of the chromosome 6q finding, which produced the most positive results reported here. Evidence for linkage was first observed in the U Chicago data set (Cao et al. 1997). Their strategy included replication in the NIMH

Table 6**Logistic Regression Analysis: IBD Probabilities and *P* Values for Intersample Heterogeneity**

A. Overall Results				
GROUP	IBD PROBABILITY FOR CHROMOSOME REGION			
	5q	6q	10p	13q
U Bonn	.52	.58	.59	.48
U Chicago	.48	.59	.54	.49
CNRS	.54	.43	.56	.54
JHU	.60	.49	.40	.64
MCV/Ireland	.61	.51	.52	.48
NIMH SGI	.43	.64	.59	.47
US/Aust	.46	.62	.44	.46
U Wales	.46	.54	.46	.47
Empirical <i>P</i>	.066	.0038	.0096	.183

B. Results When the Sample with the First Positive Report Is Omitted				
Result	MCV/Ireland	U Chicago	NIMH SGI	JHU
Empirical <i>P</i>	.40	.014	.029	.98

NOTE.—Shown are the estimated proportion of alleles shared identical by descent (IBD probabilities) in each sample, and the segment-wise *P* value for heterogeneity among samples in IBD probabilities, analyzed by logistic regression analysis (see text), for all samples and then omitting the sample in which positive evidence for linkage was first reported. *P* values are based on simulation of 20,000 replicates using the actual sample and map.

SGI data set, which was even more strongly positive (Cao et al. 1997), and in the US/Aust data set (Levinson et al. 1998) which was weakly positive (Martinez et al. 1999). All three data sets had already been included in the present consortium. The present investigators met in February 1998 to plan the present study, selecting those chromosomal regions with the most significant reported nominal *P* values among regions not yet subjected to multicenter study. The overall magnitude of the results in the U Chicago, NIMH, and US/Australia samples convinced us that a large multicenter analysis was justified, with a sample approximately three times larger than these three combined. But, by this time, complete or partial genome scan data were also available for the U Wales, MCV/Ireland, JHU, and U Bonn projects, none of which had observed highly positive evidence for linkage on chromosome 6q.

Given this sequence of events, we conclude that there is no bias in the present results, given that the sample was constituted without prior knowledge of the regions to be studied or the prior results in these regions. There may be some bias in selecting these regions *before* other regions, but the only valid correction for this will be to study all candidate regions or the entire genome. We have included one set of secondary analyses that excludes the first sample in which highly positive results were reported in that region, which at least gives some

indication of the evidence for linkage in the rest of the sample. Further “correction” would serve little purpose: if we excluded all samples for which we had some information prior to the present study, we would have only one sample (CNRS) left.

We would suggest that relative, rather than absolute, magnitude of evidence for linkage be given most weight in interpreting evidence from this and similar studies. It is not practical in a large multicenter study to take all steps to maximize evidence for linkage. For example, the JHU group observed a much higher maximum NPL score of 4.18 in their sample using additional markers to form a denser map (Blouin et al. 1998), compared with a maximum score of 3.18 when their sample was analyzed here using a 5-cM map density, which was felt to represent a reasonable balance between power and efficiency. Similarly, substantial but more modest evidence for linkage on chromosome 10p was observed here in the NIMH SGI sample, with the white and black families combined and with a different map, than was the case in the published reports for the white pedigrees from that data set (Faraone et al. 1998).

In conclusion, we have reported additional evidence in support of linkage to schizophrenia on chromosome 6q and more modest evidence in support of linkage on chromosome 10p. Multicenter analyses may be one useful factor in guiding the efforts of the field in the search for schizophrenia susceptibility genes.

Online Databases

A review of available evidence for schizophrenia loci is found in Online Mendelian Inheritance in Man as SCZD

Table 7**Logistic Regression Analysis: LOD Scores for Linkage, Allowing for Intersample Heterogeneity**

A. Overall Results				
	SCORES FOR CHROMOSOMAL REGION			
	5q	6q	10p	13q
Unweighted:	2.79	7.14	3.41	2.53
Location	152.6	105.5	46.2	84.9
Empirical <i>P</i> ^a	.091	<.0002	.045	.114
Weighted:	2.29	5.48	2.63	2.50
Location	152.6	105.5	46.2	76.2
Empirical <i>P</i> ^a	.098	.0002	.068	.061

B. Results When the Sample with the First Positive Report Is Omitted				
	MCV/Ireland	U Chicago	NIMH SGI	JHU
Unweighted:	1.11	6.08	2.55	.29
Location	152.6	105.5	19.0	84.9
Empirical <i>P</i> ^a	.37	.0004	.074	.90

^a On the basis of 20,000 replicates.

Table 8**Dominant and Recessive LOD Scores**

CHROMOSOME	DOMINANT			RECESSIVE		
	HLOD	α^a	Location (cM)	HLOD	α^a	Location (cM)
5q	.92	.08	135.0	.48	.40	140.7
6q	.68	.08	104.1	2.47	.12	101.3
10p	1.17	.08	46.2	.83	.05	52.1
13q	.66	.06	73.0	.16	.03	93.5

^a α = Maximum-likelihood proportion of linked families.

[MIM 18150]. The chromosome 13q locus studied in this article is listed as SCZD7 [MIM 603176], and the chromosome 6q locus studied here is listed as SCZD5 [MIM 603175]. There is no accession number for the chromosome 10p locus listed here. For chromosome 5q, the region described as SCZD1 [MIM 181510] is considerably proximal to the region studied here, which does not have an OMIM accession number.

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Appendix A

Statistical Analysis Plan

- A. Planned (primary) analyses
 1. Whole sample (pooled)
 - a. ASP analysis (GH 2.0), unweighted, empirical *P*
 - b. NPL analysis
 2. Logistic regression of ASP sharing proportions (*q*) with sample as covariate
 - a. Test for heterogeneity (allows different value for *q* for each sample)
 - b. Empirical *P* value (5,000–20,000 replicates)
- B. Additional (secondary) analyses
 1. Logistic regression of ASP sharing proportions
 - a. Test for overall significance of linkage allowing for heterogeneity (set *q* = .5 if actual *q* < .5)
 - b. Empirical *P* value
 2. Multipoint parametric analyses using dominant and recessive affected-only models

Appendix B

Logistic Regression Analysis

Rice's logistic regression method (Dorr et al. 1997; Rice 1997) was used to determine, for ASPs, the effect of site as a covariate in determining allele sharing, and the overall significance of allele sharing when site effects are taken into account. The method is as follows: consider a random variable *S* defined on sib pairs, where *S* = 1 if that pair inherits a marker allele IBD from a

particular parent and $S = 0$ if the allele inherited by the pair from that parent is not IBD. Assume that S has a logistic regression on a set of covariates X_1, \dots, X_n ; that is,

$$\log\left(\frac{ps}{1-ps}\right) = \alpha + \beta_1 X_1 + \dots + \beta_n X_n,$$

where ps is the probability of sharing. Note that if $\alpha = \beta_1 = \dots = \beta_n = 0$, then $ps = 1/2$ for all covariate values; this corresponds to the null hypothesis of no linkage. For each pair, the probability of sharing 0, 1, or 2 alleles IBD may be written in terms of the parent-specific IBD probabilities ps_1, ps_2 as follows, assuming that the probabilities of inheriting an allele IBD from each parent are independent: $\Pr(0 \text{ ibd}) = (1-ps_1)(1-ps_2)$, $\Pr(1 \text{ ibd}) = ps_1(1-ps_2) + ps_2(1-ps_1)$, $\Pr(2 \text{ ibd}) = ps_1 ps_2$.

Multipoint likelihoods can thus be calculated, and hypotheses regarding the parameters $\alpha, \beta_1, \dots, \beta_n$ can be tested. For example, if only ASPs are analyzed, the alternative hypothesis of overall linkage corresponds to $\alpha > 0$. The main advantage of this method for the analysis of multicenter data is that it enables differences between centers to be modeled and tested systematically, as noted by Rice (1997).

Electronic-Database Information

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

Marshfield genetic maps, <http://www.marshmed.org/genetics/> (for marker locations)

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for review of available evidence for schizophrenia loci [MIM 18150], the chromosome 13q locus studied in this article [as "SCZD7"] [MIM 603176], and the chromosome 6q locus studied here [as "SCZD5"] [MIM 603175])

Southampton genetic map, http://cedar.genetics.soton.ac.uk/public_html/ldb.html (for locations of D5S818, D10S1423, and D13S797)

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