American Journal of Medical Genetics (Neuropsychiatric Genetics) 105:375–380 (2001)

Fine Mapping Supports Previous Linkage Evidence for a Bipolar Disorder Susceptibility Locus on 13q32

Chunyu Liu,[1,2]* Judith A. Badner,[1] Susan L. Christian,[1] Juliet J. Guroff,[3] Sevilla D. Detera-Wadleigh,[3] and Elliot S. Gershon[1]

[1]*Department of Psychiatry, University of Chicago, Chicago, Illinois*
[2]*National Laboratory of Medical Genetics, Hunan Medical University, Changsha, Hunan, China*
[3]*National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland*

A region between D13S71 and D13S274 on 13q32 showed linkage to bipolar disorder (BP) based on a genome scan using markers with an average spacing of ~6 cM and an average heterozygosity of ~60% [Detera-Wadleigh et al., 1999: Proc Natl Acad Sci USA 96:5604–5609]. In an attempt to confirm this finding and achieve fine mapping of the susceptibility region, nine additional microsatellite markers with average heterozygosity of ~86%, located between D13S71 and D13S274, were typed in the same sample. The strongest linkage evidence was detected by multipoint linkage analysis (ASPEX program) around D13S779–D13S225 with maximum LOD score of 3.25 under Affection Status Model II (ASM II; $P = 0.0000546$). Data from additional nine markers resulted in a decrease of the 95% confidence interval of the linkage region. Association analyses with GASSOC TDT and ASPEX/sib_tdt detect potential linkage disequilibrium with several markers, including D13S280 (ASPEX TDT $P = 0.0033$, ASM I). These data generated using a higher marker density within the proposed susceptibility region strengthen the validity of our previous findings and suggest a finer localization of the susceptibility gene(s) on 13q32.

KEY WORDS: bipolar disorder; linkage; association; 13q; map

INTRODUCTION

Bipolar disorder (BP) is a severe mood disorder with underlying genetic factors. The region between D13S71 and D13S274 on 13q32 showed linkage to BP based on a whole genome scan, with an average marker spacing of ~6 cM and an average heterozygosity of ~60% on 13q32 [Detera-Wadleigh et al., 1999]. A slight excess allele sharing in this region in the 97 bipolar pedigrees of the National Institute of Mental Health Genetics Initiative has also been reported [Stine et al., 1997]. Kelsoe et al. [2001] reported three markers, D13S154, D13S225, and D13S796, in this region with LOD scores greater than 2.0 in the genome scan studies of bipolar disorder. In schizophrenia, evidence for a susceptibility gene has been presented and replicated in the same region [Blouin et al., 1998; Brzustowicz et al., 1999]. In order to confirm the linkage and perform fine mapping of the candidate region on 13q32, nine additional microsatellite markers were typed in the same pedigrees studied by Detera-Wadleigh et al. [1999].

MATERIALS AND METHODS

The pedigrees analyzed in this study included 371 individuals from 22 multiplex pedigrees. They have been described in detail elsewhere [Berrettini et al., 1991; Detera-Wadleigh et al., 1999]. All probands in the pedigrees are of Caucasian ancestry, including the right branch of the Old-Order Amish pedigree [Kelsoe et al., 1989] and three Ashkenazi Jewish families. Two models of the affected phenotype were used in linkage analysis: Affection Status Model I (ASM I) that includes bipolar I, bipolar II with major depression, and schizoaffective disorder; and Affection Status Model II (ASM II) that includes ASM I and is broadened to include persons with two or more episodes of major depression with impairment. Two CEPH individuals were included as controls for genotyping.

Nine markers (Table I) located between D13S71 and D13S274 with average heterozygosity of ~ 86% were selected. Combined with the markers previously typed in this region, the intermarker distances range from 0 to 3 cM with an average spacing of 0.9 cM. Primers for the nine microsatellite markers were redesigned based on their Genbank sequences to make them fit into two electrophoresis panels (Table I). All primers were synthesized by Genosys Biotechnologies (Woodlands,

*Correspondence to: Chunyu Liu, R022, BSLC, 924 E. 57th Street, Chicago, IL 60637. E-mail: cliu@yoda.bsd.uchicago.edu

Received 18 August 2000; Accepted 01 March 2001
Published online 30 April 2001

TABLE I. Nine Markers on 13q32 Used in This Study

Marker name	Heterozygosity[a]	Label	Product length (bp)	Primer sequences (5′ to 3′)[b]	Electrophoresis panel[c]
D13S154	0.93	FAM	241–276	GTGCTATAAAGGCTTGCTGC (f) CTCTTGCCCTGGTCTTFACT (r)	1
D13S1240	0.82	FAM	103–120	CGACCCTAACTCTGGAGAAG (f) GGGAGAGGCCATAAGAAAA (r)	1
D13S225	0.84	FAM	169–187	CCAAGAGTTCAAGACCAGCC (f) AAATGGGGGTAGGATGTGG (r)	1
D13S280	0.87	TET	277–303	CGGAGGAGCGTATGACATC (f) ACTAGGAACAAGTTACCCCAAT (r)	1
D13S159	0.93	TET	167–202	AGGCTGTGACTTTTAGGCCA (f) CCAGGCCACTTTTGATCTGT (r)	1
D13S158	0.82	TET	84–104	CACGGAGTGAAAGAAGATTGA (f) TGACAATTTAGCAGCATGTATTT(r)	2
D13S1241	0.93	HEX	280–304	ATAATTGTAATGGCCTTCC (f) CTCCAGTTGAGTTTGGACC (r)	2
D13S786	0.80	HEX	184–212	ATACTCCGAGCTATCTGTCTACC(f) GGTGCAGATCATGACCTCTC (r)	2
D13S122	0.82	HEX	92–118	TGGAAACCACCACTCTACTT (f) TGTGAACCTAGACTGGAATAAA (r)	2

[a]Heterozygosity is the observed value calculated by MEGA2 in the pedigrees.
[b]f = forward; r = reverse.
[c]Markers of the same panel can be pooled and analyzed in one ABI377 run.

TX). Optimization trials allowed four groups of multiplexed PCR with utilization of both hot-start and touchdown PCR. Each PCR amplification was performed with 50 ng genomic DNA in 10 μl reaction volume: amplification group 1.1 (D13S154, D13S1240, D13S225) and group 1.2 (D13S280, D13S159) used the reaction consisting of 1 × buffer, 2.75 mM Mg^{++}, 175 μM dNTP, 0.25 U AmpliTaq Gold polymerase (PE Biosystems, CA), and 0.35–0.5 μM of each relevant set of primer. PCR cycling conditions were as follows: 95°C for 12 min to activate the polymerase, followed by 10 cycles of 95°C for 25 sec, 63°C for 30 sec, 72°C for 50 sec, 30 cycles of 95°C for 25 sec, 58°C for 30 sec, 72°C for 50 sec, and final extension at 72°C for 5 min; amplification group 2.1 (D13S158) and group 2.2 (D13S1241, D13S122 and D13S786) used a less stringent reaction condition with a mixture consisting of 1 × buffer, 4 mM Mg^{++}, 175 μM dNTP, 0.25 U AmpliTaq Gold polymerase, and 0.35–0.5 μM of each relevant primer set. The annealing temperatures of both 10 and 30 cycles of the above profile were decreased to 53°C and 50°C, respectively, with the extension temperature down to 68°C.

The PCR products of the same sample from the same electrophoresis panel (Table I) were pooled with TAMRA-350 size standard (PE Biosystems) and deionized formamide and run on an ABI 377 sequencer (PE Biosystems). GENESCAN and GENOTYPER (PE Biosystems) programs were used to collect data and size all the fragments. Two CEPH samples were genotyped on every gel with other samples. The size differences between gels were mostly within the range of ± 0.4 bp, which were not beyond most of the minimum differences of 0.7 bp between allele classes. Therefore, no

TABLE II. Map Data of the Markers Used in the Study

Markers		Marshfield (sex-average, cM)	Map used (cM)
Previously typed	Typed in this article		
	D13S122	73.04	73
D13S71		73.04	73
	D13S154	75.19	75
	D13S1241	76.26	75
	D13S786	76.80	77
D13S793			77
D13S1252		77.47	78
	D13S159	79.49	80
D13S1271		79.49	80
	D13S1240	81.64	82
D13S779		82.93	83
	D13S225	83.57	84
D13S1266		84.87	85
	D13S280	85.41	85
	D13S158	84.87	86
D13S274		87.03	87

adjustment was made for the different gels. All genotype data, which could not be coded by the defined allele classes, were regenotyped to get the correct allele size. Simwalk2 [Sobel and Lange, 1996], ASPEX (ftp://lahmed.stanford.edu/pub/aspex), and GeneHunter checking for unlikely recombination and double recombination were used to pick up genotyping errors. For correcting genotyping errors, several closely related individuals from the same pedigree would be retyped at the same time as control.

To order the markers used, amplification on the BAC clones chosen from BAC contigs constructed by S. Christian (data not shown), CRIMAP calculation, and RH mapping on TNG3 panel (Research Genetics, AL) were carried out.

MEGA2 was used to calculate the heterozygosity for the markers in our sample (http://watson.hgen.pitt.edu/docs/mega2_html/). ASPEX was used for nonparametric multipoint and single-point linkage analysis. GeneHunter Plus was used to perform single-point and multipoint linkage analysis for both pedigree and pedigree broken into nuclear family [Kong and Cox, 1997]. GeneHunter Plus was also used to perform parametric analysis. To perform association analysis, both GASSOC [Schaid, 1996], which tests for linkage in the presence of association, and ASPEX/sib_tdt (sibling transmission disequilibrium test), which tests for linkage disequilibrium in sibships controlling for evidence of linkage, were used. The results from ASPEX/sib_tdt demonstrate association only if one sibship/pedigree is used. However, due to our small sample size (22 independent sibships), it may be difficult to separate the true signal from the noise. We hypothesized that a true association would also give a significant result when all sibships are studied under ASPEX/sib_tdt and when GASSOC is used. However, when a marker is significant only for the latter two analyses, this may be evidence of linkage and not linkage disequilibrium. Therefore, we present a three-stage analysis. First, all markers are tested with GASSOC TDT analysis. Second, markers that give nominally significant GASSOC results are tested with ASPEX/sib_tdt in all sibships. Third, markers that give nominally significant results for ASPEX/sib_tdt in all sibships are tested with ASPEX/sib_tdt in independent sibships.

When there were multiple sibships in a pedigree, the independent sibships were selected for showing evidence for linkage. For the ASPEX/sib_tdt analysis, this should not create a bias as the effects of linkage on allele transmission are controlled for. For the one sibship per pedigree analysis, since there is the same number of independent sibships under ASM I and ASM II, the results under the two affection status models were not expected to vary meaningfully and thus the analysis was performed only for ASM I.

RESULTS AND DISCUSSION

Amplifications on isolated BAC clones mapping to 13q32 were attempted using all 16 markers in this region, including the 7 markers typed previously (D13S71, D13S793, D13S779, D13S1252, D13S1271, D13S1266, D13S274). Positive amplifications were displayed by 13 of the 16 markers, confirming their physical locations. CRIMAP and RH mapping resolved several of the remaining problems, but the relative order between D13S1241 and D13S154 and between D13S786 and D13S793, respectively, could not be definitively established. Therefore, D13S1241 and

TABLE III. Nonparametric Single-Point Linkage Analyses of BP on 13q32*

	GHP				GHPNuc				ASPEX			
	ASM I		ASM II		ASM I		ASM II		ASM I		ASM II	
Markers[a]	LOD	*P* value	LOD	*P* value	LOD	*P* value	LOD	*P* value	LOD	*P* value	LOD	*P* value
D13S122	0.17	0.19	0.05	0.32	0.20	0.17	0.39	0.089	0.18	0.18	0.12	0.23
D13S71	0.00	0.50	0.29	0.12	0.40	0.087	0.80	0.027	0.10	0.25	0.2	0.17
D13S154	0.39	0.09	0.36	0.098	0.40	0.087	0.79	0.028	0.86	0.023	0.84	0.025
D13S1241	0.33	0.11	0.27	0.13	0.71	0.035	1.16	0.010	0.77	0.030	0.52	0.061
D13S793	0.72	0.034	1.04	0.0014	0.72	0.034	1.18	0.0098	1.29	0.0074	1.6	0.0033
D13S786	0.15	0.20	0.06	0.29	0.28	0.13	0.70	0.036	0.80	0.027	0.87	0.023
D13S1252	0.55	0.056	0.72	0.034	1.51	0.0041	1.85	0.0017	2.31	0.00055	2.58	0.00028
D13S159	0.24	0.14	0.24	0.15	0.92	0.020	1.42	0.0053	1.49	0.0044	1.61	0.0032
D13S1271	1.84	0.0018	1.80	0.0020	2.48	0.00036	2.67	0.00023	2.70	0.00021	2.54	0.00031
D13S1240	0.05	0.31	0.48	0.069	1.06	0.013	1.90	0.0015	0.53	0.059	0.73	0.033
D13S779	0.75	0.032	0.28	0.13	1.03	0.0015	0.86	0.023	1.36	0.00062	0.95	0.018
D13S225	0.34	0.10	0.04	0.34	0.79	0.028	0.70	0.37	1.52	0.0041	1	0.016
D13S1266	0.27	0.13	0.05	0.31	0.43	0.080	0.10	0.25	0.48	0.069	0	0.5
D13S280	0.24	0.15	0.05	0.32	0.71	0.036	0.78	0.029	0.60	0.048	0.12	0.23
D13S158	0.19	0.18	0.04	0.33	0.13	0.22	0.54	0.057	0.17	0.019	0.09	0.26
D13S274	0.01	0.40	0.00	0.52	0.19	0.18	0.69	0.037	0.16	0.20	0.18	0.18

*The affection status models (ASM I and ASM II) are defined in the text. GHP: Genehunter Plus; GHPNuc: nuclear family-based GHP analysis.
[a]The nine additional markers typed in this study are underlined. The others were typed by Detera-Wadleigh et al. [1999]. The markers are listed according to their map order on 13q32, from proximal to distal.

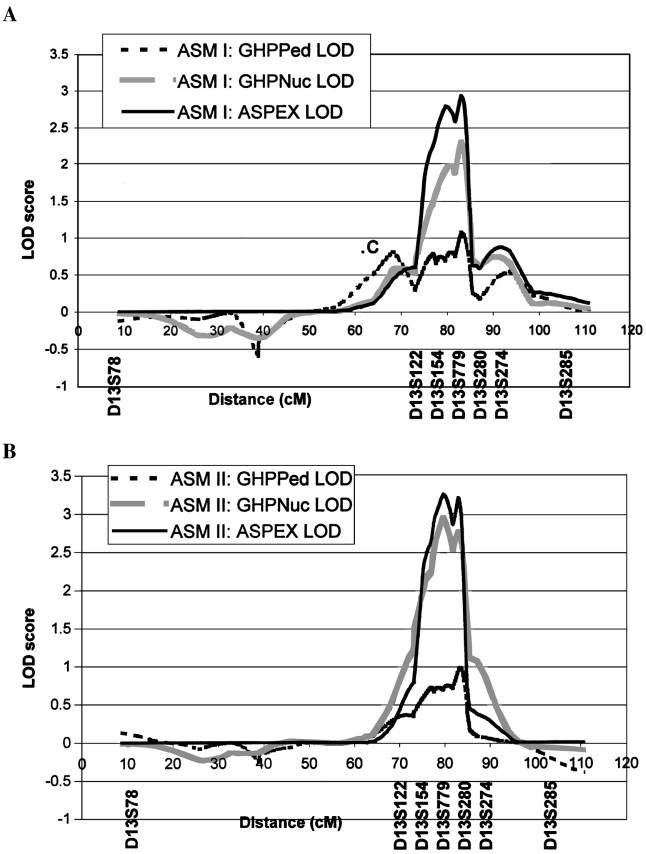

Fig. 1. Multipoint nonparametric analysis on chromosome 13 by GeneHunter Plus (GHP) and ASPEX. **A:** Under affected phenotype model ASM I. **B:** Under affected phenotype model ASM II. The affection status models (ASM I and ASM II) are defined in the text. GHP analyses include GHPPed, which used GHP pedigree analysis; GHPNuc used GHP with pedigrees separated into nuclear families.

D13S786 were used in the single-point analysis but excluded in the multipoint analyses. The genetic distances between markers were taken from the Marshfield maps with minor corrections according to our CRIMAP, RH mapping, and physical map data. (Table II).

Single-point linkage analysis localized the peak LOD score of 2.70 ($P = 0.00021$) at D13S1271 and seven other flanking markers showed LOD > 1.0 in affected sibling pair (ASP) analysis (Table III). The strongest linkage evidence was detected by multipoint linkage analysis with ASPEX, around D13S779–D13S225 with a maximum LOD score of 3.25 under ASM II ($P = 0.0000546$; Fig. 1B). This value exceeds the suggestive linkage criterion proposed by Lander and Kruglyak [1995], although this is not corrected for multiple analyses and affection status models. Nuclear family-based GeneHunter Plus (GHPNuc) revealed the peak LOD score of 2.94 ($P = 0.000117$) at the same location under the same phenotypic model (ASM II; Fig 1B). Nuclear family-based GeneHunter Plus and ASPEX detected much stronger linkage signals than pedigree-based GeneHunter Plus analysis. Simulations (not shown) suggest that these divergent results may be caused by either a common susceptibility allele that has a much lower penetrance in heterozygotes than in homozygotes (multiplicative allelic model) or by a rare recessive gene with significant intrapedigree heterogeneity. Parametric analysis revealed that our data are more consistent with a recessive model than a dominant model (data not shown). Other possible genetic models have not been studied, therefore the exact mode of transmission is still uncertain.

The region with a 95% confidence limit for the location of the susceptibility gene is determined according to the equation of Kruglyak and Lander [1995], using the peak IBD score from ASPEX under ASM I. This region was bounded by D13S122 and D13S280, i.e., from 73.0 to 85.2 cM, yielding a decrease of $\sim$2 cM compared to the previous results that showed a $\sim$14 cM candidate region between D13S122 and D13S274.

Compatibility of the new and old marker data set was tested to determine whether the new markers alone could detect evidence of linkage; analysis using only the eight additional markers was carried out (D13S1241 was excluded for its order problem with D13S154). This analysis yielded a maximum LOD score in the region spanned by D13S159 and D13S1240 (D13S225, ASM I LOD $= 2.95$, $P = 0.00011$; D13S159–D13S1240, ASM II LOD $= 2.31$, $P = 0.00055$). The linkage signals were detectable for any marker around this region. Combining the two sets of marker data into one high-density map did not change the LOD score appreciably (ASPEX LOD score, ASM II, from 3.3 to 3.25). The location of the linkage peak shifted slightly toward the distal end by$<$2 cM, i.e., from the D13S1271 and D13S779 region to the D13S779 and D13S225 region (Table II).

Sex-specific linkage analysis, looking at paternal and maternal LOD scores and using sex-specific recombination, was also performed. Both paternal and maternal allele sharing gave similar contribution to the linkage except for one pedigree, family 1442, in which eight affected siblings shared the maternal allele. Therefore, imprinting was not supported in this data set.

TDT analysis with GASSOC detected weak signals with several markers, including D13S274 (ASM I, $P = 0.0034$), D13S280 (ASM II, $P = 0.0011$), and D13S154 (ASM I, $P = 0.043$). ASPEX TDT analysis including all sibships revealed signals at markers D13S280 (ASM I, $P = 0.024$) and D13S154 (ASM I, $P = 0.014$). ASPEX/sib_tdt analysis using one sibship per pedigree was done to determine linkage-independent P values on markers significant under all sibships. Under this test in ASM I, D13S154 ($P = 0.033$) and D13S280 ($P = 0.0033$) gave signals. But after Bonferroni correction for the 16 markers tested, only D13S280 would give the P value ≤ 0.05. Two markers showed nominally significant values for all three associations tests: D13S154 and D13S280 (Table IV). Simulations have shown that when all three association tests are required to be nominally significant, the power is equivalent to requiring only that the one sibship/pedigree test be significant. However, when there is no linkage disequilibrium but there is linkage, the probability of observing a P value of 0.05 in the one

TABLE IV. *P* values of Association Analyses of BP With Markers on 13q32*

	ASM I			ASM II	
		ASPEX/Sib_tdt			ASPEX/Sib_tdt
Marker	GTDT	All Sibships	One Sibships	GTDT	All Sibships
D13S122	0.47			0.35	
D13S71	0.98			0.98	
D13S154	0.043	0.014	0.033	0.13	
D13S1241	0.59			0.23	
D13S793	0.81			0.71	
D13S786	0.057			0.25	
D13S1252	0.89			0.90	
D13S159	0.39			0.15	
D13S1271	0.22			0.27	
D13S1240	0.33			0.23	
D13S779	0.66			0.71	
D13S225	0.66			0.38	
D13S1266	0.22			0.12	
D13S280	0.017	0.024	0.0033	0.0011	0.0011
D13S158	0.70			0.79	
D13S274	0.0034	0.051		0.02	0.067

*The affection status models (ASM I and ASM II) are defined in the text. GTDT: GASSOC TDT analysis. ASPEX analyses performed on all siblings only if GTDT *P* value < 0.05. ASPEX analyses performed on one sibship/pedigree only if *P* value < 0.05 in all sibships test.

sibship/pedigree test when the other two tests are also nominally significant is approximately 0.01 (data not shown). It is difficult to know what type of correction for multiple testing to apply to these results. A genome-wide correction would make it difficult to detect any loci due to loss of power from very stringent criteria. We did test 30 markers on chromosome 13, including 14 markers typed previously out of the linkage region [Detera-Wadleigh et al., 1999], although only a significant result in 1 of the 16 markers in the linkage region would have been of interest. When the number of markers tested is taken into account, D13S280 remains significant (given the conservative nature of this test). The transmitted versus non-transmitted alleles of D13S280 were analyzed (Table V). No single allele was found to be responsible for the association, although several alleles, including 295 bp and 283 bp alleles, were nonrandomly transmitted. Because of the small size of the sample, we do not view this as conclusive evidence of linkage disequilibrium, but rather as a guide for further investigation and as a hypothesis for others to test.

In summary, linkage results of fine mapping in this study provided supportive evidence of linkage of BP on 13q32. The linkage data and association signals presented here suggested two interesting subregions for locating the susceptibility gene(s): the linkage LOD score peak region around marker D13S779–D13S225

TABLE V. Transmitted and Non-transmitted Alleles of D13S280

		All affected individuals				One affected individual per family [a]	
		ASM I		ASM II		ASM I	
Allele size (bp)	Allele code	T	NT	T	NT	T	NT
303	1	1	2	1	2	0	1
301	2	0	1	0	1	0	0
299	3	32	22	40	30	12	2
297	4	20	17	25	24	7	5
295	5	0	7	1	10	0	3
293	6	4	11	10	17	1	3
291	7	4	15	11	21	3	6
289	8	26	11	31	16	5	5
287	9	17	15	26	21	7	4
285	10	15	11	18	16	4	6
283	11	1	8	4	8	0	4
281	12	2	1	2	3	0	0
279	13	0	0	0	0	0	0
277	14	1	2	2	2	1	1

[a]Arbitrarily selected.

and the region around the most consistent association signal D13S280. The sequencing of the human genome that would help provide a high-density marker map and the identity of candidate genes in these regions should facilitate the discovery of susceptibility variants for bipolar disorder and schizophrenia.

ACKNOWLEDGMENTS

We thank Drs. Pablo V. Gejman, Alan R. Sanders, and Francis J. McMahon for providing equipment and helpful discussion. We are also grateful to Kemba Kelly and Vivian Vlamakis for their assistance in sample and instrument management. This work is supported by Distinguished Investigator Grant from National Alliance for Research in Schizophrenia and Affective Disorders (to E.S.G.).

REFERENCES

Berrettini WH, Goldin LR, Martinez MM, Maxwell ME, Smith AL, Guroff JJ, Kazuba DM, Nurnberger JI Jr, Hamovit J, Simmons-Alling S, Muniec D, Choi H, York C, Robb AS, Gershon ES. 1991. A bipolar pedigree series for genomic mapping of disease genes: diagnostic and analytic considerations. Psychiatr Genet 2:125–160.

Blouin JL, Dombroski BA, Nath SK, Lasseter VK, Wolyniec PS, Nestadt G, Thornquist M, Ullrich G, McGrath J, Kasch L, Lamacz M, Thomas MG, Gehrig C, Radhakrishna U, Snyder SE, Balk KG, Neufeld K, Swartz KL, DeMarchi N, Papadimitriou GN, Dikeos DG, Stefanis CN. 1998. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat Genet 20:70–73.

Brzustowicz LM, Honer WG, Chow EW, Little D, Hogan J, Hodgkinson K, Bassett AS. 1999. Linkage of familial schizophrenia to chromosome 13q32. Am J Hum Genet 65:1096–1103.

Detera-Wadleigh SD, Badner JA, Berrettini WH, Yoshikawa T, Goldin LR, Turner G, Rollins DY, Moses T, Sanders AR, Karkera JD, Esterling LE, Zeng J, Ferraro TN, Guroff JJ, Kazuba D, Maxwell ME, Nurnberger JI Jr, Gershon ES. 1999. A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. Proc Natl Acad Sci USA 96:5604–5609.

Kelsoe JR, Ginns EI, Egeland JA, Gerhard DS, Goldstein AM, Bale SJ, Pauls DL, Long RT, Kidd KK, Conte G, Housman DE, Paul SM. 1989. Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. Nature 342:238–243.

Kelsoe JR, Spence MA, Loetscher E, Foguet M, Sadovnick AD, Remick RA, Flodman P, Khristich J, Mroczkowski-Parker Z, Brown JL, Masser D, Ungerleider S, Rapaport MH, Wishart WL, Luebbert H. 2001. A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22. Proc Natl Acad Sci USA 98:585–590.

Kong A, Cox NJ. 1997. Allele-sharing models: LOD scores and accurate linkage tests. Am J Hum Genet 61:1179–1188.

Kruglyak L, Lander ES. 1995. High-resolution genetic mapping of complex traits. Am J Hum Genet 56:1212–1223.

Lander E, Kruglyak L. 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247.

Schaid DJ. 1996. General score tests for associations of genetic markers with disease using cases and their parents. Genet Epidemiol 13:423–449.

Sobel E, Lange K. 1996. Descent graphs in pedigree analysis: applications to haplotyping, location scores, and marker-sharing statistics. Am J Hum Genet 58:1323–1337.

Stine OC, McMahon FJ, Chen L, Xu J, Meyers DA, MacKinnon DF, Simpson S, McInnis MG, Rice JP, Goate A, Reich T, Edenberg HJ, Foroud T, Nurnberger JI Jr, Detera-Wadleigh SD, Goldin LR, Guroff J, Gershon ES, Blehar MC, DePaulo JR. 1997. Initial genome screen for Bipolar disorder in the NIMH genetics initiative pedigrees: chromosomes 2, 11, 13, 14, and X. Am J Med Genet 74:263–269.