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Further evidence for linkage of bipolar disorder to chromosomes 6 and 17 in a new independent pedigree series

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Abstract

Objectives—We have previously reported the results of a linkage analysis of bipolar disorder in an initial set of 20 pedigrees ascertained through collaboration among three sites. We now report the results of our genomewide linkage analysis in an independent sample of 34 pedigrees segregating bipolar disorder.

Methods—Families were ascertained through a bipolar I or II disorder proband for the presence of bipolar I disorder, bipolar II disorder, or recurrent major depression in at least two other family members. A total of 440 markers at an average spacing of 8 cM were genotyped in 229 family members using fluorescent methods.

Results—Initial nonparametric analyses of chromosomes 6 and 17 provided evidence for a modest replication of linkage to these chromosomes previously reported in other studies. Additional analyses using multipoint parametric methods provided further evidence to support the 6q25 region with a heterogeneity LOD score of 3.28. Evidence from two-point parametric analyses also provides a modest replication of our previous findings of linkage to the 23 cM

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region of chromosome 22q13 in our original University of California, San Diego sample of 20 families and 57 families from the National Institute of Mental Health bipolar disorder sample.

Conclusions—Our results suggest replication of some reported linkage peaks, such as 6q25 and 17p12; however, other peaks from our own previous study, such as 5p15, 13q32, and 22q13, were either not replicated or were only modestly replicated in these analyses.

Keywords

bipolar disorder; genetics; genomewide; linkage; mood disorder

Bipolar affective disorder (BD) is a severe mood disorder that affects approximately 1% of the population and is characterized by episodes of major depression interspersed with periods of mania (bipolar I disorder) or hypomania (bipolar II disorder) (1). Mania is accompanied by euphoria, grandiosity, increased energy, decreased need for sleep, rapid speech, and risk taking. Depression is associated with low mood, low energy and motivation, insomnia, and feelings of failure, worthlessness, and hopelessness. Psychosis can occur in either state, and there is a 17% lifetime risk for suicide in BD. Although the etiology is currently unknown, epidemiological data including family, twin, and adoption studies, have suggested that BD is familial with a substantial genetic component and an estimated heritability > 80% (2, 3). Family studies indicate an approximate 7-fold increase in risk to first-degree relatives of bipolar probands, and twin studies find an average 4-fold increase in risk to monozygotic versus dizygotic twins (4).

Despite the apparent role of genetics in BD, factors such as environmental influences, genetic heterogeneity, and epistatic interactions have made the identification of causal genes difficult, and the mode of genetic transmission remains unclear. Although some studies have supported the presence of autosomal dominant major loci (5, 6), it has also been argued that BD is oligogenic with multiple loci of modest effect. Linkage studies have revealed a variety of chromosomal regions that may harbor susceptibility loci, including regions on 4q, 10p, 12q, 13q, 16p, 18p, 21q, 22q, and Xq (7). Our previous linkage analysis of 20 extended pedigrees for BD susceptibility revealed strong evidence of linkage to chromosome 22q11, as well as suggestive evidence for linkage to chromosomes 3p21, 3q27, 5p15, 10q, 13q31-q34, 21q22, and 22q11 (8–10). We now report the results of a further genomewide linkage scan for BD in an independent sample of 34 pedigrees. Evidence for linkage to chromosome 13 in a subset of this sample has previously been published (11).

Materials and methods

Family ascertainment

Families were ascertained from the general North American population through both a systematic survey of clinical facilities, and through advertising and patient support groups from three sites: (i) San Diego, CA, USA; (ii) Vancouver, BC, Canada; and (iii) Cincinnati, OH, USA. Families were ascertained through a proband with bipolar disorder I or II and included if at least two additional members had either BD or recurrent major depressive disorder (MDD). We purposely chose broad criteria for ascertainment to better reflect families with BD in the population. Following informed consent procedures approved by the local institutional review boards (IRB) of the collaborative sites, the proband and all participating family members were interviewed directly using the Structured Clinical Interview for DSM-III-R (SCID) (12). Bipolar II disorder was diagnosed as bipolar disorder not otherwise specified, modified so as to require a minimum duration of two days for hypomania. Information regarding each family member was obtained from other family informants. Medical records were obtained where available, and all information was

reviewed along with the interview by a panel of experienced clinicians. Using this process, a consensus, best-estimate diagnosis was obtained for all subjects using the DSM-III-R criteria. All interviewers underwent a standardized training course for the SCID and were regularly tested for diagnostic reliability. This process ensured the most accurate diagnosis of BD, and enabled us to distinguish BD from primary substance use and anxiety disorders, which may at times present similarly to BD. However, psychiatric comorbidity is common in BD, and elevated rates of comorbid anxiety and substance use disorders are often observed. We did not exclude subjects with such comorbid diagnoses, since this would not only substantially reduce the sample size and power, but more importantly, it would result in a set of subjects that was not representative of BD in the general population. The final family sample included 34 families and 311 individuals, with an average of 9 individuals per family in an average of 2.8 generations. This represents the second set of families from this consortium following a previous report on an initial set of 20 pedigrees.

Genotyping

Blood was drawn from all subjects for the establishment of lymphoblastoid cell lines, and DNA was prepared from cultured cells by phenol/chloroform extraction. Markers were primarily tri- and tetra-nucleotide repeats from the Weber 6.0 screening set (13) supplemented with dinucleotide repeat markers from the Genethon map (14). Genotyping was conducted as follows: 50 ng of DNA was amplified in a 20 μ l reaction using an MJ Research PTC-200 thermal cycler (MJ Research, Waltham, MA, USA). Reactions contained 1.5 mM $MgCl_2$, 50 mM KCl, 200-500 nM of each primer, 10 mM Tris-HCl (pH 8.3), 0.001% gelatin, and one unit of either AmpliTaq or AmpliTaq Gold (Applied Biosystems, Foster City, CA, USA). The forward primer was fluorescently labeled. Following an initial incubation period of 10 min at 95°C (AmpliTaq Gold only), the polymerase chain reactions (PCR) were conducted using the touchdown protocol (15), in which the annealing temperature was decreased by 1°C every two cycles from 65°C to 55°C, with a final 10 cycles at 55°C. PCR products were separated by electrophoresis and detected using an ABI 377 and Genescan and Genotyper software (Applied Biosystems). Markers with different molecular weights and labeled with different fluorophores were pooled for efficiency. Two independent readers called all genotype data in a machine-assisted fashion. Standardized molecular weights were obtained by running the DNA of a Centre d'Etude du Polymorphisme Humain (CEPH) individual in multiple lanes on all gels. Data were screened for common artifacts such as shift and bleed-through using custom data cleaning software.

A total of 440 markers with an average intermarker interval of 8 cM were genotyped in 229 individuals. The resulting genotypes were evaluated using the pedstats module of Merlin to check the pedigrees for non-Mendelian inheritance (16). A total of 61 genotypes were removed due to Mendelian inconsistencies, indicating an overall error rate of approximately 0.5%. There was approximately 1% missing genotype data.

Statistical analyses

All analyses were performed under two diagnostic models of affection: (i) a narrow model (BD) that included diagnoses of bipolar I disorder, bipolar II disorder, and schizoaffective disorder (bipolar type); and (ii) a broad model (BD + MDD) that included a diagnosis from the narrow model plus a diagnosis of recurrent MDD. The number of informative relative pairs under each diagnostic model is shown in Table 1. There was an average of 2.4 and 3.9 affected individuals per family under the narrow and broad diagnostic categories, respectively, and a disease prevalence of 26% and 43% was observed for the narrow and broad models, respectively. In this sample, females comprised 63% of the affected individuals under the narrow diagnostic model and 66% of the affected individuals under the broad diagnostic model, thus outnumbering males 2 to 1 in terms of disease prevalence. The

disease prevalence across the sample was 29% for females and 21% for males under the narrow BD model, whereas prevalences of 51% and 32% were observed for females and males, respectively, under the broad model that includes MDD.

Marker order and map positions were obtained from a modified version of the deCODE genetic map (17, 18). Initial analyses were performed using model-free, nonparametric two-point, and multipoint linkage analyses methods in Merlin to analyze the extent of allele-sharing among all affected relative pairs (16). Marker allele frequencies were estimated among all individuals, the default in Merlin. Logarithm of odds (LOD) scores and corresponding p-values were converted from nonparametric scores using the Kong-and-Cox function (19) and were computed for each marker for two-point analyses. For the multipoint analyses, LOD scores and p-values were computed at a 1 cM interval across the chromosome, beginning with the first marker. The information content was also calculated for each marker from pedigree data in both two-point and multipoint analyses.

As a supplement to the nonparametric analyses, we performed additional analyses using parametric linkage methods, which require the specification of a genetic model to describe the disease segregation. Although the exact genetic mechanisms underlying BD susceptibility are currently unknown, parametric analyses can substantially improve power over their nonparametric counterparts if the appropriate disease model is applied. Parametric two-point and multipoint linkage analyses were conducted using the MLINK module of FASTLINK (20) and the parametric module of Merlin (16), respectively. For both analyses, marker allele frequencies were estimated among all individuals and analyses were conducted under an assumption of genetic homogeneity. The same narrow and broad diagnostic models used in the nonparametric analyses were reiterated here, with the addition of an autosomal dominant genetic model assuming an 85% penetrance, and an autosomal recessive genetic model assuming a 50% penetrance. Penetrance and disease allele frequencies were adjusted for each genetic model to yield an approximate 5% phenocopy rate with disease prevalences of 1% for the narrow diagnostic model and 2% for the broad diagnostic model. An age-of-onset curve was also included to reflect a minimal risk below age 15 that maximized at the defined penetrance at age 40. In the multipoint linkage analyses, LOD scores were additionally maximized over the proportion of linked families (α) for the estimation of a heterogeneity LOD score (HLOD) at each locus.

Results

Initial analyses were performed using model-free, nonparametric methods. Two-point LOD scores > 1.0 were observed on chromosomes 1, 6, 7, 8, 9, 13, 16, 17, 20, 22, and X, as shown in Table 2. Evidence for linkage to chromosomes 2, 6, 15, 17, 20, and X is further supported by multipoint analyses, which revealed linkage peaks with maximum multipoint LOD (MLOD) scores > 1.0 on these chromosomes (see Table 2 and Fig. 1). Maximum MLOD scores > 1.0 were also observed for chromosomes 4, 14, and 15. The highest MLOD scores were observed on chromosomes 17 and 20 under the narrow diagnostic model (BD), with an MLOD of 2.1 at 34 cM near D17S969 on chromosome 17 and an MLOD of 2.0 at 65 cM near D20S478 on chromosome 20.

As a supplement to the nonparametric analyses, we performed additional analyses using parametric linkage methods. Parametric analyses require the specification of a genetic model to describe the segregation of the disease, and can substantially improve power over nonparametric analyses if the appropriate disease model is applied. The parametric two-point linkage analyses provided support for linkage to chromosomes 1, 6, 7, 8, 9, 13, 16, 17, 20, and 22, consistent with the results of the nonparametric analyses, in which additional evidence was observed for linkage to chromosomes 2, 4, 5, 14, and 18 (see Table 3).

Maximum parametric two-point LOD scores ($Z_{\max}$) > 2.0 were observed on chromosome 1 under a broad diagnostic model (BD + MDD) and dominant genetic model ($Z_{\max} = 2.29$ near D1S1677 at 162 cM); on chromosome 6 under a broad diagnostic model and dominant genetic model ($Z_{\max} = 2.48$ near D6S1007 at 167 cM); and on chromosome 7 under a narrow diagnostic model (BD) and recessive genetic model ($Z_{\max} = 2.3$ near D7S2212 at 96 cM). Linkage heterogeneity analyses using multipoint parametric methods were also performed, as shown in Figure 1. These analyses provide a maximum genomewide HLOD of 3.28 ($\alpha = 0.82$) at 162 cM near D6S1007 on chromosome 6 under the broad diagnostic model (BD + MDD) and dominant genetic model. Although there were no other HLODs > 2.0 observed, we did find further support for linkage to chromosomes 1, 6, 7, 9, 15, and 17.

There were nearly twice as many affected females as males under both diagnostic models in our sample, and the disease prevalence under the broad model was substantially higher in females than males, 51% versus 32%, respectively. It is thus possible that sex could have an effect on the results of these analyses. We explored this possibility by including sex as a covariate in both the nonparametric and parametric analyses. We found no difference in the results that excluded and included sex as a covariate and thus conclude that this is not an important factor in our analyses.

Discussion

In these analyses, we have employed both parametric and nonparametric methods in an attempt to identify chromosomal regions linked to BD susceptibility. While the same diagnostic models and genetic data were utilized by both methods, the parametric analyses incorporated additional information regarding the mode of genetic transmission, which has the potential to substantially improve power. However, when the mode of genetic transmission is unknown and presumably complex, as in the case of BD, model-free, nonparametric analyses may prove to be a useful alternative. By pursuing both methods we are able to capitalize on the strengths of each and assess points of congruence, which may indicate regions of specific interest for more fine-scale analyses. We also used broad diagnostic criteria for ascertainment and analyzed the data under both broad and narrow diagnostic models, since it is unclear which diagnostic model is the most appropriate. Additionally, we did not exclude subjects with comorbid psychiatric diagnoses, which are commonly present with BD, particularly comorbid anxiety and substance use disorders. These phenomena are part of the presentation and symptoms of BD patients, and elimination of those displaying psychiatric comorbidity would result in a set of subjects that were not representative of BD in the general population. However, it is possible that different genetic loci may lead to different presentations in terms of comorbidity, and this would be an important issue to address in a much larger sample than that presented here. It is thus likely that our results have been impacted by these choices regarding ascertainment, affection status, and statistical methods.

The most prominent finding in these analyses was for chromosome 6q25 with a maximum multipoint LOD score of 3.28 observed at 162 cM near D6S1007 using a multipoint parametric method under the broad diagnostic and dominant genetic models. The nonparametric analyses also provided moderate evidence for linkage to this region with a LOD score of 1.51. The *ZDHC14* gene, which codes for a zinc finger protein, lies directly beneath this peak and contains the D6S1007 microsatellite. This is a complex locus, generating 11 different mRNAs through alternative splicing and producing several proteins with no sequence overlap and unknown function. Using a convergent functional genomics approach that combines data from human and animal model gene expression and genetic

studies, Patel and colleagues (21) have recently implicated *ZDHC14* as a top candidate gene for BD.

While the microsatellite primarily affiliated with this linkage peak lies directly within the *ZDHC14* gene, the 1-LOD interval around the peak implicates the 6q24-25 region, spanning 19 Mb and encompassing many genes of potential interest. In fact, a recent genomewide association study of BD identified a SNP within the *SYNE1* gene on 6q25 with a p-value of 3.6×10^{-6} and an odds ratio of 1.22 in a combined analysis of 4,387 BD cases and 6,209 controls (22). Although not genomewide significant in this study, this report provides further evidence that a gene in this region may indicate susceptibility to BD. *SYNE1* is located approximately 5 Mb from *ZDHC14* and well within the 1-LOD interval in our analysis. Given the 8 cM resolution of our linkage scan, we cannot exclude *SYNE1* or any other gene in this region as harboring a causal variant.

The 6q24-25 chromosomal region has been implicated previously in several other studies. In the original NIMH study of 153 families with BD a maximum nonparametric linkage (NPL) score of 2.5 (corresponding LOD = 1.4) was observed for D6S311 at 154 cM on chromosome 6q24 under a broad diagnostic model (23). In another study of the NIMH families with BD, Cheng and colleagues (24) found evidence for linkage to the 6q24-25 region for both BD and suicidal behavior with maximum multipoint NPL LOD scores of 2.08 near D6S1848 at 146 cM for suicidal behavior and 1.74 near D6S1035 at 165 cM for BD. Evidence for linkage to schizophrenia has also been reported for this region with a maximum two-point LOD score of 3.45 for D6S264 on 6q25, which rose to a maximum multipoint LOD score of 7.7 with the inclusion of additional markers in the 6q25 region (25). Interestingly, an autism-susceptibility locus also has been mapped to the 6q25 region (26), and deletions of this region have been shown to result in developmental problems and brain anomalies (27). Collectively, these results suggest that the 6q25 region may contain genes important for normal brain function and development that may in turn influence susceptibility to psychiatric illness. Thus, the mounting evidence that the 6q25 region may be a susceptibility locus for BD and other psychiatric disorders suggests that further investigation of this region through a fine scale SNP screen in families and case-control samples may be warranted.

Several other regions of potential interest were identified in this study. An additional NPL peak on chromosome 6 was observed at 104 cM under the narrow diagnostic model, replicating the results of Dick and colleagues (28), which indicated a maximum LOD of 2.2 at 107 cM on this chromosome in the wave 3 bipolar data from the NIMH study. Our finding of suggestive evidence for linkage to chromosome 17p12 with a nonparametric MLOD of 2.12 at 34 cM is consistent with the findings of Park et al. (29). This study of families with BD found increasing evidence for linkage to 17p12 with increasing family members with psychosis for a maximum LOD of 2.42. The linkage peaks observed on chromosomes 20 (MLOD = 2.01 at 66cM near D20S478) and 15 (MLOD = 1.85 and HLOD = 1.74 at 44 cM near D15S659) may represent novel findings in these chromosomal regions.

It is striking that regions that have been implicated as potentially promising by several research groups in addition to our own, such as 13q, 18, and 22q (10, 30-31), were not prominent in this study. Earlier analyses of chromosome 13 in a subset of the 34 families in this sample were previously published (11). These analyses found suggestive evidence for linkage to the 13q32 region with a maximum LOD score of 2.29, replicating the results of our previous analyses in an independent sample of 20 families (10). These results were not replicated in this expanded dataset. These analyses also did not replicate evidence for linkage to chromosome 5p15 found in the first 20 families (8). Additionally, only limited support for linkage was obtained in these analyses for chromosome 22q13, a region for

which we have previously reported evidence for linkage in the first 20 families (10). However, both parametric and nonparametric two-point linkage analysis in this new set of 34 families did yield some modest evidence for linkage at D22S315, which appeared as a secondary linkage peak at 23 cM on chromosome 22 in the initial 20 families. D22S315 lies within intron 1 of the *GRK3* gene (*ADRBK2*) for which we have previously reported the association of a functional promoter variant with BD (32, 33).

Our results thus suggest replication of some reported linkage peaks, such as 6q25 and 17p12; however, other peaks from our own previous study, such as 5p15, 13q32, and 22q13, were either not replicated or only modestly replicated in these analyses. While it is highly possible that the relatively low density of this linkage scan has caused us to miss linkage to potentially interesting regions and fail to replicate the results of others, such inconsistencies in linkage replication are common and have widely been attributed to a high degree of locus heterogeneity. As some have suggested, the replication of specific linkage results is considerably more difficult in a second sample, since the frequencies of predisposing or protective genetic variants may vary between samples (34). This is also likely due in part to differing population substructures, which produce inconsistent results. Collectively, linkage studies and genomewide association studies suggest a high level of both locus and allelic heterogeneity associated with BD susceptibility. As next generation sequencing technology becomes increasingly feasible, sequencing studies in large extended family sets may ultimately have the best power to detect causative alleles.

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Fig. 1.

Multipoint linkage results of the genomewide linkage scan in the 34 families for the narrow (BD) and broad (BD + MDD) diagnostic models using parametric autosomal dominant (red), parametric autosomal recessive (blue), and nonparametric (NPL) linkage analysis methods (green). Results are shown with the logarithm of odds (LOD) score on the y-axes and the genetic location and corresponding chromosome on the x-axes. BD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders; BD + MDD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders and major depressive disorder

Table 1

Total number of genotyped relative pairs and affected relative pairs with genotype and phenotype information under each model of affection

Relationship	Total (N = 229)	BD (n = 80)	BD + MDD (n = 133)
Siblings	197	24	75
Half siblings	9	1	4
Parent-child	384	21	74
Grandparent-grandchild	220	2	6
Avuncular	196	11	36
Cousins	41	5	13

BD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders; BD + MDD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders and major depressive disorder.

Table 2
Nonparametric two-point and maximum multipoint linkage results for the narrow (BD) and broad (BD + MDD) diagnostic models

Chromosome	NPL Two-point			NPL Multipoint			
	Marker	Position (cM)	Diagnostic model	LOD	Nearest marker(s)	Position (cM)	MLOD
1q23	D1S1677	162	BD	1.67			
2q35					D2S2944, D2S434	212	BD
4p16					D4S1582, D4S1605	23	BD + MDD
6q16					D6S1056, D6S1021	104	BD
6q25	D6S1007	167	BD + MDD	1.03	D6S1007	162	BD + MDD
7q21	D7S2204	90	BD	1.27			
8q24	D8S592	119	BD + MDD	1.17			
9q31	D9S938	106	BD	1.91			
13q32	D13S225	96	BD + MDD	1.28			
14q22					D14S306, D14S285	48	BD
15q21					D15S659	44	BD
15q21					D15S659	44	BD + MDD
16q22	D16S2624	87	BD	1.13			
17p13	D17S974	31	BD	1.64			
17p12	D17S969	34	BD	1.27	D17S969	34	BD
17q21					D17S791	73	BD
20q11	D20S478	61	BD	1.27	D20S478, D20S481	66	BD
22q11	D22S315	23	BD	1.21			
22q11	D22S315	23	BD + MDD	1.40			
Xq25	DXS1047	131	BD + MDD	1.45	DXS1047	131	BD + MDD
							1.21

BD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders; BD + MDD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders and major depressive disorder; NPL = nonparametric linkage; LOD = logarithm of odds; MLOD = multipoint LOD.

Table 3

Parametric two-point and maximum multipoint linkage results for the narrow (BD) and broad (BD + MDD) diagnostic models and dominant and recessive genetic models

Chromosome	Marker	Position (cM)	Disease model	Diagnostic model	Z _{max}	Theta	HILOD	Alpha
1q23	D1S1677	162	Dom	BD	2.29	0.05	1.38	0.35
1q23	D1S1677	162	Rec	BD	1.14	0.15		
2q35	D2S434	216	Dom	BD	1.03	0.10	1.02	0.51
4q25	D4S2623	114	Rec	BD			1.11	0.45
4q28	D4S2394	128	Dom	BD	1.25	0.20		
4q31	D4S1644	138	Dom	BD	1.05	0.20		
4q31	D4S1625	140	Dom	BD			1.25	0.52
4q31	D4S1625	140	Dom	BD + MDD			1.48	0.34
5p13	D5S418	65	Dom	BD	1.29	0.20		
5q15	D5S1462	109	Dom	BD			1.12	0.36
6q16	D6S1056	101	Rec	BD	1.34	0.15	1.21	0.63
6q25	D6S1003	158	Dom	BD			1.16	0.56
6q25	D6S1007	167	Dom	BD + MDD	2.48	0.10	3.28	0.82
7q21	D7S669	89	Rec	BD	1.72	0.15	1.41	0.49
7q21	D7S2204	90	Rec	BD	1.94	0.10		
7q21	D7S2204	90	Dom	BD + MDD	1.37	0.15		
7q21	D7S2212	96	Rec	BD	2.30	0.05		
7q21	D7S821	106	Rec	BD + MDD	1.80	0.10	1.46	0.53
8q21	D8S270	97	Rec	BD	1.29	0.10		
8q24	D8S592	119	Dom	BD + MDD	1.04	0.20		
8q24	D8S592	119	Dom	BD + MDD	1.31	0.15		
9q31	D9S938	106	Dom	BD	1.33	0.10	1.18	0.40
9q31	D9S938	106	Rec	BD	1.16	0.10		
11p15	D11S1999	17	Dom	BD			1.17	0.46

Chromosome	Marker	Position (cM)	Disease model	Diagnostic model	$Z_{\max}$	Theta	HLOD	Alpha
13q32	D13S154	89	Dom	BD	1.18	0.15		
13q32	D13S225	96	Dom	BD + MDD	1.75	0.15		
14q22	D14S306, D14S285	49	Rec	BD + MDD			1.17	0.63
14q23	D14S592	61	Dom	BD + MDD	1.24	0.15		
15q11	D15S817	1	Dom	BD + MDD			1.34	0.47
15q11	D15S817	1	Rec	BD + MDD	1.26	0.15		
15q11	D15S817	5	Rec	BD + MDD			1.51	0.61
15q21	D15S659	48	Dom	BD + MDD			1.74	0.47
16q22	D16S2624	87	Dom	BD	1.60	0.15	1.10	0.36
17p13	D17S974	31	Dom	BD	1.11	0.10		
17p12	D17S969	34	Dom	BD	1.01	0.10	1.15	0.52
17p12	D17S969	34	Rec	BD			1.09	0.39
18p11	D18S40	40	Dom	BD	1.22	0.15		
18q11	D18S45	42	Dom	BD	1.44	0.05		
18q11	D18S45	42	Dom	BD + MDD	1.26	0.10		
20q13	D20S173	99	Rec	BD + MDD	1.45	0.10		
22q11	D22S925	22	Dom	BD	1.07	0.20		
22q11	D22S419	23	Dom	BD	1.12	0.15		
22q11	D22S315	23	Dom	BD	1.94	0.10		
22q11	D22S315	23	Dom	BD + MDD	1.77	0.10		
22q12	D22S684	39	Dom	BD	1.61	0.10		
22q12	D22S684	39	Dom	BD + MDD	1.03	0.20		

BD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders; BD + MDD = bipolar I, bipolar II, and schizoaffective (bipolar-type) disorders and major depressive disorder; HLOD = heterogeneity logarithm of odds; Dom = dominant; Rec = recessive.