# A genome survey indicates a possible susceptibility locus for bipolar disorder on chromosome 22

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**Bipolar disorder or manic depressive illness is a major psychiatric disorder that is characterized by fluctuation between two abnormal mood states. Mania is accompanied by symptoms of euphoria, irritability, or excitation, whereas depression is associated with low mood and decreased motivation and energy. The etiology is currently unknown; however, numerous family, twin, and adoption studies have argued for a substantial genetic contribution. We have conducted a genome survey of bipolar disorder using 443 microsatellite markers in a set of 20 families from the general North American population to identify possible susceptibility loci. A maximum logarithm of odds score of 3.8 was obtained at D22S278 on 22q. Positive scores were found spanning a region of nearly 32 centimorgans (cM) on 22q, with a possible secondary peak at D22S419. Six other chromosomal regions yielded suggestive evidence for linkage: 3p21, 3q27, 5p15, 10q, 13q31-q34, and 21q22. The regions on 22q, 13q, and 10q have been implicated in studies of schizophrenia, suggesting the possible presence of susceptibility genes common to both disorders.**

Bipolar disorder is a severe psychiatric disorder that affects approximately 1% of the world's population (1). It is characterized by extreme swings in mood between mania and depression. 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 worthlessness and hopelessness. Psychosis can occur in either state, and there is a 17% lifetime risk for suicide.

The etiology is currently unknown, but epidemiological studies argue for a strong genetic component. Family studies indicate an approximately 7-fold increase in risk to first-degree family members (2). Twin studies find an average 4-fold increase in risk to monozygotic vs. dizygotic twins. The mode of genetic transmission is unclear. Although some studies have supported the presence of autosomal dominant major loci (3, 4), it has also been argued that bipolar disorder is oligogenic with multiple loci of modest effect.

Although initial attempts at linkage studies met with inconsistent replication (5–8), more recently, the accumulation of multiple studies of larger family sets has led to the reproducible identification of several genetic loci. These include 4p, 12q, 13q, 18, 21q, and Xq among others (9–15). We have previously reported on studies of our set of 20 North American pedigrees, which indicated suggestive evidence of linkage to 5p15 and 22q11 (16, 17). We now report the results of a genome survey using 443 microsatellite markers. These data provide strong evidence for a locus on 22q and support previously reported loci on several other chromosomes. Overlap for some of these loci with those reported for schizophrenia also provides additional data arguing for possible common susceptibility loci for these two disorders.

## Methods

**Subjects.** Families were ascertained from the general North American population through both systematic survey of clinical facilities and through advertising and patient support groups from two sites: San Diego and Vancouver. Families were ascertained through a proband with bipolar I or bipolar II disorder and included if at least two additional members were affected under our broad diagnostic model. Power analyses using SIMLINK (18) were conducted to select both families and members for maximum power. The family sample included 20 families and 164 subjects. Thirty-three subjects had a diagnosis of bipolar I, 15 had bipolar II, and 28 had recurrent major depression. There were averages of 8.2 subjects and 3.8 affected members per family.

Family members were interviewed directly using the Structured Clinical Interview for DSM-3-R (SCID) (19) except for one family, the earliest in the study, which was interviewed using the Schedule for Affective Disorders and Schizophrenia (SADS-L) (20). All diagnoses were made using DSM-3-R criteria, modified to require a 2-day minimum duration for hypomania. Wherever possible, information was also obtained from other family informants and from medical records. Information from all sources was reviewed by a committee of experienced psychiatric clinicians to determine a consensus, best-estimate diagnosis. All interviewers underwent a rigorous, standardized training program for the SCID. Diagnostic reliability was regularly tested by review of videotaped interviews and was consistently high.

DNA samples were obtained from the Coriell Institute for 57 families with bipolar disorder, which were collected as part of the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. These families were used as a replication set and were genotyped for selected markers from our genome survey. These 57 families included 345 subjects with the following diagnoses: 169 with bipolar I disorder, 36 with bipolar II disorder, and 45 with recurrent major depression. Ascertainment and diagnostic methods for these families have been described elsewhere (21).

**Genotyping.** After obtaining informed consent, blood was drawn on all subjects for the establishment of lymphoblastoid cell lines. DNA was prepared from cultured cells by phenol/chloroform extraction.

Markers were primarily tri- and tetranucleotide repeats from the Weber 6.0 screening set (22). These were supplemented with

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Abbreviations: lod, logarithm of odds; cM, centimorgans.

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dinucleotide repeat markers from the Genethon map (23). A total of 443 markers was examined. The average intermarker interval was 8 cM; the maximum interval between markers was 33 cM. Map positions were derived primarily from the Marshfield integrated map (24), except for the map used for multipoint analyses on chromosome 22, which was calculated from our genotypic data as described below.

In total, 363 of the microsatellite markers were genotyped at the Novartis laboratory as follows. The PCR was performed in a volume of 20 $\mu$l containing 100 ng of genomic DNA, 0.3 $\mu$M of each primer (the forward primer had been labeled at the 5′ end with fluorescein), dNTP at a concentration of 130 $\mu$M each, 50 mM KCl, 1.5 mM $MgCl_2$, 10 mM Tris-HCl (pH 9.0), and 1 U *Taq* DNA polymerase (Amersham Pharmacia). The PCR amplification was carried out in a Biometra Thermo Cycler with the following cycles: 1×, 5 min at 95°C; 40×, 40 s at 95°C, 40 s at 55°C, and 40 s at 72°C; 1 × 7 min at 72°C. After completion of the amplification, 20 $\mu$l of loading buffer (99% of formamide/1 mM EDTA/0.05% bromphenol blue/0.05% xylene cyanol were added to the PCR reaction. The samples were heated up for 3 min at 95°C and then chilled on ice; then, 5 $\mu$l of each sample were loaded on a 5% to 8% Long Ranger polyacrylamide/7 M urea gel. The percentage of the gel was dependent on the size of the PCR product. The separated, fluorescently labeled PCR products were visualized by using the Molecular Dynamics FluorImager and ImageQuant software. The instrument scan parameters were adjusted to optimize signal intensity (900 volts, 200-$\mu$m pixel size, normal sensitivity).

The remainder of the markers were genotyped at the University of California, San Diego, laboratory as follows: 50 ng of DNA was amplified in either a 5-$\mu$l reaction using an ABI 877 catalyst robotic PCR workstation or a 20-$\mu$l reaction using an MJ Research PTC-200 thermal cycler. 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 1 unit of either AmpliTaq or AmpliTaq Gold (Perkin–Elmer). The forward primer was labeled with one of three fluors. After an initial 10 min at 95°C (AmpliTaq Gold only), the PCR reaction was conducted using the touchdown protocol (25) in which the annealing temperature was decreased by 1° every two cycles from 65° to 55°, followed by a final 10 cycles at 55°. PCR products were separated by electrophoresis and detected using an ABI 377 and Genescan and Genotyper software. Multiple markers labeled with different fluors and in different molecular weight ranges were pooled along with a molecular weight standard for multiplex detection of between 6 and 12 markers per lane.

All genotypes from each lab were read in a machine-assisted fashion independently by two readers. Standard samples were used for checking consistency between gel molecular weights, and all data were screened for common artifacts using custom data cleaning software. Genotypic data from each laboratory was transferred to University of California, Irvine, for linkage analysis.

**Statistical Analysis.** A power analysis of this sample was first conducted to aid in the interpretation of results. For this simulation analysis, assumptions were made of an autosomal dominant genetically homogeneous trait and a marker with 4 alleles of equal prevalence, which was 5 cM from the disease gene. Under the narrow disease model, an average logarithm of odds (lod) score of 3.55 was obtained, and there was 65% power to obtain a lod score >3.0. Under the broad model, the average lod score was 5.06, and there was 85% power to detect a lod score >3.0.

Data were recoded to ensure straightforward notation for the multiple alleles in such a way as to allow direct comparison across the two laboratories. Allele frequencies for the markers were estimated from the families using MENDEL (26). These estimates were then compared with published frequencies when the latter were available. Most of the estimates were comparable, and if there were large discrepancies, the pedigrees were reviewed for possible errors. No frequency discrepancies were of sufficient magnitude to warrant multiple runs using different estimates for the same marker(s).

Linkage analyses were carried out using the parametric lod score approach to maximize power over the sample size available. Calculations were performed both for disease vs. marker and then for marker vs. marker combinations in any area that gave some indication of being a potential disease gene location. The marker information was used to confirm the map relations among markers within our data as compared with the published maps (Cooperative Human Linkage Center, etc). One set of data errors for a single chromosome was detected using the map information, and markers were rerun and corrected.

LIPED (27) was used to calculate the two-point lod scores, as that program readily permits calculating the scores using different values for male and female recombination. We modeled the disease in three ways: (i) autosomal dominant with 0.85 penetrance (AD85), (ii), autosomal dominant with 0.50 penetrance (AD50), and (iii) autosomal recessive with 0.50 penetrance (AR50). Markers on the X chromosome were analyzed using a dominant model with 0.85 penetrance. Analyses were conducted under an assumption of genetic homogeneity. Preliminary analyses had indicated that similar results were obtained under heterogeneity as under homogeneity and that the sample did not have adequate power to detect heterogeneity. In addition, we modeled the affected status for bipolar disorder because it is not yet certain which forms may represent the same genetic disease. We defined affected for the narrow diagnostic model (BP only) as bipolar I plus bipolar II plus schizoaffective, bipolar type. The broad diagnostic model (BP + RD) added the category of recurrent major depression to affected status. Subjects with other psychiatric diagnoses were considered of unknown affection status. The three genetic and two diagnostic models resulted in six models that were considered. Penetrance and disease allele frequency was adjusted for each model so as to yield an approximately 5% phenocopy rate and disease prevalences of 1% for the BP only model and 2% for BP + RD. An age-of-onset curve was included with minimal risk below age 15, maximizing at the defined penetrance at age 40.

The lod scores were reviewed by chromosome region to detect inconsistencies. For example, one marker showed some evidence of linkage, but the markers on either side were strikingly negative. Careful review of the pedigrees indicated that the "linked" marker was generated by data from very few informative individuals who by chance had no recombinant offspring. The markers on either side had data from many more informative individuals, and numerous recombinants could be identified. This area was discounted as a potential disease gene region. After the inconsistency review, regions of interest were defined as those with an lod score greater than or equal to 1.0. To increase the density of the map in the regions of interest, additional markers were genotyped.

Three regions were investigated in depth with multipoint analyses using the FASTLINK implementation of the LINKAGE package (28, 29). Two of these regions were on chromosome 22, and one was on chromosome 5. We chose to use only those families that showed potential linkage in each region for the multipoint analyses. Only in one instance was there improvement in the lod score using the multipoint approach.

## Results

The results of the genome survey are illustrated in Fig. 1. Twelve markers yielded lod scores greater than 2.0 across the genome. The region with the highest lod scores is on chromosome 22, which is further illustrated in Fig. 2. Thirteen markers spanning

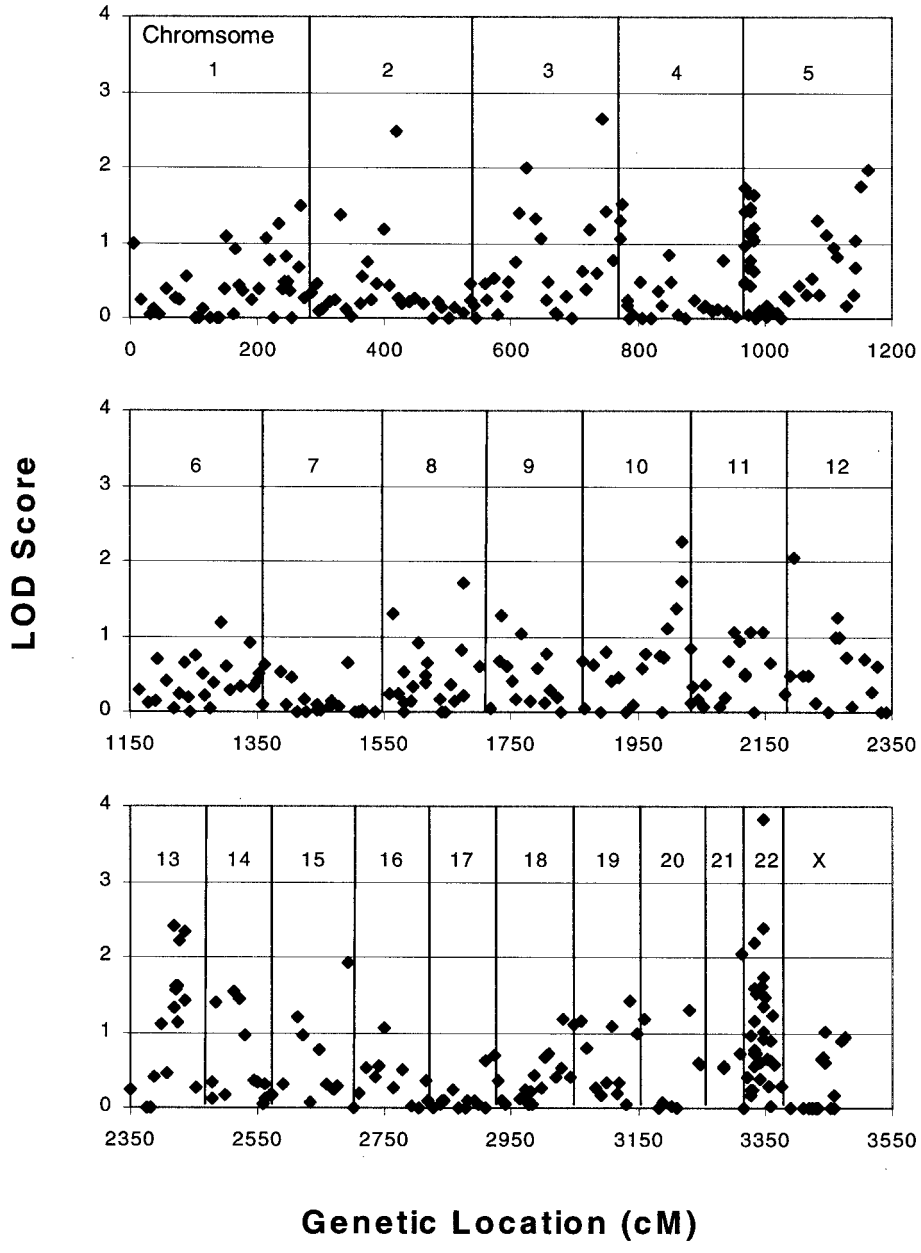


**Fig. 1.** Four hundred forty-three microsatellite markers were examined spanning the genome. Each point represents the maximum lod score obtained for a microsatellite marker under all models examined. The genetic map was derived primarily from that of the Marshfield laboratory. Genetic location is displayed with chromosomes end to end across the genome. The maximum lod score is displayed as zero if no positive lod score was obtained under any model.



32 cM yielded lod scores greater than 1.0. A maximum lod score of 3.84 was obtained at D22S278 on 22q12. Six other markers within 5 cM also yielded lod scores greater than 1.0, including an lod score of 2.39 at D22S683, which is in close proximity to D22S278. These results were all obtained under the narrow diagnostic model and the high penetrance dominant genetic model. A multipoint analysis was conducted using the eight families with the highest two-point lod scores to further localize the linkage peak. This analysis was consistent with the two-point analysis and yielded a maximum lod score of 3.1 at D22S278. Outside of this immediate region, the next highest lod score was 2.19 at D22S419, 15 cM proximal to D22S278. The length of this overall region of positive lod scores is consistent with other linkage findings in complex disorders (30). Although these results suggest a separate peak near D22S419, it is premature to estimate whether there might be multiple loci involved.

In an attempt to examine these results in an independent sample, we examined 57 families from the NIMH Bipolar Disorder Genetics Initiative sample (21). This is a subset of the larger NIMH family set, which was selected based on size and informativeness of pedigrees. As the results of the NIMH genome scan have already been reported, these results were not intended to provide a new sample for replication but simply to analyze the existing and available NIMH sample using the same markers and analytical methods as for our 20 pedigrees. The results, as illustrated in Table 1, were consistent with those from our genome scan. Eleven of the 16 markers examined on chromosome 22 yielded lod scores greater than 1.0. These positive lod scores spanned the same region implicated in the University of California, San Diego/University of British Columbia (UCSD/UBC) sample. The maximum lod score in the NIMH sample was 2.72 obtained at D22S419. Six other markers

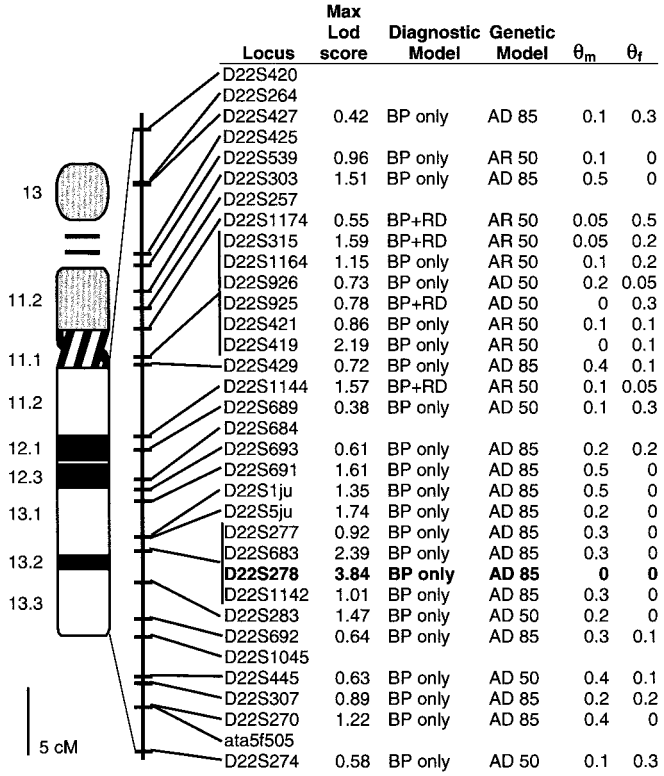


**Fig. 2.** Maximum lod score represents the highest two-point lod score obtained for each marker for all models examined. For each marker, the diagnostic and genetic models are indicated, as is the sex-specific recombination fraction that yielded the maximum lod score. No lod score is indicated if no positive lod score was obtained under any model.

within 2 cM also yielded lod scores greater than 1.0. D22S278, which gave the strongest results in the UCSD/UBC sample, yielded a maximum lod score of 1.58. Three other nearby markers also obtained lod scores greater than 1.0. Therefore, for each of the two putative linkage peaks on 22q, positive scores were obtained in both samples. However, the region near D22S419 was strongest in the NIMH sample, whereas the region near D22S278 was strongest in the UCSD/UBC sample.

Table 2 details several other genomic regions that yielded suggestive evidence of linkage in the genome scan of the UCSD/UBC family set. Each of these regions includes at least one marker with an lod score greater than 2.0, which is flanked by other markers with lod scores greater than 1.0. Two separate regions on chromosome 3 were implicated. Each region is approximately 30 cM long, and the regions are separated by 60 cM. D10S1223 yielded an lod score of 2.27 and is flanked by several markers with lod scores greater than 1.0 over an interval of 20 cM. Another region with particularly suggestive data is 13q. Three markers, D13S154, D13S225, and D13S796, generated lod scores greater than 2.0. Six other makers in this 20-cM interval also yielded lod scores greater than 1.0. On 21q, the marker, PFKL, yielded a lod score of 2.04.

5p15 is of particular interest because it includes an important candidate gene, the dopamine transporter. Although the combined family sample yielded only modest evidence of linkage, one large family (family 16) generated suggestive evidence of linkage. As shown in Table 3, a maximum lod score of 2.77 was obtained for this family at D5S417. These results are consistent with those we have previously reported in the same family set with a less extensive set of markers (16).

Several other regions deserve mention. Lod scores above 2.0 were detected on chromosomes 2q and 12p. However, the absence of any supporting evidence from immediately flanking markers caused us to dismiss the importance of these results. Several other regions yielded modestly positive lod scores in the range of 1.0 to 2.0 and are interesting because of other reports in these regions. These include 4p, 5q, and 16p.

## Discussion

We examined 443 microsatellite markers in a set of 20 North American families with bipolar disorder. The genome-wide maximum was a lod score of 3.8 at D22S278 on 22q13 under the narrow diagnostic definition and an autosomal dominant model. Other regions with suggestive evidence for linkage include 3p21, 3q27, 5p15, 10q, 13q31-q34, and 21q22.

We first reported suggestive evidence of linkage to 22q in 1997 in a subset of this sample (31). This earlier study examined 13 of the 20 families reported here and obtained a maximum lod score of 2.51 at D22S303. This report extends our results by examining an expanded number of markers in a larger family set. In the current sample, the maximum evidence of linkage is found approximately 20 cM distal to the original result; however, D22S303 is near the possible second peak of linkage reported here at D22S419. Our results are consistent with several other reports examining this region. The NIMH Bipolar Disorder Genetics Initiative consortium reported an lod score of 2.5 at

**Table 1. Two-point lod scores for bipolar disorder in 57 NIMH families**

| Locus | Position (cM) | Max LOD score* | Diagnostic model | Genetic model | $\theta_m$ | $\theta_f$ |
|---|---|---|---|---|---|---|
| D22S303 | 16.4 | 0.83 | BP only | AR 50 | 0.5 | 0.2 |
| D22S1174 | 19.3 | 0.86 | BP only | AD 50 | 0.5 | 0.2 |
| D22S315 | 21.5 | 1.14 | BP only | AR 50 | 0.5 | 0.2 |
| D22S925 | 21.5 | 2.25 | BP only | AR 50 | 0.5 | 0.1 |
| D22S421 | 21.5 | 1.12 | BP only | AR 50 | 0.5 | 0.2 |
| D22S419 | 21.5 | 2.72 | BP only | AR 50 | 0.5 | 0.1 |
| D22S533 | 22.0 | 1.17 | BP only | AR 50 | 0.3 | 0.1 |
| D22S1144 | 27.5 | 1.85 | BP only | AR 50 | 0.5 | 0.05 |
| D22S689 | 28.6 | 2.17 | BP only | AR 50 | 0.5 | 0.05 |
| D22S691 | 32.4 | 0.82 | BP only | AR 50 | 0.5 | 0.1 |
| D22S1ju | 35.2 | 1.46 | BP only | AR 50 | 0.4 | 0.1 |
| D22S683 | 36.2 | 1.34 | BP only | AR 50 | 0.4 | 0.1 |
| D22S278 | 36.2 | 1.58 | BP + RD | AD 50 | 0.5 | 0.2 |
| D22S283 | 38.6 | 1.00 | BP only | AR 50 | 0.4 | 0.2 |
| D22S692 | 41.4 | 0.28 | BP only | AR 50 | 0.5 | 0.3 |
| D22S1045 | 42.8 | 0.63 | BP only | AD 85 | 0.5 | 0.3 |

*The maximum lod score obtained under any model tested.

**Table 2. Two-point lod scores from other regions with suggestive evidence of linkage**

| Chrom | Locus | Position (cM) | Max LOD Score* | Diagnostic model | Genetic model | $\theta_m$ | $\theta_f$ |
|---|---|---|---|---|---|---|---|
| 3 | D3S2409 | 70.61 | 0.74 | BP only | AR50 | 0.001 | 0.5 |
| 3 | D3S1766 | 78.64 | 1.40 | BP only | AD85 | 0.001 | 0.3 |
| 3 | D3S4542 | 89.91 | 2.01 | BP only | AD85 | 0.2 | 0.001 |
| 3 | D3S2406 | 102.64 | 1.32 | BP only | AD85 | 0.1 | 0.2 |
| 3 | GATA128C02 | 112.42 | 1.07 | BP only | AD50 | 0.05 | 0.2 |
| 3 | D3S2459 | 119.09 | 0.25 | BP only | AD85 | 0.2 | 0.3 |
| 3 | D3S3053 | 181.87 | 0.38 | BP only | AD85 | 0.001 | 0.4 |
| 3 | D3S2427 | 188.29 | 1.18 | BP only | AD85 | 0.4 | 0.001 |
| 3 | D3S1602 | 201.14 | 0.61 | BP only | AD85 | 0.3 | 0.1 |
| 3 | D3S2398 | 209.41 | 2.66 | BP only | AD85 | 0.2 | 0.001 |
| 3 | D3S2418 | 215.84 | 1.41 | BP only | AR50 | 0.5 | 0.001 |
| 3 | D3S1311 | 224.88 | 0.78 | BP only | AD50 | 0.05 | 0.4 |
| 10 | D10S1237 | 134.7 | 1.11 | BP + RD | AD85 | 0.05 | 0.5 |
| 10 | D10S587 | 147.57 | 1.37 | BP only | AD50 | 0 | 0.3 |
| 10 | D10S1223 | 156.27 | 2.27 | BP only | AR50 | 0.001 | 0.5 |
| 10 | D10S217 | 157.89 | 1.74 | BP only | AR50 | 0 | 0.5 |
| 13 | D13S154 | 75.19 | 2.4 | BP + RD | AR50 | 0.01 | 0.4 |
| 13 | D13S793 | 76.26 | 1.32 | BP only | AR50 | 0.05 | 0.5 |
| 13 | D13S770 | 79.49 | 1.62 | BP + RD | AD50 | 0.01 | 0.5 |
| 13 | D13S128 | 79.49 | 1.56 | BP only | AR50 | 0.05 | 0.5 |
| 13 | D13S1240 | 81.64 | 1.61 | BP only | AR50 | 0.001 | 0.5 |
| 13 | D13S779 | 82.93 | 1.14 | BP only | AD50 | 0.001 | 0.05 |
| 13 | D13S225 | 83.57 | 2.22 | BP only | AR50 | 0.001 | 0.5 |
| 13 | D13S173 | 93.52 | 1.41 | BP + RD | AR50 | 0.05 | 0.5 |
| 13 | D13S796 | 93.52 | 2.34 | BP + RD | AD85 | 0.01 | 0.3 |
| 21 | PFKL | 65.6 | 2.04 | BP + RD | AD50 | 0.4 | 0.001 |

*The maximum lod score obtained under any model tested.

D22S533 using a multipoint sib pair analysis (32). This is approximately 1 cM from our secondary peak at D22S419. The 57 NIMH families we examined are a subset of the NIMH Genetics Initiative pedigrees, and our results are consistent with theirs. These results on chromosome 22 are also consistent with a separate set of 21 families collected by the NIMH intramural program. Detera-Wadleigh *et al.* (11) reported a maximum lod score of 2.5 using a multipoint sib pair analysis in the interval between D22S689 and D22S685. Linkage maps position this region approximately halfway between the peaks at D22S419 and D22S278 found in our study. However, more recent genomic sequence and physical mapping data indicate that this region is more telomeric, approximately 2 Mb centromeric to D22S278 (33).

This 22q region has also been implicated in several studies of schizophrenia. Pulver *et al.* (34) first reported evidence of linkage of schizophrenia to 22q at the IL2RB locus near D22S278. Subsequently, this region has been implicated in several other linkage studies and the marker D22S278 in several linkage disequilibrium studies (35–38). Although it is this region near D22S278 that has been primarily reported in studies of schizophrenia, Myles-Worsley *et al.* have recently reported evidence of linkage of schizophrenia to a marker near our possible secondary peak at D22S419 (39). They examined a composite inhibitory endophenotype in families with schizophrenia and found a genome-wide maximum lod score of 3.5 at D22S315, which is very close to D22S419. Together, these data provide a considerable amount of evidence for loci for both bipolar disorder and schizophrenia on 22q. Furthermore, the data for both disorders suggest the possibility of more than one linkage peak on this chromosome.

Other regions of suggestive evidence for linkage in our study are consistent with previous reports and provide supportive evidence for these loci. 13q has been implicated in a recent study

**Table 3. Two-point lod scores at 5p15 in family 16**

| Locus | Position (cM) | Max lod score* | Diagnostic model | Genetic model | $\theta_m$ | $\theta_f$ |
|---|---|---|---|---|---|---|
| D5S2005 | 1.72 | 2.08 | BP only | AD85 | 0.001 | 0.001 |
| D5S678 | 1.72 | 2.14 | BP only | AD85 | 0.001 | 0.001 |
| D5S1981 | 1.72 | 1.89 | BP only | AD85 | 0.001 | 0.001 |
| D5S1970 | 5.43 | 0 | | | 0.5 | 0.5 |
| D5S417 | 6.67 | 2.77 | BP + RD | AD85 | 0.05 | 0.1 |
| D5S675 | 9.41 | 1.57 | BP + RD | AD85 | 0.05 | 0.5 |
| D5S405 | 9.41 | 1.64 | BP only | AD85 | 0.001 | 0.001 |
| D5S2088 | 9.41 | 0.70 | BP only | AR85 | 0.001 | 0.001 |
| D5S1492 | 9.41 | 2.02 | BP + RD | AD85 | 0.001 | 0.2 |
| D5S406 | 11.85 | 2.01 | BP + RD | AD85 | 0.001 | 0.001 |
| D5S2054 | 14.3 | 1.84 | BP only | AD85 | 0.001 | 0.001 |
| D5S464 | 14.3 | 1.88 | BP only | AD85 | 0.001 | 0.001 |
| D5S2505 | 14.3 | 1.51 | BP only | AD85 | 0.001 | 0.001 |
| D5S635 | 14.91 | 1.45 | BP only | AD85 | 0.001 | 0.001 |

*The maximum lod score obtained under any model tested.

of bipolar disorder by Detera-Wadleigh *et al.* (11) who reported a lod score of 3.5 in this region. Our data represent a significant replication of these results (40). Like 22q, this region has also been implicated in studies of schizophrenia (41). Evidence for linkage of bipolar disorder to the PFKL locus on 21q was reported in 1994 by Straub *et al.* (14). Subsequently, this locus has been supported by several other studies, and our data provide further support for this result. Markers on 10q were implicated by the NIMH Genetics Initiative consortium who found evidence for linkage at D10S188, about 20 cM proximal to the positive region in our data. Linkage has also been reported in a German sample of bipolar families at D10S217 (S. Cichon, personal communication). Two other groups have also reported evidence of linkage to schizophrenia in this region (42). Few studies of bipolar disorder have implicated chromosome 3; however, Edenberg *et al.* have reported increased allele sharing at D3S3038 in studies of the NIMH Genetics Initiative for Bipolar Disorder sample (32).

Our results must be qualified based on the number of different models examined. We chose a parametric approach because of its greater power, and we chose to use a limited number of both diagnostic and genetic models to best cover the most likely modes of transmission. The complexity and non-independence of the models used make it difficult to estimate the exact significance of these results. Rather, the strength of our results must be interpreted relative to other regions in our genome survey and in the context of supporting data in our examination of the NIMH sample and other independent data sets.

Three of the regions implicated in this study (22q, 13q, and 10q) have also been reported in studies of schizophrenia. Such a correspondence has also been reported for 18p and 10p (43). Although such an overlap could occur by chance or reflect two nearby but separate susceptibility genes, it also raises the intriguing possibility that many susceptibility genes are common for the two disorders. Although family studies have generally found these two disorders to "breed true," a small degree of familial overlap has frequently been observed. Recent family study data have further supported some degree of overlap (44). Only the identification of specific genes will resolve this question. However, these data raise the hypothesis that some genes contribute to susceptibility in a nonspecific way or that different mutations in the same gene may predispose to different illnesses.

In summary, our results support the presence of a susceptibility locus for bipolar disorder on chromosome 22. They also provide support for regions previously reported on 5p, 10q, 13q, and 21q and suggestive evidence for novel loci on 3p and 3q. It is intriguing that three of these regions have also been implicated in studies of schizophrenia. These molecular data raise the possibility that common susceptibility genes may be involved and that the relationship between these two disorders may be more complex than previously thought.

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