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IMMEDIATE COMMUNICATION

Genome-wide scan of bipolar disorder in 65 pedigrees: supportive evidence for linkage at 8q24, 18q22, 4q32, 2p12, and 13q12

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The purpose of this study was to assess 65 pedigrees ascertained through a Bipolar I (BPI) proband for evidence of linkage, using nonparametric methods in a genome-wide scan and for possible parent of origin effect using several analytical methods. We identified 15 loci with nominally significant evidence for increased allele sharing among affected relative pairs. Eight of these regions, at 8q24, 18q22, 4q32, 13q12, 4q35, 10q26, 2p12, and 12q24, directly overlap with previously reported evidence of linkage to bipolar disorder. Five regions at 20p13, 2p22, 14q23, 9p13, and 1q41 are within several Mb of previously reported regions. We report our findings in rank order and the top five markers had an NPL > 2.5. The peak finding in these regions were D8S256 at 8q24, NPL 3.13; D18S878 at 18q22, NPL 2.90; D4S1629 at 4q32, NPL 2.80; D2S99 at 2p12, NPL 2.54; and D13S1493 at 13q12, NPL 2.53. No locus produced statistically significant evidence for linkage at the genome-wide level. The parent of origin effect was studied and consistent with our previous findings, evidence for a locus on 18q22 was predominantly from families wherein the father or paternal lineage was affected. There was evidence consistent with paternal imprinting at the loci on 13q12 and 1q41.
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Introduction

Bipolar I (BPI) disorder is a severe psychiatric illness that affects approximately 0.5–1% of the population.[1] The features of the illness include mania, a condition with expansive grandiose (or irritable) moods with elevated energy and pressured speech.[1] The depressive phase includes a depressed mood, decreased energy, and anhedonia. A milder form of the illness, bipolar II (BPII) disorder, is characterized by hypomania (symptoms of mania but less severe) and depression. Family,[2] twin,[3] and adoption studies[4] have established that there is a genetic contribution to bipolar disorder, but no mechanism of transmission has been established. It is widely believed that multiple genes contribute to the increased familial risk.[5,6] Although the limits of phenotypic expression are not known, family studies suggest that BPI, BPII, recurrent major (unipolar) depression (RUP), and schizoaffective–manic disorder (SAM) are part of a bipolar spectrum.[2] Since major depression is so widely prevalent, many RUP cases, even in families ascertained through BPI probands, may be genetically unrelated to bipolar disorder.[7] Therefore, genetic linkage analyses have generally used at least two definitions of the affected phenotype, including and excluding RUP.[8]

Genome-wide linkage analyses of family samples with bipolar disorder provide convincing evidence that single locus forms of the disorder, if they exist, are uncommon.[9,10] However, several susceptibility loci throughout the genome have been implicated in independent samples. These include 18p11, 18q21–23,

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21q22, 4p16, 4q35, 12q24, 13q31–32, 22q11–13, and Xq24–28.[6,11] Recently, a genome-wide screen identified 8q24 and 10q25–26 as regions of suggestive linkage to bipolar disorder.[12] For an extensive review of all the implicated genetic regions, the reader is referred to publications of the chromosomal workshops of the World Congress in Psychiatric Genetics.[13] Several chromosomal regions have been implicated by genome-wide findings of only nominal significance, but have been similarly identified by other independent scans,[12,14–17] suggesting that even seemingly modest findings may point to rule bipolar loci. This seriously challenges the strict standards for thresholds for suggestive and significant linkage findings,[18] and encourages investigators to report all nominally significant results.

We recently reported parametric analysis and a 'simultaneous search' linkage analysis of the first 50 families ascertained for this project,[10] concluding that no single gene or a set of two genes was responsible for susceptibility to bipolar disorder in these families. We present here the results of nonparametric analyses of our genome-wide scan of a larger set of bipolar pedigrees ($n=65$), which includes all pedigrees that we have previously reported[10,19,20] and all genotype data from 842 markers that have been typed in these families, including genotype data from the Center for Inherited Disease Research (CIDR) in 43 of the 65 pedigrees. There are 15 regions that show nominal significance in this scan, eight of which immediately overlap regions that have been previously reported and five that are within a modest distance of other previously suggested regions.

Methods

Family ascertainment

Pedigrees were ascertained from in-patient and outpatient clinics in Maryland and Iowa. Most of the families have been previously described.[10,19–21] Ascertainment was through a treated BPI proband and at least two affected first-degree relatives. The affected phenotypes included BPI, BPII, RUP, and SAM. The ascertainment protocol sought families that were unilineal (ie the affected phenotype apparently segregated through only one parent). After ascertainment, families were excluded only if the genotype data were inconsistent with the pedigree structure (eg false paternity in the proband) or when the final diagnosis of the proband was something other than BPI. All other pedigrees meeting the initial ascertainment criteria were included. A total of 71 pedigrees were originally ascertained; three were excluded because of non-Mendelian inheritance of marker alleles, and three were excluded because of a best-estimate diagnosis in the proband other than BPI. The study protocol was approved by the JHU IRB, and all subjects gave written informed consent after the protocol and risks were explained to them.

Sample and clinical evaluation

The analyzed family sample consisted of 573 interviewed and genotyped subjects ascertained through 65 BPI probands. Among the 508 relatives, 64 were diagnosed with BPI, 97 with BPII, 69 with RUP, and seven with SAM. The mean age of onset for the BPI subjects (including probands) was 21.6 ± 11.9 years, for BPII 22.6 ± 10.5 years, for RUP 26.8 ± 11.5 years, and for SAM 22.2 ± 12.3 years. The average number of subjects per family was 8.8; the number of affected relatives ranged from 2 to 8.

Clinical assessments included family history information and available medical records. The preferred source of clinical data was direct clinical interviews conducted by experienced psychiatrists (SGS, MGM, DFM, FJM, JBP, and JRD) using the schedule for affective disorders and schizophrenia—lifetime version (SADS-L).[22] Diagnoses were established using the Research Diagnostic Criteria (RDC).[23] Best-estimate diagnoses[24] were made by two non-interviewing psychiatrists. Diagnostic reliability for interview and best-estimate diagnoses was very good, with kappa values for all affective diagnoses ranging from 0.7 to 0.98.[25]

Genotyping, genetic markers and map

Genotyping was completed in stages. A total of 842 highly polymorphic simple sequence repeat markers have been typed at various times in this collection of bipolar families. In the total set of 65 pedigrees, 245 markers have been typed in all families. The Center for Inherited Disease Research (CIDR) genotyped 43 pedigrees for 357 markers, and the remaining genotyping was completed at the Johns Hopkins University or Stanford University. The average observed heterozygosity across the chromosomes ranged from 0.72 to 0.79 with a mean observed heterozygosity of 0.73. The average information content (measured in GENEHUNTER) across the genome was 0.68. The maximum information content (0.83) was in the 18q22 region. In 54 of the pedigrees both parents were available for genotyping, nine had one parent for genotyping, and two pedigrees had neither parent. As part of quality control, CIDR genotyped 22 blind duplicates, which yielded an error rate of 0.22%; the initial error rate estimation between JHU and SU was 1 %.[19] The genotyping was completed using either ^{32}P labeled PCR primers, polyacrylamide gel electrophoresis, and autoradiography as described by Stine *et al*,[19] or by chemiluminescence[10] and since 1996 fluorescent labeled primers and electrophoresis on an ABI automated sequencing apparatus. The output from the ABI sequencer was scored using Genotyper (PE Biosytems, Foster City, CA, USA), and the alleles binned using the Genetic Analysis System (GAS).[26] There were several levels of checking the genotype data beginning with GAS that identified inconsistent inheritance patterns, a second and third level of inheritance checking was performed within the programs CRIMAP[27] and UNKNOWN.[28]

The genetic maps were generated using CRIMAP based on the genotype data of the total sample with all markers included. Between one-half and two-thirds of markers were typically placed at 1000 : 1 odds using the build option of CRIMAP. For the remainder of the markers, the relative physical position on the Celera database was used to place the markers. The 'flips' option of CRIMAP was then used to determine if the order was the most likely given the genotype data. For each of the chromosomes, we also built a map on the Marshfield web site using the 'Build your own map' function. Of the 842 markers in our data set, 142 were not in the Marshfield data set. There were 12 order discrepancies on seven chromosomes where the order of two markers was reversed; the order that was most likely based on the flips analysis in our data was used. The average spacing of markers was 4.7 cM, there were 14 gaps of 15 cM or greater and one gap greater than 20 cM (5q35). Our markers span 3944 cM across the genome and this represents 11% inflation from the 3562 cM calculated from the cumulative Marshfield map. The corresponding physical distance calculated from the Celera database is 2811 Mb (www.celera.com).

Analyses

Two definitions of the 'affected' phenotype were used. The narrow definition (BP) included BPI, BPII (with RUP), and SAM; the broad definition (BPUP) added RUP to the affected phenotype. Two affection models were selected to limit the number of analyses performed. Nonparametric multipoint linkage analyses were performed with the GENEHUNTER-PLUS (GHP)[29] modification of the GENEHUNTER package.[30] The score function 'ALL' was used based on the recommendation in the GENEHUNTER manual indicating that this statistic had proven to be a more powerful test in real pedigree data.[30] GHP allows pedigree analysis of complex inherited traits, and it estimates the statistical significance of shared alleles identical-by-descent between all affected members of the pedigree. The GHP modification[29] permits exact calculation of likelihood ratios on the basis of an exponential allele-sharing model. The nonparametric LOD scores based on the allele sharing can be used within the same inferential framework as is used for traditional LOD scores.[29] All pedigrees were weighted equally in the analysis. The number of all possible sib pairs was 186 under the BP model, and 325 under the BPUP model; the number of all possible relative pairs was 275 and 489 for the BP and BPUP model, respectively.

Genome-wide empirical significance levels for the resulting NPL scores were estimated by a modified simulation approach implemented in the study by Kehoe *et al*.[31] using a subset of 513 markers distributed across the genome. In all, 200 replicates for markers on each chromosome were simulated based on the original family structure and the observed allele frequency of each marker under the assumption of no linkage. Extended families were divided into nuclear families, and genotype data were simulated only for typed subjects. Analyses of the simulated data were completed using the same methods as for the real data (BP model). Genome-wide empirical *P*-value thresholds for the NPL scores were then determined by a tally of the number of NPL peaks in these replicates generated under the null hypothesis.

The parent of origin effect was studied across the genome in several ways. First, we used an approach described previously[19] to divide the 65 pedigrees according to the parental lineage of the disorder, then we carried out linkage analyses with the sib_ibd routine of ASPEX (v2.2) in the two groups separately. Among the 65 pedigrees, there were 23 paternal pedigrees, 34 maternal pedigrees, and eight that were unclassifiable (four with no parent or parental relative affected and four with parental relatives affected on both sides of the proband's family). Second, we used the sib_ibd routine of ASPEX to obtain separate estimates of IBD sharing of maternal or paternal alleles among affected siblings in the full sample. We elected to use ASPEX in order to compare results of these two different approaches (pedigree stratification according to sex of affected parent *vs* sharing of the parental chromosome) using the same program. We used the sib_ibd routine of ASPEX because sib_ibd allows for specific estimation and subsequent comparison of the sharing of the maternal and paternal alleles, this is not possible in the sib_phase routine of ASPEX. Finally, we analyzed the complete data set using the GENEHUNTER-IMPRINTING analytic program that is designed to uncover evidence of genomic imprinting.[32] Under this parametric model we allowed for age-dependent penetrance of the given parental allele from 0.63 to 0.85.

To further study the parent-of-origin effect, we carried out an additional multipoint analysis, following an approach suggested by Rice,[33] that used all available data and provided for a more stringent region-wide test of differences in IBD sharing among maternal *vs* paternal pedigrees or chromosomes. In this approach, the probability '*P*' of sharing alleles IBD for each affected sib pair was determined. Differences in IBD sharing between maternal and paternal pedigrees were then assessed by maximizing the likelihood with '*P*' taking different values in these pedigrees and comparing the lod score thus obtained to that obtained from maximizing the likelihood assuming that 'p' is the same for all pedigrees. The test statistic was the maximum value of the differences between these LOD scores across the test region. A region-wide *P*-value was obtained by randomly permuting the 'paternal' and 'maternal' designations among the pedigrees and comparing the resulting test statistics to the observed value. A similar method was used to test IBD differences between maternally and paternally inherited chromosomes in the affected sib pairs.

Results

The nonparametric multipoint genome-wide analyses are presented in Figure 1 for the narrow definition of affected status (BP) and in Figure 2 for the broader definition (BPUP). Table 1 further describes these 15 regions of interest in rank order of significance by individual marker, NPL with its associated *P* value, corresponding LOD score, and chromosomal band location. In the simulation study and analyses, an NPL of 2.65 was observed by chance on average once per genome scan. There were nine chromosomal regions under the BP affection status model and 12 regions under the BPUP model that exceeded nominal significance ($P \leq 0.05$; NPL > 1.6). Six regions (Figures 1 and 2) were significant under both affection status models; Table 1 shows the model with the greater significance. None of the NPL scores surpassed the level[18] required for significant linkage in a genome-wide basis.

The two strongest overall findings were identified under the narrow BP model and are on chromosome 8q and 18q. The highest peak is on 8q24 at D8SS256 with an NPL of 3.13 ($P < 0.003$) and a LOD of 2.1. The region of significant elevated allele sharing (defined with nominal $P \leq 0.05$) spans 20 cM from D8S1128 to D8S272. The next highest peak is at 18q22, with an NPL of 2.9 ($P < 0.004$) in a 20 cM region of elevated sharing from D18S1357 through D18S446, the corresponding LOD is 1.8.

There were four additional regions at 2p12, 10q26, 19p13, and 20q13 identified under the narrow BP affection status model. On chromosome 2p, the peak NPL score of 2.54 ($P < 0.007$) is at D2S99, and the associated LOD score is 1.5. The region of nominal significance spans 20 cM. On chromosome 10q26 the region of significance is much smaller, with D10S1223 producing a peak NPL of 2.12 ($P < 0.02$) in a 6 cM region; the corresponding LOD is 1.5. On 19p13, one marker D19S586 showed an NPL of 1.8 ($P \leq 0.04$) with no significance at flanking markers. A single marker, D20S480, was responsible for an NPL of 1.81 ($P < 0.04$) on 20q13.

On the long arm of chromosome 4, there are two broad regions, at 4q32 and 4q35, identified under the BPUP affection status model. At 4q32, there is a peak at D4S1629 in a 10 cM region between D4S1629 and D4S243, with an NPL of 2.80 ($P \leq 0.004$) and a LOD of 1.9. At 4q35, the peak finding is at D4S3051 with an NPL of 2.43 ($P < 0.01$) and a LOD of 1.2 in a 30 cM region from D4S2417 to D4S1652. The peaks of these two regions are separated by 50 cM on the genetic map and 30 Mb on the physical map and are likely to represent separate susceptibility loci.

Several additional potential susceptibility loci were identified under the BPUP model including a 20 cM region on 13q12 (NPL = 2.53, $P \leqslant 0.009$; LOD = 1.6), a 10 cM region on 1q41 (NPL = 2.27, $P \leqslant 0.01$; LOD = 1.4), as well as regions on 20p13, 12q24, 9p13, 14q23, and 2p22 having associated *P* values between 0.01 and 0.05.

Parent-of-origin analyses

Table 2 presents results of the analyses of the parent-of-origin effect using three separate analytical approaches. In the first approach, the pedigrees were stratified according to the sex of the affected parent or parental lineage as previously described.[19] The parent-of-origin effect that we originally reported on chromosome 18q21–22 continues to be suggested in this enlarged sample; the MLS (sib_ibd, ASPEX) was

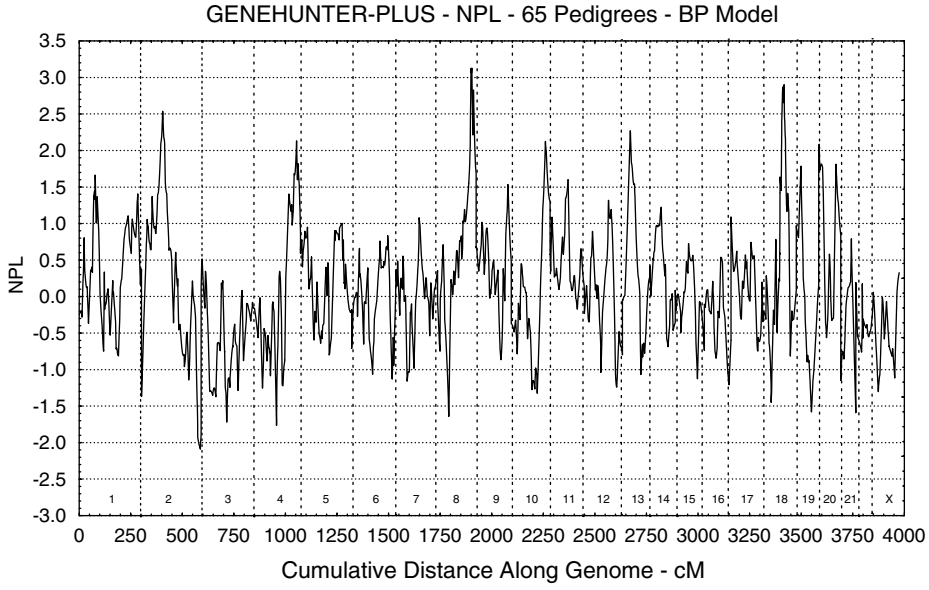

Figure 1 Results of nonparametric analyses using GENEHUNTER-PLUS under the narrow definition of the phenotype that includes BPI, BPII, and SAM. Chromosomes are indicated along the bottom of the figure. The cumulative distance is the additive cM distance of the genome beginning at 1p–Xq.

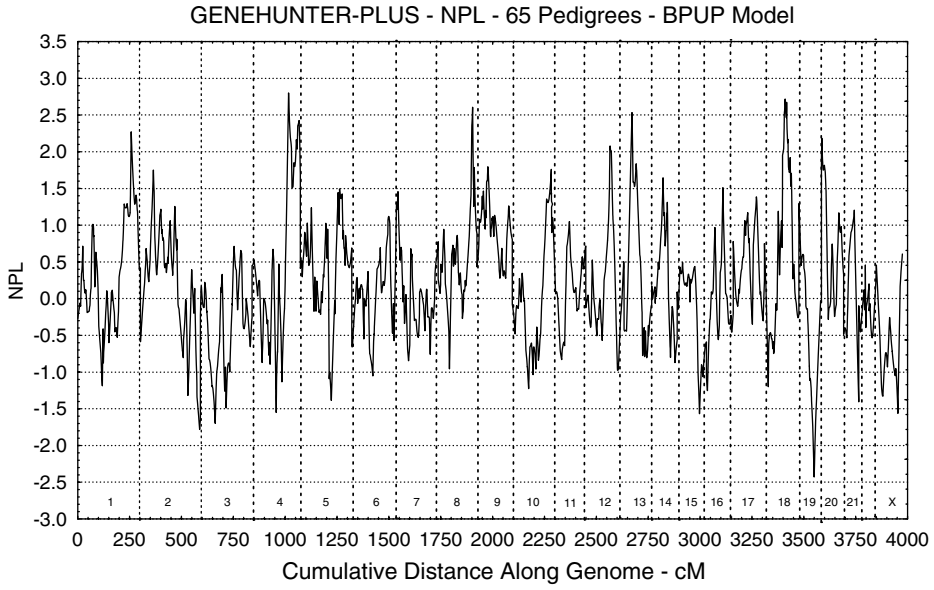

Figure 2 Results of nonparametric analyses using GENEHUNTER-PLUS under the broad definition of the phenotype that includes BPI, BPII, RUP, and SAM. Chromosomes are indicated along the bottom of the figure. The cumulative distance is the additive cM distance of the genome beginning at 1p–Xq.

Table 1 Total sample of 65 bipolar pedigrees, regions showing nominal significance ($P \leq 0.05$) presented in rank order

Chromosome[a] (peak marker)	*Model[b]*	*Dist pter[c] (cM)*	*Physical position[a] (Mb)*	*NPL (*P *value)*	*LOD (ASM)*
8q24 D8S256	BP	166	133	3.13 (0.003)	2.1
18q22 D18S878	BP	107	62	2.90 (0.004)	1.8
4q32 D4S1629	BPUP	175	158	2.80 (0.004)	1.9
2p12 D2S99[d]	BP	103	73	2.54 (0.007)	1.5
13q12 D13S1493[d]	BPUP	38	16	2.53 (0.009)	1.6
4q35 D4S3051	BPUP	226	188	2.43 (0.01)	1.2
1q41 D1S549	BPUP	257	196	2.27 (0.01)	1.4
20p13 D20S117	BPUP	2	0.7	2.18 (0.02)	1.2
10q26 D10S1223[e]	BP	165	128	2.12 (0.02)	1.5
12q24 D12S69[d]	BPUP	117	100	2.08 (0.02)	1.2
20q13 D20S480	BP	84	49	1.81 (0.04)	0.8
9p13 D9S1118[d]	BPUP	52	32	1.8 (0.04)	0.7
19p13 D19S586	BP	22	10	1.78 (0.04)	0.8
2p22 D2S1788	BPUP	62	37	1.75 (0.04)	0.7
14q23 D14S592	BPUP	55	42	1.64 (0.05)	0.7

[a]Determined from the Celera database (www.celera.com).
[b]BP model includes BPI, BPII, and schizoaffective disorder. BPUP model includes recurrent unipolar depression in addition to the phenotypes of the BP model.
[c]Distance from the p telomere as estimated by CRIMAP.
[d]The assignment of cytogenic band differs from the UCSC database (2p13, 9p21, 12q23, and 13q13).
[e]D10S1223 position based on UCSC (not found in Celera).

1.51 in the paternal pedigrees but only 0.06 in the maternal ones. The second approach compared the sharing of parental alleles among affected sibling pairs. The most impressive finding in these analyses was the elevated sharing of the maternal chromosome at 13q12, where the MLS for maternal alleles was 3.05 and −0.18 for paternal alleles. The third approach used the GENEHUNTER-IMPRINTING analytical program and the most impressive finding was again at 13q12 wherein the paternal imprinting model resulted in an HLOD of 1.98. Paternal imprinting implies silencing of the paternal alleles allowing expression of maternal alleles, this is consistent with the elevated sharing of maternal alleles identified in the second approach using sib_ibd analyses of ASPEX. A second region suggesting paternal

Table 2 Parent-of-origin analyses

Chromosome	*Marker*	*Model*	*Pedigree Stratification*[a]		*Parental Chromosome*[b]		*Imprinting*[c]	
			Paternal (23 peds) MLS[d]	*Maternal (34 peds) MLS*[d]	*Paternal MLS*[d]	*Maternal MLS*[d]	*Paternal (maternal expression) HLOD*	Maternal *(paternal expression) HLOD*
8q24	D8S256	BP	0.17	2.2	0.13	1.22	1.44	0.5
18q22	D18S878	BP	1.51	0.06	0.95	0.44	0.3	1
4q32	D4S1629	BPUP	1.5	0.51	0.62	0.4	0.7	0.76
2p12	D2S1394	BP	0.44	1.82	−0.49	1.04	1.05	0.4
13q12	D13S1493	BPUP	0.69	0.65	−0.18	3.05	1.98	0
4q35	D4S3051	BPUP	0.55	0.36	−0.11	0.41	1.19	0.01
1q42[d]	D1S163	BPUP	1.14	0.01	−0.65	1.43	1.14	0
20p13	D20S117	BPUP	0.47	0.72	1.2	0.39	0.9	1.2
10q26	D10S217	BP	0.4	0.11	0.05	0.11	1.2	0
12q***24***	D12S69	BPUP	0	1.37	0.01	0.021	0.8	0.7

[a]Pedigrees stratified according to the sex of the affected parent, 23 'paternal' pedigrees had either an affected father or affected family member in paternal lineage. Analyses using sib_ibd package of ASPEX.
[b]Sharing of parental chromosomes analyzed (total sample of 65 pedigrees) among affected sibling pairs. Analyses using sib_ibd package of ASPEX.
[c]Imprinting analyses performed using GENEHUNTER-IMPRINTING. Paternal imprinting implies silencing of paternal chromosome to allow expression of maternal alleles.
[d]This locus is 30 cM telomeric from the 1q41 region identified using GENEHUNTER.

imprinting was at 1q41 where there was evidence of increased sharing of maternal alleles (MLS = 1.43) and the GENEHUNTER-IMPRINTING analyses showed an HLOD of 1.14 under the paternal imprinting model, suggesting expression of the maternal alleles. In the multipoint region-wide analysis there was a significant difference in the sharing of maternal *vs* paternal alleles on 13q12 ($P = 0.02$) and 1q41 ($P = 0.02$), both loci sharing maternal alleles above paternal. Under the broad affection status model GENEHUNTER-IMPRINTING identified two additional regions at D5S2848 with an HLOD of 1.5 and at D7S513 with an HLOD of 2.1, both with a paternal patern of imprinting.

Discussion

The results of these nonparametric analyses have been presented in rank order for clarity and to represent a hierarchical likelihood of the presence of susceptibility genes. No one region reaches what has been considered to be of statistical significance for a genome-wide scan,[18] nor is it clear how these strict criteria should be applied to disorders of complex inheritance. However, a comparison of our results with other findings in the field suggest that a number of regions are repeatedly being identified in independent samples, increasing the likelihood of gene identification in the coming years.

Several of the linkage regions identified in the current analyses are consistent with results from previous reports of bipolar linkage studies. The best evidence for a bipolar susceptibility gene in the present sample occurred at D8S256 on 8q24.3 (NPL = 3.13, $P < 0.003$). This region had been previously identified in a parametric analysis of our first 50 pedigrees.[10] It is noteworthy that this region overlaps with the strongest linkage finding identified by Cichon *et al*[12] (LOD = 3.6), which surpasses the criteria suggested by Lander and Kruglyak[18] for significant linkage. Cichon *et al*[12] studied 75 bipolar pedigrees from German, Israeli, and Italian origins. The strong findings in these two independent samples meet the criteria for replication as defined by Lander and Kruglyak,[18] and should be given serious consideration for future fine-mapping efforts. A gene encoding a protein tyrosine kinase is in the region[34] as well as in the thyroglobulin gene,[35] but otherwise there do not appear to be any obvious candidate genes in the region.

The evidence for a susceptibility locus on chromosome 18q21–22 remains consistent with our three previous analyses on subsets of this pedigree collection.[10,19,20] The peak NPL score at D18S878 was 2.9 ($P = 0.004$). The increased sharing reported in the current genome scan spans a broad region of ~30 cM for either BP or BPUP affection status. This broad 30 cM region overlaps with regions identified by Stine *et al*[19] and McMahon *et al*.[20] In the initial parametric analyses of Friddle *et al*,[10] using the first 50 families ascertained, an HLOD of 0.9 was reported under a dominant model. However, under nonparametric analyses of the same pedigree set an NPL of 2.6 ($P = 0.005$) was seen at D18S1270, a marker flanking D18S878 (data not shown). There were an additional 20 markers typed on chromosome 18q in the current

data set of 65 pedigrees and the HLOD at D18S878 is 1.6 (alpha 0.25) (data not shown). An analysis in a subset of these pedigrees indicates that siblings with BPII disorder contribute a significant portion of the increased allelic sharing.[36] Several other studies of bipolar disorder have implicated 18q,[15,37–39] but as might be expected with a complex disorder,[40] not all studies have replicated this finding.[38,41–43]

The next strongest finding in the present study was at D4S1629 on 4q32 (NPL = 2.8, $P<0.004$) using the BPUP affection model, which coincides with a region identified by Ekholm *et al*.[44] Ekholm *et al*[44] studied 41 Finnish pedigrees and reported a Z_{max} of 3.3 at D4S1629. Taken together, these two studies provide strong evidence for a potential bipolar susceptibility gene in this region. Potential candidate genes for consideration include: the tryptophan oxygenase gene (TDO2)[45] and potentially genes encoding a glycine receptor (GLRB)[46] and glutamate receptor (GRIA2).[47] We observed a second peak on chromosome 4 at marker D4S3051 on 4q35 (NPL = 2.43, $P<0.01$). This region overlaps with a report by Adams *et al*[48] who found a parametric LOD = 3.19 under a dominant model and broad affection status. This marker is within 1 Mb of the melatonin receptor gene.[49]

Our fourth strongest finding is on 2p12 with D2S99 representing the peak in a 20 cM region (NPL = 2.54, $P<0.004$) and overlaps with a weak finding of Cichon *et al*[12] at D2S286, wherein they reported a LOD of 1.26 under a recessive model. Our nominally significant finding at 2p22 is very near a modest finding by Cichon *et al*[12] at D2S367 with a recessive LOD of 1.08.

On chromosome 13q12 we observed an NPL of 2.5 ($P<0.009$) at D13S1493. These results provide support for the region identified by Badenhop *et al*.[14] A maximum NPL of 4.09 ($P=0.008$) was found at D13S1272 in a broad region of significance defined by D13S218 and D13S153, which directly overlaps our region. This locus is 10 Mb distal from the locus identified by Cichon *et al*.[12] Other reports have implicated this region and included the NIMH collaborative study[50] and in the Old Order Amish.[51] A candidate near this region is the serotonin 2A receptor gene (HTR2A),[52] although the initial studies on this candidate have not been promising.[53–56]

The linkage region on 1q41 at D1S549 is within 4 Mb of the broad region between D1S471 and D1S237 identified by Detera-Wadleigh *et al*[57] in a collection of 22 North American pedigrees. Our finding is within 10 Mb of the region implicated in a Finnish study of schizophrenia[58] and a UK study[59] which is of interest in the light of the reports of overlap of genetic regions for schizophrenia and bipolar disorder.[60] The first report implicating this region was a study that suggested 1q32 was more likely to harbor fragile sites in subjects with bipolar disorder compared to controls.[61] A large Scottish family with both affective disorder and schizophrenia identified a translocation at 1q42[62] involving the DISC1 gene; the LOD score in this one family was 7.1 when both phenotypes were included.

There are several other regions where our data provide some evidence of increased allele sharing near previously reported linkages to potential bipolar susceptibility loci. A maximum NPL = 2.18 on chromosome 20p is approximately 5 Mb telomeric from a region identified by Radhakrishna *et al*.[63] This region is rather gene rich with one potential candidate, the alpha 1-adrenergic receptor subtype (ADRA1D).[64] The NIMH collaborative BP sample also reported modest findings on 20p.[8]

A peak on chromosome 10 at 10q26 (NPL = 2.12, $P<0.02$) coincides with the second strongest linkage finding by Cichon *et al*[12] in this same region (NPL = 3.12, $P=0.0013$). Further, this region was recently implicated in a haplotype analysis of patients with bipolar disorder in an isolated Faroese population.[17] Kelsoe *et al*[16] also identify this region in a population of North American families with a LOD score of 1.74 at D10S217 and a LOD of 2.23 at the flanking marker D10S1223. Both these markers were typed in our sample and were nominally significant. A potential candidate immediately in this region is a protein tyrosine phosphatase receptor (PTPRE).[65] A susceptibility locus for schizophrenia has been reported[66,67] in the 10q25–26 region and is within a few Mb of the bipolar locus.

The chromosomal region 12q23–24 has attracted considerable interest following the report of linkage between the Darrier's gene locus and bipolar disorder.[68] Our signal at D12S69 at 12q24 is found within the broad region suggested by Morissette *et al*.[69] The region reported by Degn *et al*[70] is over 20 Mb telomeric from our locus and may be a separate locus. This very broad region of modest findings in independent studies is not uncharacteristic of complex disorders and the significant heterogeneity in each sample results in the peak finding shifted by the negative contributions of unlinked families.

Our nominally significant finding on 14q23 is near that identified in the NIMH collaborative study[50] and in a more recent Irish study.[71] The same Irish group studied an estrogen receptor gene in the region and found no association with bipolar disorder.[72] A pericentromeric inversion inv (9)(p11–q21) has been associated with bipolar disorder[73] near our finding at 9p13.

Finally, this genome-wide scan provides little support for the presence of the susceptibility locus first reported by Berrettini *et al*[74] on chromosome 18p. In our initial report on chromosome 18, we found evidence for a susceptibility locus on 18p at a number of loci including D18S37, D18S53, and D18S464.[19] In that report,[19] only half of the possible genotype data was available for D18S37. Analysis of the complete genotype data now available for the initial 28 pedigrees continues to indicate an increase in allele sharing among affected sibs at D18S53 and D18S464, although not at D18S37. In the larger set of 65 pedigrees, the IBD sharing at D18S53 is not significantly increased. D18S464 was not typed beyond the initial 28 families. Although the evidence for linkage

at 18p diminished with more complete genotype data and more families, the results remain inconclusive.

Parent-of-origin effect

In contrast with some retrospective analyses,[75,76] several clinical studies suggest a parent-of-origin effect in bipolar pedigrees, suggesting a basis for familial heterogeneity.[77–80] Whether this is a genetic effect, and if so, by what mechanism, reflects unanswered but important questions with implications for the mode of inheritance. Possible molecular genetic explanations could involve X-linkage, mitochondrial inheritance, or other forms of non-Mendelian inheritance such as genomic imprinting. It is unclear what the best analytic strategy for studying the parent-of-origin effect is. We, therefore, used different but complementary approaches.

In bipolar disorder, the parent-of-origin effect has been most extensively studied on chromosome 18. In a previous analysis of a subset of the current sample, we divided the pedigrees according to the parental lineage of the disorder and found increased evidence of linkage on 18q primarily among the paternal pedigrees.[19] Several groups subsequently incorporated these analyses into their reports. Gershon *et al*[81] and Nothen *et al*[38] reported evidence for a similar parent-of-origin effect on chromosome 18, while others failed to confirm such findings.[42,82] In the current analysis of our expanded sample and using a similar approach, we again find increased evidence of linkage among the paternal pedigrees. Notably, there is a 30 cM region with 14 consecutive markers showing an MLS > 1 in the paternal pedigrees on 18q. None of the markers showed the same pattern in the maternal pedigrees. Further, we have identified phenotypic features within these pedigrees that may focus the search in this region; McMahon *et al*[36] reported 80% sharing of paternal alleles in BPII affected sibling pairs. The parent-of-origin effect on chromosome 18, therefore, may be limited to a specific clinical subtype of bipolar families.

The most compelling evidence for a parent-of-origin effect in the current analysis is observed on chromosome 13q12. Although we found no difference in allele sharing among maternal *vs* paternal pedigrees, we observed substantially increased sharing of maternal alleles across three consecutive markers. A multipoint comparison in this region indicated that the difference between the sharing of the parental and maternal alleles was significant. This significant elevation in sharing of the maternal chromosome is consistent with our finding from the analyses with GENEHUNTER-IMPRINTING of increased evidence of linkage in the region under a paternal imprinting (maternal expression) model in the region. Genomic imprinting occurs in a serotonin receptor (HTR2) gene near these loci,[83] where exclusive maternal expression of HTR2 has been associated with delayed onset of retinoblastoma. Similar evidence of a paternal imprinting (maternal expression) model was found at 1q41 with significant evidence under a multipoint comparison in the region. The GENEHUNTER-IMPRINTING finding at D5S2848 is near the dopamine transporter gene on 5p15 that has been implicated by Kelsoe *et al*.[84] There have been no reports of linkage to the other finding at the 7p15 region.[85] There was no evidence of imprinting at 14q23 or 16q21 as reported earlier by Cichon *et al*.[12]

Further study of this phenomenon is clearly warranted and there are a number of approaches to study the parental sex effect. Clustering of pedigrees according to the sex of the affected parent was initially reported in nuclear pedigrees but is not useful in pedigrees of three or more generations, where there are both affected fathers and mothers, this case, a third category of mixed inheritance pedigrees must be added.[81] A more straightforward approach is the estimation of elevated sharing of the maternal or paternal allele, respectively, in affected sibling pairs as can be done in the program ASPEX. This approach is complimented by GENEHUNTER-IMPRINTING, which allows for age-dependent penetrance of individual parental alleles.[32]

Conclusion

In summary, a genome-wide scan of 65 bipolar pedigrees shows 15 regions that surpass the nominal significance level. Eight of these regions directly overlap with previously reported linkage findings for bipolar disorder and include chromosomal segments on 8q24, 18q22, 4q32, 13q12, 4q35, 10q26, 2p12, and 12q24. Five regions were within a 5–10 Mb distance of previously reported findings on 20p13, 2p22, 14q23, 9p13, and 1q41. This suggests that findings for linkage to bipolar disorder are beginning to converge towards a number of valid loci of interest. The results presented in the present study, in conjunction with the existing studies, provide more supportive evidence for the regions discussed here, but are inadequate to resolve the location of individual susceptibility loci that predispose for bipolar disorder. Resolution will require pooling of resources with combined analyses of datasets from multiple studies with standardization to the extent possible of genotype and phenotype data. Subsequent follow-up of regions suggestive of linkage in the combined samples should include: (1) high-resolution genotyping using conventional microsatellite markers completed at a centralized facility to allow across-sample analyses and, (2) for those regions that remain at least suggestive of linkage genotyping of single nucleotide polymorphisms (SNPs) for association and linkage disequilibrium studies. Finally, sequencing of regional candidate genes including associated promotor regions will need to be done in a systematic way in an initial attempt to identify gene variants that may be associated with or predispose to illness. These may be useful as SNPs in subsequent case/control studies in larger populations.

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