Linkage of Bipolar Disorder to Chromosome 18q and the Validity of Bipolar II Disorder

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Background: An analysis of the relationship between clinical features and allele sharing could clarify the issue of genetic linkage between bipolar affective disorder (BPAD) and chromosome 18q, contributing to the definition of genetically valid clinical subtypes.

Methods: Relatives ascertained through a proband who had bipolar I disorder (BPI) were interviewed by a psychiatrist, assigned an all-sources diagnosis, and genotyped with 32 markers on 18q21-23. Exploratory findings from the first 28 families (n=247) were tested prospectively in an additional 30 families (n=259), and the effect of confirmed findings on the linkage evidence was assessed.

Results: In exploratory analyses, paternal allele sharing on 18q21 was significantly (P=.03) associated with a diagnostic subtype, and was greatest in pairs where both siblings had bipolar II disorder (BPII). Prospective analysis confirmed the finding that BPII-BPII sibling pairs showed significantly (P=.016) greater paternal allele sharing. Paternal allele sharing across 18q21-23 was also significantly greater in families with at least one BPII-BPII sibling pair. In these families, multipoint affected sibling-pair linkage analysis produced a peak paternal lod score of 4.67 (1-lod confidence interval, 12 centimorgans [cM]) vs 1.53 (1-lod confidence interval, 44 cM) in all families.

Conclusions: Affected sibling pairs with BPII discriminated between families who showed evidence of linkage to 18q, and families who did not. Families with a BPII sibling pair produced an increased lod score and improved linkage resolution. These findings, limited by the small number of BPII-BPII sibling pairs, strengthen the evidence of genetic linkage between BPAD and chromosome 18q, and provide preliminary support for BPII as a genetically valid subtype of BPAD.

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SUBJECTS AND METHODS

FAMILY ASCERTAINMENT AND EVALUATION

Ascertainment and evaluation methods are detailed elsewhere.7,20 All families included in this study were ascertained with the following criteria: a proband with a history of bipolar I disorder (BPI); at least 1 additional sibling, or 1 sibling and only 1 parent, with a major affective disorder; and no evidence of major affective disorder in both parental lineages by family history. (Two families in which major affective disorder was discovered in both parental lineages after direct interview, and 3 families whose probands were not felt at final diagnosis to have typical BPI, were included.) Informed consent was obtained from all participants.

Subjects were interviewed by a psychiatrist using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L).21 Two additional psychiatrists reviewed the interview, family informant data, and any medical records before assigning a best-estimate diagnosis under Research Diagnostic Criteria.22 The diagnosis of bipolar II disorder (BPII) required a subject’s having recurrent major depression as well as hypomanias. Using these methods, we have achieved excellent diagnostic reliability (κ values for BPI, BPII, and recurrent major depression all equalled or exceeded 0.99).

SAMPLES STUDIED

We used a 2-sample design to allow some exploratory data analysis while minimizing chance findings. In the first sample, family set A, we carried out exploratory analyses aimed at formulating a hypothesis as to which clinical features predict allele sharing. Clinical data came from the manic, hypomanic, and depression sections of the SADS-L, and from the diagnostic subtype (BPI, BPII, recurrent major depression, schizoaffective-manic) assigned by the best-estimate psychiatrists. We subsequently tested the findings from set A in the second independent set B.

Data for set A were originally reported elsewhere.4 Briefly, it consisted of 286 diagnosed subjects in 28 families. Of these, 59 subjects (21%) had BPI, 49 subjects (17%) had BPII (plus recurrent major depression), and 28 subjects (10%) had recurrent major depression (RUP). A best-estimate diagnosis of “phenotype uncertain” was assigned to 69 subjects (24%), and 81 subjects (28%) were considered unaffected. Based on informativeness for linkage analysis, 247 subjects were selected for genotyping.

Set B was also originally described elsewhere.7 It consisted of 30 families, and was completed after set A, but before August 1, 1996 (when the data set was “frozen” for analysis upon meeting prior thresholds for statistical power).7 Of the 300 subjects to whom a best-estimate diagnosis could be assigned, 59 (20%) had BPI, 40 (13%) had BPII plus recurrent major depression, 42 (14%) had RUP, and 6 (2%) had schizoaffective manic disorder. Of the remaining subjects, 70 (23%) were considered unaffected, and 83 (28%) were considered “phenotype uncertain.” The 259 most informative subjects were selected for genotyping.

GENOTYPING

Genotyping was performed as described previously.7 DNA was genotyped by polymerase chain reaction using multiplexed, fluorescent-labeled primers and electrophoresis on an automated sequencer (Perkin Elmer Applied Biosystems Inc, Foster City, Calif) with semiautomated allele scoring. For the exploratory analyses, we used data from the markers D18S487, D18S1095, and D18S538 (the 18q markers most strongly linked to BPAD when we originally analyzed these data4) typed in 28 families. For the prospective analyses, we used a dense set of 32 markers spanning the region between D18S487 and D18S1095 at a mean odds. These studies can be interpreted as supporting a pericentromeric locus,5,6 an 18q21-22 locus,7,8 both loci,9,10 2 other chromosome 18 loci,11,12 or no compelling chromosome 18 linkage at all.14-17 Thus, while linkage of BPAD to chromosome 18 seems likely, the evidence in individual samples is modest, and the linkage signals are not well localized, particularly across samples. This is the expected situation with genes of small effect, when significant genetic heterogeneity is present, or when at least some of the results represent false positives.18,19

We investigated whether a systematic analysis of the relationship between clinical features and allele sharing could clarify the question of genetic linkage between BPAD and markers on chromosome 18q21-22. We studied the Johns Hopkins/Dana Foundation Bipolar Disorder Pedigrees, a series of multiplex families showing evidence of linkage to chromosome 18q21-22 in prior studies.4,7 The overall goals were to define the clinical features characteristic of families linked to 18q21-22, verify the prior linkage findings, and improve their resolution as the basis for future work aimed at cloning a susceptibility allele.

RESULTS

EXPLORATORY ANALYSES

Thirty-one variables were analyzed (Table 1). Nominal significant differences (P<.05) were observed between sharing and nonsharing pairs in occurrence of mania immediately before or after major depression, and in occurrence of mood-congruent psychotic features during major depression. Neither result remained significant after Bonferroni correction. In contrast, a highly significant difference (overall χ2 = 20.89, P < .001) between sharing and nonsharing pairs was observed for diagnostic subtype, which remained significant (P = .03) after Bonferroni correction. No significant differences were detected for the other 28 variables.

The significant effect of diagnostic subtype was examined further by direct comparison of allele sharing in sibling pairs grouped into all 6 possible combinations of diagnostic subtype: BPI-BPI, BPI-BPII, BPI-RUP, BPII-BPII, BPII-RUP, and RUP-RUP. Sibling pairs in which both siblings were diagnosed with BPII disorder were most
sex-averaged interval of 2.4 cM. The first analysis of these data has been reported previously.7

STATISTICAL METHODS

Exploratory Analyses

Set A genotypes were used to score each sibling pair for unambiguous sharing or nonsharing of marker alleles. The clinical features of sharing vs nonsharing of marker alleles were compared. For categorical variables with more than 2 categories, all discordant pairs were pooled. Paternal and maternal alleles were analyzed separately, since earlier analyses indicated that on 18q only paternal marker alleles were shared in excess by affected sibling pairs.1,2 Continuous variables were analyzed by the t test; categorical variables, by a maximum-likelihood χ² test. The 2 level of significance was set at .05; multiple comparisons underwent Bonferroni correction. Statistics were calculated using STATISTICA (Release 4.5, StatSoft Inc, Tulsa, Okla).

It was not possible to score allele sharing by all sibling pairs using the single-marker genotype data, so we reanalyzed allele sharing by diagnostic subtype using multipoint haplotypes that take genotypes at adjacent markers into account, and reduce the effect of variable marker informativeness. Multipoint haplotype analyses were performed on both sets A and B using data from the set of 32 markers. Haplotypes were assembled with GENEHUNTER,23 and sibling pairs were scored based on unambiguous sharing or nonsharing of phased alleles at each marker. Again, paternal and maternal chromosomes were analyzed separately. Haplotypes were also used to edit out probable genotype errors prior to linkage analysis, as detailed elsewhere.7

Linkage Analysis

Linkage analysis was performed using the sib_ibd and sib_phase programs in ASPEX.24 Based on the results of the prior analyses, we partitioned the 58-pedigree sample into those families that had at least 1 BPII-BPII sibling pair (n=16 nuclear families; 1 pedigree was split into 2 nuclear families) and those that did not (n=43 nuclear families). Sex-specific maps were generated using the sib_map program in ASPEX24; marker order was determined genetically as described previously; but it cannot be considered definitive for such densely placed markers. Bipolar I disorder and BPII were considered affected phenotypes, and paternal and maternal allele sharing was estimated for all possible affected sibling pairs under an additive genetic model.

The effect of BPII-BPII allele sharing on linkage resolution was assessed by comparing linkage results in the total set of 59 nuclear families with those of the 16 nuclear families with at least 1 BPII-BPII sibling pair. For purposes of comparison, resolution was based on 1-lod confidence intervals. Linkage was tested under the same affection status model (BPI and BPII) in both analyses.

The significance of lod score changes was assessed by generating 5000 samples of 16 nuclear pedigrees randomly selected from the total set, and subjecting each sample to multipoint linkage analysis as described above. A more conservative assessment was based on those random samples with at least 48 sibling pairs, since our actual selection strategy implicitly required at least 48 sibling pairs (16 nuclear families × [2 BPII siblings + 1 BPI proband per family]), and larger samples have more power to detect linkage.

Data Management

Data management was achieved using a relational database system based on PARADOX (versions 5 and 8, Corel Corporation, Ottawa, Ontario), as described elsewhere.25 The data in this system have undergone rigorous cleaning and editing procedures, with a residual error rate estimated at less than 0.6% per 10000 data items.

likely to share an excess of paternal alleles. Fifteen of 15 BPII-BPII pairs (100%) shared paternal alleles identical by descent (IBD), compared with 22 of 30 pairs (73%) for BPI-BPII sibling pairs and IBD proportions close to the expected 50% for each of the 4 other types of affected sibling pairs. This result was confirmed by multipoint haplotype analysis. Again, paternal allele sharing was significantly associated with a diagnostic subtype (overall χ² = 16.16, P = .007) and was greatest in BPII-BPII sibling pairs (Table 1A).

PROSPECTIVE ANALYSIS

Based on these results, we formulated the hypothesis that BPII-BPII sibling pairs share paternal alleles on 18q21 more often than the other types of sibling pairs. Subsequently, this hypothesis was tested in an independent set of 30 families using multipoint data (Figure 1B). This indicated that BPII-BPII sibling pairs shared 9 of 11 paternal marker alleles (82% IBD), which was significantly more than the 71 of 129 (55% IBD) proportion of allele sharing observed in the other types of affected sibling pairs taken together (Fisher exact test = 0.016). An apparent decrease in paternal allele sharing by RUP-RUP pairs was based on only 8 pairings and was not significant.

EFFECT ON LINKAGE EVIDENCE

Inspection of allele sharing in each family revealed that BPII-BPII sibling pairs shared paternal alleles with BPII-BPII sibling pairs in the same family. We therefore hypothesized that entire families with 1 or more BPII-BPII sibling pairs would show genetic linkage to 18q, while other families would not. The results are presented in Table 2. The BPII sibling pair families demonstrated linkage to several 18q markers. In these families, there was highly significant (P ≤ .005) linkage to paternal alleles at five 18q21 markers, near the markers tested in the initial clinical analyses, and to 4 more distal markers. The evidence for linkage peaked at D18S346 in 18q21 (86.0% IBD; χ² = 22.35, P = .000002) and again distally at D18S1106 in 18q22-23 (80.8% IBD; χ² = 19.69, P = .000009).
Families of BPII sibling pairs accounted for essentially all of the evidence of linkage to 18q previously observed in this pedigree sample. No evidence of linkage was detected in the 43 families with no BPII-BPII sibling pairs, even though these families had a larger total number of affected sibling pairs and would display more evidence of linkage if it existed. When paternal allele sharing across D18S38 (58 families) in affected sibling pairs, grouped by pair type. Data for families from set A are given in the top half of the figure, and those from set B are provided in the bottom half. The total number of scored pairs ([n*(n-1)]/2) is indicated under each pair type on the x-axis. BPI indicates bipolar I disorder; BPII, bipolar II disorder; and RUP, recurrent unipolar depression.

The linkage resolution was substantially improved in families with a BPII-BPII pair (Figure 2). In these families, the 1-lod confidence interval for linkage spanned approximately 12 cM (sex averaged), compared with a confidence interval of more than 44 cM (sex averaged) for all 58 families. This approximately 3-fold improvement in linkage resolution is consistent with published simulations,19 and it implies a substantial decrease in genetic heterogeneity. Also consistent with a decrease in heterogeneity was an increase in the peak paternal lod score, from 1.53 in the total sample to 4.67 in the 16 BPII sibling pair families. This occurred despite a reduction in sample size from 16+ to 81 affected sibling pairs.

The observed increase in lod score was highly significant by asymptotic theory ($\chi^2 = 18.79$, $P < .001$) and by simulation. A paternal lod score greater than 4.67 was observed 22 times in 5000 simulations — equivalent to an empirical $P$ value of .004. The empirical $P$ value remained significant ($P = .01$) when the estimate was restricted to random samples containing at least 48 sibling pairs (see the “Subjects and Methods” section).

In both exploratory and prospective analyses performed on independent sets of families, affected sibling pairs with BPII were distinguished between families who showed evidence of genetic linkage to chromosome 18q and families who did not. The families with BPII-BPII pairs demonstrated significantly higher allele sharing at several 18q markers, accounting for essentially all the evidence of linkage to this region previously observed in this sample. Furthermore, families with BPII-BPIII pairs substantially improved the peak lod score and the resolu-
This study has several strengths. All subjects were interviewed and diagnosed by psychiatrists. Perhaps as a result of this, we achieved high interrater reliability. In particular, the diagnosis of BPII disorder showed a κ score of 0.99 at the best-estimate level in this sample. The clinical data were managed using stringent error prevention, detection, and correction procedures, and the genotype data were derived from a dense microsatellite marker map. The potential effect of multiple comparisons on type I error was minimized by a 2-sample design and by assessing the significance of the lod score change through simulation.

The major weakness of this study is the small number of BPII-BPII sibling pairs in each set of families. Although to our knowledge this is one of the largest BPAD family samples studied to date, with 586 subjects in 58 pedigrees, set A contained only 15 independent BPII-BPII pairs, and set B contained only 11. Our linkage results are based on all 81 affected sibling pairs in the 16 BPII sibling pair families, not just the BPII-BPII pairs; however, even this sample is not large by current standards. Stratification can be a valuable strategy when it results—as in this study—in increased allele sharing; however, the shrinking of comparison groups is an inevitable consequence of subdividing the affected phenotype in an attempt to define more genetically homogeneous groupings. One could avoid stratification, and perform instead a covariate-based linkage analysis, a method that is now becoming feasible. Such a method should also ideally allow the simultaneous assessment of many clinical variables with allele-sharing, thus minimizing multiple comparisons. Another weakness of this study is the reliance on the retrospective self-report of clinical symptoms by subjects. The effect of any misreporting was minimized by seeking corroborative data in medical records and in the reports of family informants. The more severe forms of a phenotype are traditionally considered easier to map by linkage analysis. Accordingly, some authorities have recommended using only BPII cases in linkage studies. Our data suggest that this strategy may not be optimal for detecting genetic linkage to 18q, even in families ascertained through BPII proband of the multipoint linkage analysis. These results strengthen the evidence that a gene important in BPAD resides on chromosome 18q and provides preliminary support for BPII as a genetically valid subtype of BPAD.

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Table 2. Point-Wise Identical by Descent Sharing at 18q Marker Loci

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*BPII indicates bipolar II disorder; BPI, bipolar I disorder; and IBD, identical by descent. All paternal and maternal percentage IBD values are proportions of sibling pairs sharing alleles identical by descent. All P values are estimated with 1 df.
bands. In our sample, the siblings with BPII contributed substantially to the detection of linkage, and they clustered in families that had the greatest evidence of linkage to 18q. Bipolar I disorder may actually represent complications of a milder, genetically less complex disorder, as we have suggested previously.31

Parent-of-origin effects encompass an important and growing class of clinical genetic phenomena, wherein the phenotype in the offspring depends on the sex of the transmitting parent.32 We have previously reported that the parent of origin influences the linkage of BPAD to chromosome 18q. In the same 28 families that constitute set A, Stine et al30 found greater lod scores in families with apparently transmitting fathers—an effect that was most striking for 18q21 markers. In the same 30 families that constitute set B, McMahon et al7 observed the largest IBD excess allele sharing was not confined to families with apparently transmitting fathers. Thus, the paternal parent-of-origin effect seems to be robust when based on observed transmission of marker alleles, but not when based on apparent transmission of illness. This may reflect uncertainty in the classification of families by apparent pattern of illness transmission, hidden bilineality, or other factors.

In order to take the prior findings on 18q into account while avoiding these uncertainties, we chose to base the present analysis on observed transmission of marker alleles. We again found robust evidence of linkage to paternal, but not maternal alleles. Only 4 of the 16 families with BPII sibling pairs had an apparently transmitting father. This is consistent with our conclusion that the clustering of BPII-BPII sibling pairs is the key feature of families linked to 18q in this sample. The importance of paternally transmitted marker alleles remains, and perhaps implicates genomic imprinting or other mechanisms.

MacKinnon et al31 evaluated the effect of panic attack comorbidity on linkage of BPAD to 18q. Post hoc analyses of set A indicated that the linkage evidence was strongest in families where the proband had panic attacks. This could not be adequately tested in set B, since only 2 families had a proband with panic attacks. We cannot rule out that another factor correlated with BPII, and perhaps also with panic attacks, may account for our findings, and we have not tested the effect of BPII on linkage elsewhere in the genome. Nevertheless, diagnostic subtype was the only 1 of 31 variables we analyzed that successfully discriminated linked and unlinked families in our sample.

The peak paternal lod score of 4.67 that we observed in the BPII sibling pair families should be viewed with caution. This lod score was obtained after past analyses of the same data sets that evaluated linkage in a variety of ways.4,7,14,31 Our simulation studies indicate that the increase in lod score that was observed in the BPII sibling pair families would rarely be seen by chance alone. Furthermore, the increase in lod score was not diffuse, but it was focused at a few adjacent markers, thus increasing the resolution of the linkage signal and fulfilling one of the chief aims of this study.

Friddle et al35 published a genome-wide linkage study of BPAD, using 50 of the 58 families included herein. That study found little evidence of linkage to 18q or any other locus, either by single-locus nonparametric analyses or by a 2-locus heterogeneity analysis. Several important differences with the present study may account for the discrepant results. Friddle et al employed a less dense marker map on 18q21-23 (an approximately 9-cM mean interval, compared with 2.4 cM in the present study), and the marker data they analyzed were fully informative in only about half as many sibling pairs.34 Marker density and sample size can be critical factors in detecting alleles of modest effect.35 In addition, Friddle et al35 did not analyze their results by parent of origin. Since most of the positive linkages between BPAD and 18q report a parent of origin effect, this may be an important factor in detecting linkage to this region. Friddle et al also failed to detect linkage under their heterogeneity model, which assumed 2 major loci that each accounted for linkage in at least half of the families.34 This failure would not be surprising if, as we now conclude, the 18q linkage is primarily confined to BPII sibling pair families, which constitute much less than half (27%) of this sample.

Our results offer a potential explanation for the apparently inconsistent results of previous chromosome 18q linkage studies and point to a strategy for replication. Future studies should take careful account of the families with BPII-BPII sibling pairs and should analyze linkage separately for paternal and maternal marker alleles. By decreasing heterogeneity, this approach may lead to more consistent results that could ultimately clarify the complex molecular anatomy of BPAD, moving us closer to the identification of susceptibility alleles.

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