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, 99 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 D18S41, D18S64, and D18S38 (the 18q markers most strongly linked to BPAD when we originally analyzed these data7) 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 density of 1 marker per 79 centimorgans.

RESULTS

EXPLORATORY ANALYSES

Thirty-one variables were analyzed (Table 1). Nominally 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, BPII-RUP, BPII-BPIII, 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 un-
ambiguous sharing or nonsharing of marker alleles. The
clinical features of sharing vs nonsharing were then
compared. For categorical variables with more than 2 cat-
egories, all discordant pairs were pooled. Paternal and ma-
ternal alleles were analyzed separately, since earlier analy-
ses indicated that on 18q only paternal marker alleles were
shared in excess by affected sibling pairs.12 Continuous vari-
ables were analyzed by the t test; categorical variables, by
a maximum-likelihood $\chi^2$ test. The $\alpha$ level of significance
was set at .05; multiple comparisons underwent Bonferroni correction. Statistics were calculated using STATISTICA

It was not possible to score allele sharing by all sibling
pairs using the single-marker genotype data, so we reana-
lyzed allele sharing by diagnostic subtype using multipoint
haplotypes that take genotypes at adjacent markers into ac-
count, and reduce the effect of variable marker informativ-
ness. Multipoint haplotype analyses were performed on both
sets A and B using data from the set of 32 markers. Haplo-
types 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 mater-
nal chromosomes were analyzed separately. Haplotypes were
also used to edit out probable genotype errors prior to link-
age 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;7 but it cannot be con-
sidered definitive for such densely placed markers. Bipolar
I disorder and BPII were considered affected pheno-
types, and paternal and maternal allele sharing was esti-
ated for all possible affected sibling pairs under an
additive genetic model.

The effect of BPII-BPII allele sharing on linkage reso-
lution 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 pro-
band per family), and larger samples have more power to
detect linkage.

Data Management

Data management was achieved using a relational data-
base system based on PARADOX (versions 5 and 8, Corel
Corporation, Ottawa, Ontario), as described elsewhere.26
The data in this system have undergone rigorous cleaning
and editing procedures, with a residual error rate esti-
rated at less than 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 af-
fected sibling pairs. This result was confirmed by mul-
tipoint haplotype analysis. Again, paternal allele shar-
ing was significantly associated with a diagnostic subtype
(overall $\chi^2 = 16.16, P = .007$) and was greatest in BPII-
BPII sibling pairs (Figure 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. Subse-
quently, this hypothesis was tested in an independent set
of 30 families using multipoint data (Figure 1B). This in-
dicated that BPIII-BPII sibling pairs shared 9 of 11 pat-
ernal 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 appar-
ent 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 siblings shared paternal alleles with BPII-BPII
sibling pairs in the same family. We therefore hypothe-
sized that entire families with 1 or more BPII-BPII sib-
ling 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 link-
age to several 18q markers. In these families, there was
highly significant ($P \leq .005$) 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; $\chi^2 = 22.35, P = .000002$) and again distally
at D18S1106 in 18q22-23 (80.8% IBD; $\chi^2 = 19.69, P = .000009$).
Table 1. Clinical Variables Analyzed*

<table>
<thead>
<tr>
<th>Feature/Variable</th>
<th>No. of Pairs†</th>
<th>Feature/Variable</th>
<th>No. of Pairs†</th>
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<td>No. of episodes of mania</td>
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<td>Mood congruent psychotic features with mania</td>
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<td>Age at first episode of mania</td>
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<td>Felt guilty during major depression</td>
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<tr>
<td>No. of episodes of major depression</td>
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<td>Problem concentrating during major depression</td>
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<td>Suicidal thoughts/behavior during major depression</td>
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<td>Overactive during mania</td>
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<td>Appetite change during major depression</td>
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<td>Low energy during major depression</td>
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<td>Low interest during major depression</td>
<td>82</td>
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<td>Needed less sleep during mania</td>
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<td>Psychomotor changes during major depression</td>
<td>76</td>
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<td>Distractable during mania</td>
<td>34</td>
<td>Mania immediately preceded/followed depression</td>
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<td>Poor judgment during mania</td>
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<td>Depression associated with pregnancy</td>
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<td>Depression associated with menopause</td>
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<td>Depression followed somatic treatment</td>
<td>78</td>
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<tr>
<td></td>
<td></td>
<td>Mood congruent psychotic features with depres</td>
<td>ion</td>
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</table>

*Age at first inpatient treatment was dropped since only 9 pairs could be scored for this feature.
†No. of pairs indicates the number of affected sibling pairs contributing data for each feature or variable.

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 in the 2 sets of families was directly compared (Table 2), there was significantly (P≤.01) increased sharing at 12 markers in BPII sibling pair families; the most significant difference (80.8% vs 47.2% IBD; χ² = 20.19, P<.001) was observed at D18S1106. Little evidence of linkage to maternal alleles was seen in either group of families. These data are consistent with one or more 18q loci linked to BPAD in BPII sibling pair families.

**EFFECT ON LINKAGE RESOLUTION**

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, 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 (χ² = 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).

**COMMENT**

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-BPII pairs substantially improved the peak lod score and the resolu-
tion 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.

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 retest correlation 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 as-

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

<table>
<thead>
<tr>
<th>Locus</th>
<th>% IBD Paternal</th>
<th>$\chi^2$ Paternal</th>
<th>P Paternal</th>
<th>% IBD Maternal</th>
<th>$\chi^2$ Maternal</th>
<th>P Maternal</th>
<th>% IBD BPI vs BPII</th>
<th>$\chi^2$ BPI vs BPII</th>
<th>P BPI vs BPII</th>
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<td>.67</td>
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<td>1.60</td>
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*BPI 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.

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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. 

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. 

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 al 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 al observed the largest IBD scores for paternally transmitted marker alleles, but the 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 al 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. 

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 al 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. Marker density and sample size can be critical factors in detecting alleles of modest effect. In addition, Friddle et al 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. This failure would not be surprising if, as we now conclude, the 18q linkage is primarily confined to BPII sibling pairs, 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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