Bipolar Disorder and Panic Disorder in Families: An Analysis of Chromosome 18 Data

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Objective: *The authors performed an analysis of their published chromosome 18 linkage data on 28 families in which there was bipolar disorder to test the potential of comorbid panic disorder to define a genetic subtype of bipolar disorder.* *Method:* *Families ascertained through probands with bipolar I disorder were stratified into three groups based on a history of panic disorder, panic attacks, or no panic attacks in the probands. Multipoint nonparametric linkage analysis was performed on data from bipolar I and II family members in each group.* *Results:* *Linkage scores for five consecutive 18q marker loci were highest in the families of the probands with panic disorder and lowest for the families of the probands without panic attacks.* *Conclusions:* *This study supports the authors' previously reported clinical hypothesis of a genetic subtype of bipolar disorder identified by comorbid panic disorder. The hypothesis merits prospective testing.*

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Panic disorder may be a marker for a genetic subtype of bipolar disorder. We have reported a high familial risk of panic disorder in the bipolar relatives of probands diagnosed with both panic and bipolar disorder (1); in these families panic disorder was diagnosed in one-half of the individuals with bipolar disorder but in no one without bipolar disorder. Families from the same linkage study sample provided evidence for linkage of bipolar disorder to marker loci on the long arm of chromosome 18 (18q) (2). We report here an analysis of our linkage data, stratified by familial comorbid panic disorder, as an initial test of the hypothesis that panic disorder is a marker of genetic heterogeneity in bipolar disorder.

METHOD

Twenty-eight clinically ascertained probands with bipolar I disorder from multiplex unilineal families and 215 relatives, all having received a complete description of the study and given written informed consent, were administered Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (3) interviews by a psychiatrist (S.G.S., J.R.D., F.J.M., or M.G.M.). In addition, family history information and data from psychiatric records were collected. Two noninterviewing psychiatrists, using all sources of information, made best-estimate diagnoses based on the Research Diagnostic Criteria (4) with two modifications: hypomania and recurrent episodes of major depression were required for the diagnosis of bipolar II disorder, and the diagnosis of panic disorder was not excluded by concurrent major depression. Excellent interrater reliability has been established for affective disorders and for panic disorder in our group (1).

DNA was isolated both directly from leukocytes and from transformed cell lines. Markers were genotyped at Johns Hopkins University and Stanford University. Thirty-one highly polymorphic markers were selected along chromosome 18, and a polymerase chain reaction

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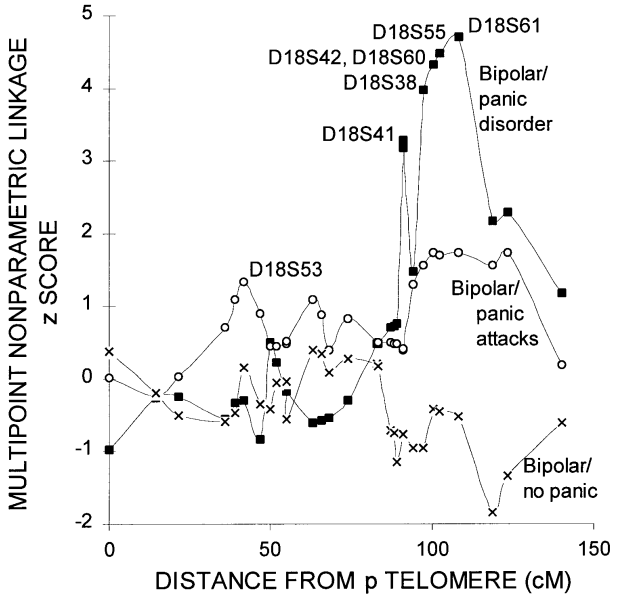
FIGURE 1. Stratified Bipolar Disorder Linkage Analysis of Chromosome 18 Markers in Families Transmitting Bipolar Disorder With and Without Panic Symptoms



was performed using oligonucleotides purchased from Research Genetics (Huntsville, Ala.) and Genethon (Evry, France). Amplified products were separated on polyacrylamide gels, and fragments were detected by either radioactivity or immunoactivity. Genotypes were then read by two independent raters blind to diagnosis (M.G.M. and O.C.S.). Marker order and distances were estimated from the data set with the use of CRIMAP and are consistent with the published genetic map (5). Detailed descriptions of the methods for the ascertainment and evaluation of families, the isolation of DNA, and the selection, amplification, and genotyping of DNA markers are presented in a report by Stine et al. (2).

Stratification of families. SADS-L interviews provided information about panic symptoms in all 28 bipolar probands and their relatives. Five bipolar probands had panic disorder; families of these probands constituted the bipolar/panic disorder group. Six bipolar probands had experienced a panic attack but did not meet diagnostic criteria for panic disorder; their families were in the bipolar/panic attack group. The remaining 17 bipolar probands had no history of panic attacks; their families made up the bipolar/no panic group.

Affection status. For the purposes of this study of the bipolar/panic disorder phenotype, only the 59 bipolar I and 42 bipolar II individuals were included in the linkage analysis. The mean age at onset was 20.8 years (SD=3.9) for bipolar disorder and 22.8 years (SD=7.2) for panic disorder. In 13 of 15 subjects with comorbid panic and bipolar disorder, bipolar disorder preceded panic disorder.

Statistical analysis. Multipoint nonparametric linkage analysis was performed with use of the GENEHUNTER software (6) on a Sun workstation. GENEHUNTER uses information on shared alleles in all affected pedigree members to derive a normally distributed statistical z score.

RESULTS

Stratified linkage results (nonparametric linkage z scores) for the 31 marker loci on chromosome 18 are shown in figure 1. The peak z score for bipolar disorder in all 28 families occurred at D18S61 ($z=1.2$, $p\leq0.19$). The 17 bipolar/no panic families had no z scores greater than 0.4 across the entire chromosome and had negative z scores over much of 18q. The five bipolar/panic disorder families support bipolar disorder linkage over five consecutive 18q marker loci ($z\geq4.0$, $p\leq0.0001$), with a maximum z score of 4.7 at D18S61. The six bipolar/panic attack families had intermediate z scores at the same five markers. The 11 bipolar/panic disorder and panic attack families combined support linkage of bipolar disorder at these five 18q markers ($z>3.8$, $p<0.0003$).

Since one bipolar/panic disorder family contributed a large proportion of the z score, we repeated the analyses excluding this family. The z scores at the peak region on 18q were positive for the four remaining bipolar/panic disorder families ($0.91<z<1.6$, $p\leq0.26$) and for the 10 remaining bipolar/panic disorder and panic attack families combined ($1.8<z<2.4$, $p\leq0.08$). The scores for this region, even without the family providing the strongest evidence for linkage, were thus considerably higher than those in the 17 bipolar/no panic families, which had z scores ranging from –0.96 to –0.41.

DISCUSSION

In this analysis of previously published linkage data on chromosome 18, we found that families of bipolar probands with comorbid panic symptoms show stronger statistical evidence for linkage of bipolar disorder to chromosome 18q than do families of probands without panic symptoms. These results are consistent with the hypothesis of genetic heterogeneity in bipolar disorder marked by high risk of panic disorder. Because we have analyzed data from a population already known to be genetically linked to 18q, however, this study does not represent an independent test of linkage.

The results of this analysis differ from our previous linkage report on chromosome 18 data (2) in two ways. Our previous report, based on single-point analyses and the stratification of families by parent of origin, suggested a linked locus 20 centimorgans centromeric to the locus with the highest z scores in the present analysis. The difference appears to be due to the use of recently available multipoint analytic methods for the present analysis. This conclusion is supported by the results of the multipoint linkage analysis carried out in the original 28 families as well as 30 new families at our center (7). Finally, the relationship of the bipolar/panic findings to the previously reported parent-of-origin effect (2, 7, 8) is not clear. Six of the 11 bipolar/panic disorder or panic attack families showed paternal transmission.

We have observed a most interesting phenomenon, but we have limited ability to explain it from these data. The close association of panic with bipolar disorder in our families implies a common genetic mechanism for the two disorders in some families. If confirmed in prospective analyses, the relationship of panic and comorbid disorders in some families may illuminate the search for genes related to bipolar disorder.

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