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A Linkage Search for Joint Panic Disorder/Bipolar Genes

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Abstract

There is comorbidity and a possible genetic connection between Bipolar disease (BP) and panic disorder (PD). Genes may exist that increase risk to both PD and BP. We explored this possibility using data from a linkage study of PD (120 multiplex families; 37 had ≥ 1 BP member). We calculated 2-point lodscores maximized over male and female recombination fractions by classifying individuals with PD and/or BP as affected (PD +BP). Additionally, to shed light on possible heterogeneity, we examine the pedigrees containing a bipolar member (BP+) separately from those that do not (BP–), using a Predivided-Sample Test (PST). Linkage evidence for common genes for PD +BP was obtained on chromosomes 2 (lodscores =4.6) and chromosome 12 (lodscores =3.6). These locations had already been implicated using a PD-only diagnosis, although at both locations this was larger when a joint PD +BP diagnosis was used. Examining the BP+ families and BP– families separately indicates that both BP+ and BP– pedigrees are contributing to the peaks on chromosomes 2 and 12. However, the PST indicates different evidence of linkage is obtained from BP+ and BP– pedigrees on chromosome 13. Our findings are consistent with risk loci for the combined PD +BP phenotype on chromosomes 2 and 12. We also obtained evidence

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of heterogeneity on chromosome 13. The regions on chromosomes 12 and 13 identified here have previously been implicated as regions of interest for multiple psychiatric disorders, including BP.

Keywords

bipolar disorder; panic disorder; linkage; phenotype; genome scan; genetic heterogeneity

INTRODUCTION

Several clinical and epidemiological studies have noted a high comorbidity between panic disorder (PD) and bipolar disorder (BP) [Savino et al., 1993; Young et al., 1993; Kessler et al., 1994; Chen and Dilsaver, 1995; Kessler, 1995; Szadoczky et al., 1998; Goodwin and Hoven, 2002]. From 10% to 60% of patients with BP also have PD. Conversely, studies investigating PD patients found that 13–23% of patients with PD also have BP [Savino et al., 1993; Bowen et al., 1994]. Both PD and BP are relatively common diseases, with a lifetime prevalence of 1.6–2.2% for PD [Weissman et al., 1997; see also Grant et al., 2004; Kessler et al., 2005] and about 1% for BP [Bebbington and Ramana 1995]. If there were no association between PD and BP, then the expected co-occurrence would be the product of each prevalence rate: 0.016 to 0.022%. The observed comorbidity exceeds this value several-fold. Furthermore, the co-occurrence of PD and BP is seen not only in patients but also in their families. While it is commonly accepted that family members of BP probands are at higher risk for BP, it is also striking that in those family members PD is seen more often than expected from the general population rate of PD [MacKinnon et al., 1997; Edmonds et al., 1998].

In this article, we use linkage analysis, classifying all individuals with either PD and/or BP as affected (PD + BP), in order to identify regions likely to contain joint PD and BP risk loci. We utilize a unique sample of 120 families ascertained for a PD genetic study. This sample has been described elsewhere [Fyer and Weissman, 1999; Hamilton et al., 2003; Fyer et al., 2006]. Thirty-seven of these families had at least one family member affected with BP. We analyzed the families allowing for the possibility that male and female recombination fractions may not be equal. Then, we separated families into those with at least one member affected with BP (BP+) versus those with no BP members (BP–) and analyzed each group separately to look for evidence of heterogeneity. The significance of this analysis was evaluated using the Predivided-Sample Test (PST)

SAMPLE AND METHODS

Families

Family ascertainment, selection, and clinical methods have been described in detail elsewhere [Fyer and Weissman, 1999]. For the present study, all subjects who had been flagged for bipolar disorder or had been diagnosed with bipolar I, bipolar II, or cyclothymia by direct interview were re-best estimated for bipolar disorder. Here we used a broad definition as our diagnosis of PD including PD definite + probable + possible + any as affected (referred to as “panic broad” category previously [Knowles et al., 1998; Fyer and Weissman, 1999; Hamilton et al., 2003; Fyer et al., 2006]).

A total of 120 families were collected with at least two family members affected with PD. Thirty-seven of those families had at least one member affected with BP (BP+ families). Eighty-three families did not have any member with BP (BP– families). These 120 families consist of 1,591 family members. Seven hundred eighty-seven family members were affected either with PD and/or BP (average 6.5 affected family members per family). Seven

hundred thirty-nine family members had PD only and 22 members had BP only. Twenty-six family members had both, PD and BP.

Genotyping

CIDR performed a complete genome scan (<http://www.cidr.jhmi.edu>). The CIDR marker set consisted of 384 simple tandem repeats (mostly tri- and tetra-nucleotides), at an average spacing of 9 cM, with no gap greater than 20 cM (<http://www.cidr.jhmi.edu/download/CIDRmarkers.txt>). Here we present an analysis of the 371 autosomal markers from this set. Genotypes were available on 992 family members.

Linkage Analysis

We analyzed PD +BP using parametric lodscores because of the high power of parametric methods when analyzing large pedigrees with many affected members. We calculated 2-point lodscores allowing for independent male and female recombination fractions $\theta = (\theta_m, \theta_f)$ using KELVIN [Huang et al., 2006; Wang et al., 2007]. We allow for independent male and female recombination fractions for several reasons: (1) because gender-dependent recombination rates can vary drastically across the genome [Mohrenweiser et al., 1998; Lynn et al., 2000] with predictable consequences for linkage analysis [Daw et al., 2000]; (2) because gender-specific phenomena are strongly suspected in PD as well as in BP, and allowing for sex-specific recombination may increase power in cases where sex-specific effects are present; and (3) because this technique has previously proven useful in the search for PD susceptibility loci in this sample [Fyer et al., 2006].

The genetic parameters for the analyses were guided by the results from our previous segregation analysis of PD [Vieland et al., 1993]. We used a disease gene frequency of 0.01 under an assumed dominant model and of 0.2 under a recessive model. The penetrance for both models was set to 0.5 and the phenocopy rate was 0.01. We are aware that these parameters might be only approximations of the unknown genetic model for PD +BP, but extensive research has shown that lodscores are relatively robust to misspecification of the penetrance and gene frequency [Hodge et al., 1997; Pal et al., 2001], as long as the “mode of inheritance” (MOI, i.e., dominant or recessive) at the locus being examined is correct. Therefore, we performed our analyses twice, once assuming a dominant MOI and once assuming a recessive MOI, as suggested by Hodge et al. [1997].

Next, we look for possible evidence of heterogeneity between the BP+ families and the BP− families. First, we computed lodscores for these pedigrees separately. Then, we computed a Predivided Sample Test (PST) for heterogeneity [Morton, 1956; Hodge et al., 1983; Ott, 1983]. The PST statistic follows an approximately χ^2 distribution with one degree of freedom (as long as the max lodscore does not occur at $\theta = 0$).

Computing lodscores under two genetic models and maximizing over separate male and female recombination fractions alters the nominal significance level of a lodscore of 3. However, corrections for maximization over these two elements are well characterized. Allowing for independent male/female recombination fractions is accomplished by raising the threshold level from a lodscore of 3 to 3.3 [Ott, 1999]. Similarly, computing a lodscore under both a dominant and recessive genetic model is accommodated by raising the significance criteria by 0.3 [Hodge et al., 1997]. Therefore, we use 3.6 as our criteria for “significance.” This criteria was not further adjusted for the testing of multiple markers. Lodscores of the PD-only analysis are presented in the discussion section for completeness and comparison purposes. We refer to our previous publication for a discussion of the significance of lodscores observed using the PD-only diagnosis [Fyer et al., 2006]. We judge the significance of the separate analyses of the BP+ and BP− families through the use of the

PST. However, PST is a test for heterogeneity and not a test for linkage per se. That is, it can be significant even when the individual lodscores are not large enough to establish linkage in either dataset, nevertheless indicating heterogeneity between the datasets. Nominal per-marker *P*-values of the PST are presented.

The two-stage analysis method used here—analyzing the data with a combined phenotype and then testing for heterogeneity with the PST—shares some resemblance to using logistic regression to model the probability of allele sharing among relative pairs as a function of covariate information as suggested in Rice [1997] and elsewhere [Devlin et al., 2002; Glidden et al., 2003; Tsai and Weeks, 2006]. However, our desire to utilize extended pedigrees as a whole precludes the use of these covariate analysis methods. Furthermore, the hypothesis being examined in our lodscore analysis is a test for linkage assuming homogeneity rather than a test of linkage in the presence of heterogeneity as in Rice [1997].

RESULTS

Figure 1 shows the results of the genome scan of PD +BP in all 120 families. The highest lodscores occurred on chromosome 2 and 12 under a dominant model and on chromosome 13 under a recessive model. The highest lodscore of 4.6 occurred on chromosome 2q at marker D2S125 (261 cM) under a dominant model with maximizing $\underline{\theta}=(\theta_m, \theta_f)=(0.12, 0.32)$. On chromosome 12, the highest lodscore was 3.6 at marker PAH (109 cM) at $\underline{\theta}=(0.15, 0.33)$. Lodscores on chromosome 12 are above 1 for a genetic distance of over 62 cM, from D12S1300 to 12qtel. An additional marker on chromosome 2p had a lodscore which exceeded 3, but did not meet our more stringent significance criteria: a lodscore of 3.1 was observed at D2S1788 under a dominant model at $\underline{\theta}=(0.50, 0.25)$. The highest lodscore under an assumed recessive model occurred at marker D13S793 (76 cM) with a value of 2.1 at $\underline{\theta}=(0.5, 0.08)$.

Table I includes a summary of the results for all 120 pedigrees and the separate BP+ and BP – analyses. Nominally significant evidence of heterogeneity was obtained at a single locus: $\chi^2_1=8.1$ ($P=0.004$) on chromosome 13 at D13S779 (83 cM). A lodscore of 2.4 was observed in the 37 BP+ families. This is substantially higher than the lodscore of 1.4 observed at D13S799 when the 120 families were analyzed together, suggesting that the BP+ families may be genetically different than the BP– families at D13S799. However, this score is not significant if we were to perform a Bonferroni correction to control the type 1 error rate for the entire set of markers ($P<0.0001$).

DISCUSSION

Previously, we analyzed our families with multiple occurrence of PD and found evidence for linkage on chromosome 2p (D2S1788), 2q (D2S125), 9p (D9S925), 12 (PAH), and 15q (near GABA-A receptor subunit genes) [Fyer et al., 2006]. Guided by clinical observation of greater than expected co-occurrence of PD and BP, we decided to define the phenotype more broadly, to include not only PD but also BP as affected.

Using a PD +BP affectedness model we found evidence for linkage on chromosome 2q and 12 with lodscores of 4.6 and 3.6, respectively. Including those with BP as affected increased lodscores from their values when PD-only was used as the diagnosis. Using the same genetic parameters but classifying only family members with PD (and not BP) as affected, the corresponding lodscores were 3.9 at D2S125 and 2.8 at PAH. The lodscore of 3.1 obtained at marker D2S1788 on chromosome 2p is less than the lodscore of 3.3 observed in the PD-only analysis.

Imprinting or parent-of-origin effects have been suggested as a possibility in BP inheritance [Stine et al., 1995; Kornberg et al., 2000; Borglum et al., 2003]. At D2S125, we observed a difference of 0.7 lodscore units when we maximized the lodscore over θ_m and θ_f , versus maximizing the lodscore over equal θ (lodscore of 4.6 under independent recombination and 3.9 if the rates are held equal). However, the map in this region is not concordant with the values at which the lodscore maximizes. That is, the recombination rate on chromosome 2 in the region of this marker (near the telomere) is larger in males than in females, yet the lodscore maximizes at $\theta_f > \theta_m$. In contrast, the lodscores obtained at PAH were concordant with the greater rate of female than male recombination in the region. The discordance of the maximizing male and female recombination rates observed at D2S125 is consistent with heterogeneity where some fraction of the families show genetic imprinting [Greenberg et al., 2002].

On chromosome 9, where we previously reported high lodscores in the PD-only analysis [Fyer et al., 2006], the lodscores were lower in the PD +BP analysis. However, the highest PD-only lodscores were observed under a narrower PD diagnostic scheme (intermediate PD) than we used in the PD +BP analysis (PD broad and/or BP). The difference in the lodscore is attributable more to the change in PD category than to the inclusion of BP in the affectedness model, with a lodscore of 1.7 under “PD broad-only” and to 2.0 under “PD broad +BP” at marker D9S925. In contrast to the PD-only analysis of Fyer et al. [2006], there was no support for linkage between PD +BP and any location on chromosome 15.

In our previous PD-only analysis we had observed substantial evidence of heterogeneity. We therefore postulated that PD with BP might be genetically different from PD without BP. We have identified a region on chromosome 13, where BP+ families and BP- families yielded substantially different evidence for linkage, as demonstrated by the PST. Under a dominant MOI, only BP+ families showed evidence for linkage at D13S779, yielding a lodscore of 2.4. At the neighboring marker, D13S1793, we observed a lodscore of 2.5 under a recessive model in the BP- pedigrees. This chromosomal area is identical to the one where we had obtained high lodscores under a different classification scheme that included PD and a “syndrome” that comprised bladder/kidney problems, headache, thyroid problems and/or mitral valve prolapse [Weissman et al., 2000; Hamilton et al., 2003; Talati et al., 2008]. However, differential linkage on chromosome 13 cannot be explained as a correlation between a family’s BP+/- status and the syndrome phenotype; the percentage of syndrome individuals is nearly identical in these two groups (percentage = 33.8% both BP+ and BP- families, $P = 0.98$).

In conclusion, our results point to linkage of a PD +BP phenotype to chromosome 2q and chromosome 12 and indicate a region of heterogeneity on chromosome 13. The region implicated in PD +BP susceptibility on chromosome 12 (12q23) has been noted in multiple linkage studies of bipolar and unipolar disorder [Dawson et al., 1995; Ewald et al., 1998; Morissette et al., 1999; Maziade et al., 2001; Abkevich et al., 2003; Curtis et al., 2003; Ekholm et al., 2003; Zubenko et al., 2003; Green et al., 2005]. Furthermore, a SNP in this region has been associated with severity scores on a severity scale of panic and agoraphobia symptoms [Erhardt et al., 2007]. Similarly, the region on chromosome 13 where we found evidence of heterogeneity has been implicated in multiple studies of both schizophrenia and bipolar disorder [Lin et al., 1997; Blouin et al., 1998; Shaw et al., 1998; Brzustowicz et al., 1999; Detera-Wadleigh et al., 1999; Kelsoe et al., 2001; Liu et al., 2001; Chumakov et al., 2002; Faraone et al., 2002; Hattori et al., 2003; Mulle et al., 2005; Cheng et al., 2006]. The most studied candidate locus in this region is G72(DAOA)/G30 [Hattori et al., 2003; Chen et al., 2004; Korostishevsky et al., 2004; Schumacher et al., 2004; Fallin et al., 2005; Detera-Wadleigh and McMahon, 2006; Williams et al., 2006; Li and He, 2007; Kvajo et al., 2008; Prata et al., 2008]. While the location of G72(DAOA)/G30 is not well characterized

according to the Marshfield map (90–93 cM), it is undoubtedly close to D13S779 (83 cM). A 2 lod-unit support interval around the peak lodscore of 2.4 observed in the BP+ families at D13S799 indicates that sex-averaged θ values between 0.13 and 0.41 are plausible. This recombination rate is greater than expected if G72(DAOA)/G30 was responsible for the peak at D13S779 (given the 7–10 cM distance between the two). However, misspecification of the genetic model (such as residual heterogeneity within the BP+ families) could easily cause an inflated θ estimate. Therefore, we can not rule out the possibility that G72(DAOA)/G30 plays a role in the heterogeneity implied by the PST at D13S799. This region has also been noted in a linkage study of recurrent major depressive disorder [McGuffin et al., 2005]. While a complete examination of the possible genetic overlap between BP, PD, and major depressive disorder (MDD) is beyond the scope of this article (given our prior hypothesis of the overlapping genetic diathesis of BP and PD) it would be unreasonable to assume that this region did not play a role in the development of MDD. In fact, MDD is quite prevalent in this sample, and in a prior (unpublished) 2-point sex-averaged lodscore analysis of this data using major depressive disorder as the outcome variable, the largest lodscore of 2.3 occurred at D13S793 (76 cM). Meta-analyses of BP and schizophrenia linkage scans have obtained conflicting results, with one finding the strongest evidence of linkage at this region [Badner and Gershon, 2002] and others failing to find linkage to chromosome 13 [Levinson et al., 2003; Segurado et al., 2003; McQueen et al., 2005]. Nevertheless, it is hard to dismiss the convergence of linkage findings on chromosome 13 for several different psychiatric diseases as false positives.

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FIG 1.
Genome Scan of PD + BP.

TABLE I
Analysis of PD +BP in all 120 Families, 37 BP+ Families, and 83 BP− Families

Marker-MOI	All families		BP+ families		BP− families ^a		PST χ^2
	lod	(θ_m, θ_f)	lod	(θ_m, θ_f)	lod	(θ_m, θ_f)	
D2S125-D	4.6	(0.12, 0.32)	1.9	(0.22, 0.22)	3.5	(0.06, 0.36)	3.5 ^{ns}
PAH-D	3.6	(0.15, 0.33)	2.6	(0.05, 0.50)	1.5	(0.24, 0.31)	2.8 ^{ns}
D2S1788-D	3.1	(0.50, 0.25)	1.1	(0.50, 0.23)	2.0	(0.50, 0.26)	0.0 ^{ns}
D13S793-R	2.1	(0.50, 0.08)	0.3	(0.30, 0.22)	2.5	(0.50, 0.00)	3.3 ^{ns}
D13S779-D	1.4	(0.25, 0.30)	2.4	(0.01, 0.32)	0.8	(0.49, 0.26)	8.1 *
D20S477-R	1.7	(0.14, 0.50)	2.2	(0.02, 0.46)	0.2	(0.25, 0.50)	1.1 ^{ns}
D5S211-R	1.8	(0.15, 0.50)	0.0	(0.33, 0.50)	2.2	(0.10, 0.50)	1.7 ^{ns}

Lodscores are maximized over mode of inheritance (MOI) and independent male/female recombination fractions. The upper section displays markers with the highest lodscores in the total sample, the lower section displays results for markers with the largest lodscores in the BP+ and BP− groups (apart from markers already noted). PST = predivided sample test statistic;

* $P < 0.005$;
ns $P > 0.05$.
^aFor the BP− families, the analysis of PD +BP is equivalent to analysis of a PD-only diagnosis.