

ORIGINAL RESEARCH ARTICLE

Linkage analysis of psychosis in bipolar pedigrees suggests novel putative loci for bipolar disorder and shared susceptibility with schizophrenia

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The low-to-moderate resolution of linkage analysis in complex traits has underscored the need to identify disease phenotypes with presumed genetic homogeneity. Bipolar disorder (BP) accompanied by psychosis (psychotic BP) may be one such phenotype. We previously reported a genome-wide screen in a large bipolar pedigree sample. In this follow-up study, we reclassified the disease phenotype based on the presence or absence of psychotic features and subgrouped pedigrees according to familial load of psychosis. Evidence for significant linkage to psychotic BP (genome-wide $P < 0.05$) was obtained on chromosomes 9q31 (lod = 3.55) and 8p21 (lod = 3.46). Several other sites were supportive of linkage, including 5q33 (lod = 1.78), 6q21 (lod = 1.81), 8p12 (lod = 2.06), 8q24 (lod = 2.01), 13q32 (lod = 1.96), 15q26 (lod = 1.96), 17p12 (lod = 2.42), 18q21 (lod = 2.4), and 20q13 (lod = 1.98). For most loci, the highest lod scores, including those with genome-wide significance (at 9q31 and 8p21), occurred in the subgroup of families with the largest concentration of psychotic individuals (≥ 3 in a family). Interestingly, all regions but six—5q33, 6q21, 8p21, 8q24, 13q32 and 18q21—appear to be novel; namely, they did not show notable linkage to BP in other genome scans, which did not employ psychosis for disease classification. Also of interest is possible overlap with schizophrenia, another major psychotic disorder: seven of the regions presumed linked in this study—5q, 6q, 8p, 13q, 15q, 17p, and 18q—are also implicated in schizophrenia, as are 2p13 and 10q26, which showed more modest support for linkage. Our results suggest that BP in conjunction with psychosis is a potentially useful phenotype that may: (1) expedite the detection of susceptibility loci for BP and (2) cast light on the genetic relationship between BP and schizophrenia.

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Bipolar disorder (BP) is a severe mental disorder characterized by elated or irritable mood alternating with episodes of depression. BP is a major public health concern owing to world-wide lifetime prevalence of 0.5–1.5%, frequent need of long-term care, and complications such as psychosocial impairment, substance abuse, and suicide.

The etiology of BP is uncertain, but a strong genetic component is supported by family, twin, and adoption studies (reviewed in Craddock and Jones¹ and Taylor *et al.*²). Linkage studies, including whole-genome scans, have implicated multiple candidate regions. Although some of these findings show

promise, there is lack of agreement among studies partly attributable to complex inheritance and etiologic heterogeneity (reviewed in Baron³ and Segurado *et al.*⁴). Other complex disorders face similar challenges. Attempts to redress this issue have included a search for clinical phenotypes that flag genetically homogeneous illness subsets. This strategy has been successful with several complex disorders, which previously seemed genetically intractable (eg diabetes mellitus, Alzheimer disease, breast cancer).

Whole-genome linkage studies of BP have generally utilized standard definitions of the disease phenotype. BP coupled with psychosis (symptoms like delusions and/or hallucinations), or psychotic BP, is a narrower disease phenotype, which may enhance the prospects of linkage studies. The potential utility of psychotic BP as a distinct disease phenotype is suggested by: (1) severity of the clinical syndrome,⁵ (2) familial aggregation of psychosis in bipolar pedigrees,^{6,7} (3) linkage of BP and schizophrenia

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(a major mental disorder with psychotic features) to the same genomic regions (eg 10p, 13q, 22q), suggesting common 'psychosis genes',^{3,8} and (4) evidence that psychosis enhances linkage to BP in selected regions, specifically 13q and 22q.⁹ However, comprehensive genome-wide data on psychosis and BP in large pedigree samples are lacking.

We previously reported a genome-wide scan (343 markers spaced at 10 cM intervals) in a large bipolar pedigree sample (373 individuals in 40 pedigrees).¹⁰ In the present study, we reanalyzed these data using BP with psychotic features as the disease phenotype. We present evidence for novel, previously unreported putative loci for BP, as well as loci that may be common to BP and schizophrenia.

Materials and methods

Subjects

Our research protocol, including ascertainment, diagnostic procedures, and affection status models, was described in detail elsewhere^{10,11} and is summarized briefly. The genotyped sample consists of 373 individuals in 40 extended pedigrees with high density of BP (at least two members per pedigree, including the proband, with a lifetime history of mania: BPI or schizoaffective disorder-manic type; the BPI category comprised about 90% of manic syndromes in this sample, with schizoaffective disorder accounting for the remaining 10%). Clinical assessment was based on personal interviews using the Schedule for Affective Disorders and Schizophrenia,¹² modified for BP (SADS-LB), and supplemented by family history information and medical records. Best estimate consensus diagnoses were based on the Research Diagnostic Criteria (RDC)¹³ using all available sources of information. The pedigree sample was obtained in the US (29 pedigrees of European ancestry) and Israel (11 pedigrees of Middle-Eastern extraction) using the same research protocol. American and Israeli families showed similar rates of BP and related mood disorders. The protocol and consent forms were approved by the Institutional Review Boards at the pedigree collection sites.

In our previous study,¹⁰ we employed three diagnostic models or affection status definitions, ranging from narrow to broader phenotypic boundaries: BP1 (manic syndromes; mostly BPI, or mania and depression, including some cases of schizoaffective-manic disorder), BP2 (same as BP1 plus BPII, or hypomania and depression), and BP3 (same as BP2 plus recurrent major depression, or MDD, including some cases of recurrent schizoaffective-depressed-only disorder). These disorders are considered part of the bipolar 'spectrum' by virtue of their aggregation in families of bipolar probands. These models included 119 individuals with manic syndromes, 90 with BPII and 98 with recurrent MDD. In the present study, we required the presence of psychosis (delusions and/or hallucinations in the manic or depressive phase)

for considering a subject affected. The diagnostic models for psychotic BP were BP-P1, BP-P2, and BP-P3, corresponding to BP1, BP2, and BP3, respectively. These models included 68, 72, and 79 psychotic individuals, respectively, with the following distribution of diagnoses: BPI, 68; BPII, 4; and recurrent MDD, 7. Of the 40 families, 36 included at least one psychotic member, 25 families included at least two, and 14 families included at least three such individuals. The 'uncertain' phenotype category in these models was comprised of all affective disorders that were not considered 'affected' under a particular model (including nonpsychotic individuals). In all models, the 'unaffected' category consisted mainly of 'never mentally ill'; also included were disorders that do not aggregate in families of BP probands.

Genotyping

We used semiautomated fluorescence-based genotyping with 343 microsatellite markers. The average marker spacing was about 10 cM (range, 0–7.5 cM), with an average heterozygosity and polymorphic information content of 0.75 and 0.72, respectively. The genotyping procedure is described in detail elsewhere.¹⁴ Briefly, PCR reactions were aliquoted onto 384-well plates using a TECAN Genesis robot and cycled on MJ thermocyclers. PCR products were separated and detected on ABI 377 DNA sequencers, and then analyzed using GeneScan v. 2.1 (Perkin-Elmer). Allele sizes were called automatically with the ABI software package GENOTYPER v. 2 (Perkin-Elmer), and were then double-checked visually blind to clinical diagnosis. Genotypes were then stored in LABMAN,¹⁵ a FOXPRO 2.0 database.

Linkage analysis

Mendelian inconsistencies in marker data were checked using the Pedcheck program.¹⁶ The RelCheck program¹⁷ was used to evaluate biological kinship. Allele frequencies were estimated using the Gconvert program (<http://www2.Qimr.edu.au/davidD>). Linkage was examined using the three diagnostic models, BP-P1, BP-P2, and BP-P3.

The MLINK program from the FASTLINK package¹⁸ was used for two- and multipoint parametric analyses. Since the mode of inheritance is unknown, we tested both dominant and recessive transmissions. We used the same parameters described in our general scan paper:¹⁰ dominant model, disease allele frequency of 0.01, and a penetrance of 80% for gene carriers and 0.1% for noncarriers; recessive model, same penetrance in gene carriers and noncarriers but a disease allele frequency of 0.10. To reduce the impact of nonpenetrant disease alleles on the analysis, all unaffected individuals were coded as unknown. The *A*-test of linkage homogeneity¹⁹ was carried out using the HOMOG program.²⁰

ASP analysis was performed using MAPMAKER/SIBS (version 2.0).²¹ The identity by descent (IBD) distribution (ie sharing 2, 1, or 0 alleles) was then estimated between sib pairs and compared with the

IBD distribution under the assumption of no linkage, that is, 0.25, 0.50, and 0.25. The maximum-likelihood score was then calculated by comparing the estimated IBD distribution and the null distribution at no linkage. Since this analysis can only be carried out in nuclear families, and each nuclear family is not totally independent, we only analyzed the first sib pair from each nuclear family.

To gauge the genome-wide significance of our results, we employed two methods: (1) The commonly used Lander and Kruglyak²² criteria and (2) simulated data sets under the assumption of no linkage, using the SIMULATE program²³ with 100 replicates. Each replicate was then analyzed using FASTLINK,¹⁸ and a genome-wide occurrence expectation, O_E , was computed for the strongest two-point lod score, as described.²⁴

Results

Parametric analysis

The results are shown in Tables 1 and 3. A graphical display, illustrating the signal-to-noise ratio, is shown in Figures 1–3.

Table 1 shows two-point linkage results that met the Lander and Kruglyak's²² criteria for significant (lod ≥ 3.3 , corresponding to genome-wide $P=0.05$) or suggestive (lod ≥ 1.9) linkage, as well as 'near-suggestive' lod scores (> 1.5 but < 1.9) and multipoint lod score (MLOD) results. Also included are two-point lod scores > 1 for these loci under other model configurations.

Two loci showed evidence of significant linkage using the Lander and Kruglyak's²² criteria: D9S389 at 9q31 (lod = 3.33, MLOD = 3.55; BP-P3, recessive

Table 1 Maximum two-point parametric lod scores > 1.5 , corresponding multipoint results, and two-point lod scores > 1 with other model configurations at these loci

Chromosome	Locus	Position (cM)	Two-point lod score	Diagnostic model	Genetic model	Multipoint lod score
5q33	D5S820	159.77	1.78 (0.00)	BP-P3	Dominant	1.37
			1.67 (0.00)	BP-P2	Dominant	
			1.52 (0.05)	BP-P1	Recessive	
6q21	D6S474	118.64	1.81 (0.05)	BP-P1	Recessive	1.18
			1.36 (0.10)	BP-P1	Dominant	
8p12	D8S1477	60.34	2.06 (0.05)	BP-P2	Dominant	1.75
			1.91 (0.05)	BP-P2	Recessive	
			1.68 (0.05)	BP-P1	Dominant	
			1.64 (0.10)	BP-P3	Recessive	
			1.63 (0.00)	BP-P3	Dominant	
8p21	D8S382	51.15	2.09 (0.00)	BP-P1	Dominant	3.46
			1.53 (0.00)	BP-P3	Dominant	
			1.20 (0.05)	BP-P2	Dominant	
8q24	D8S1179	135.08	2.01 (0.10)	BP-P3	Dominant	1.12
			1.91 (0.10)	BP-P2	Dominant	
			1.69 (0.10)	BP-P1	Dominant	
9q31	D9S938	110.93	3.33 (0.00)	BP-P3	Recessive	3.55
			2.75 (0.00)	BP-P2	Recessive	
			2.74 (0.00)	BP-P1	Recessive	
			1.92 (0.05)	BP-P3	Dominant	
10q22	D10S2327	100.92	1.60 (0.05)	BP-P3	Recessive	1.27
			1.26 (0.10)	BP-P3	Dominant	
13q32	D13S779	82.93	1.68 (0.00)	BP-P1	Recessive	1.96
			1.43 (0.10)	BP-P3	Dominant	
			1.43 (0.00)	BP-P1	Dominant	
			1.14 (0.10)	BP-P3	Recessive	
15q26	D15S652	90.02	1.96 (0.10)	BP-P1	Dominant	1.79
			1.74 (0.15)	BP-P2	Dominant	
			1.69 (0.10)	BP-P1	Recessive	
17p12	D17S921	36.14	2.42 (0.05)	BP-P2	Dominant	1.39
			1.98 (0.10)	BP-P1	Dominant	
			1.90 (0.05)	BP-P2	Recessive	
			1.51 (0.10)	BP-P3	Recessive	
			2.40 (0.00)	BP-P2	Dominant	
18q21	D18S851	76.58	2.11 (0.05)	BP-P3	Dominant	2.12
			1.77 (0.05)	BP-P1	Dominant	
20q13	D20S480	79.91	1.43 (0.05)	BP-P2	Dominant	1.98

Numbers within parentheses, theta (recombination fraction). Multipoint results are shown only for model configurations with the largest two-point lod scores.

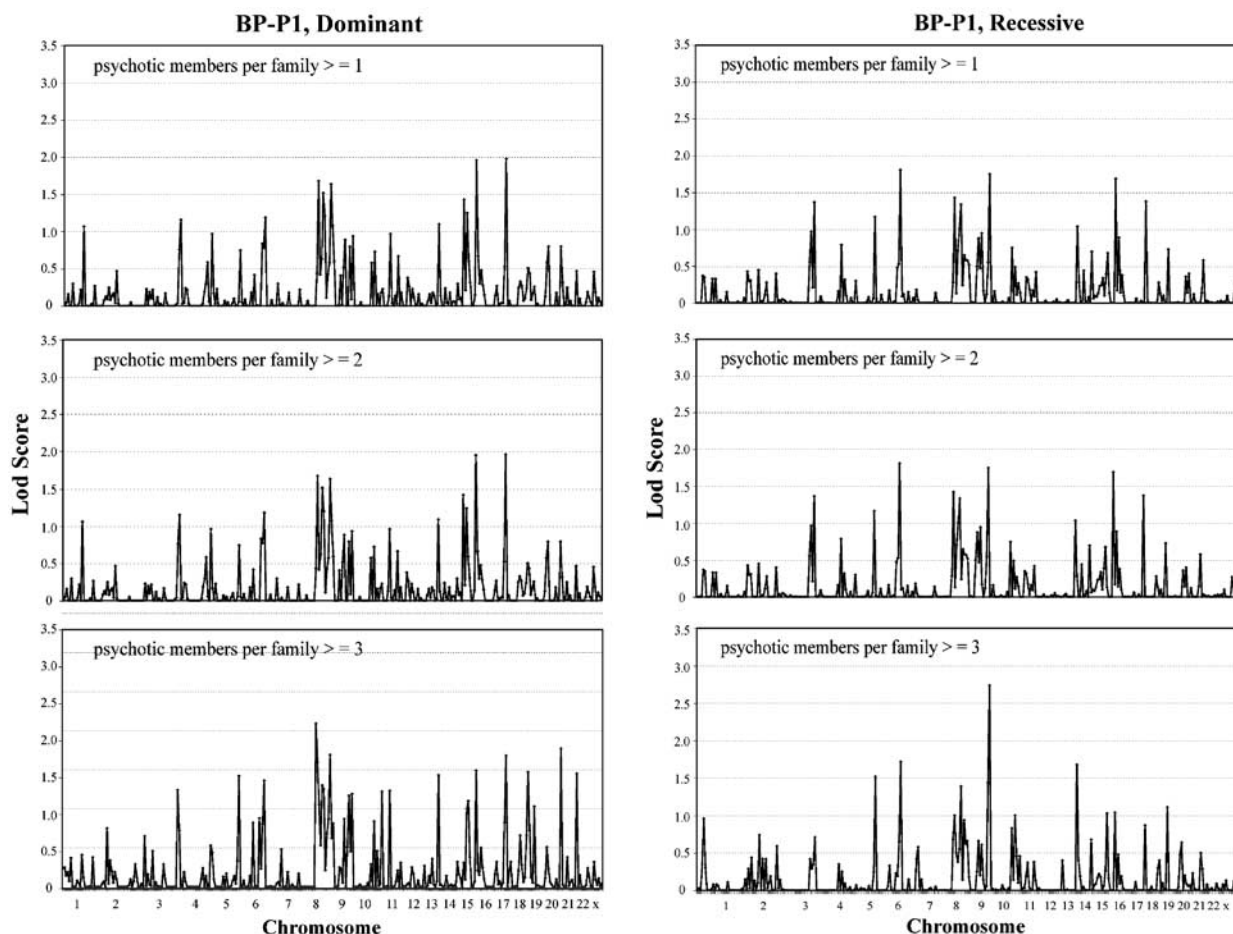


Figure 1 Genome-wide scan results for diagnostic model BP-P1 and dominant and recessive modes of transmission. The six panels depict two-point lod score support (Y-axis) per chromosomal location (X-axis) according to familial load of psychosis.

model) and D8S382 at 8p21 (MLOD = 3.46; BP-P1, dominant model). Our simulation analysis yielded $O_E = 0.027$ for the strongest two-point result (lod = 3.33), which is in good agreement with the Lander and Kruglyak²² approach.

Seven other loci showed evidence of suggestive linkage: D8S1477 at 8p12 (lod = 2.06; BP-P2, dominant model), D8S1179 at 8q24 (lod = 2.01; BP-P3, dominant model), D13S779 at 13q32 (lod = 1.96; BP-P1, recessive model), D15S652 at 15q26 (MLOD = 1.96; BP-P1, dominant model), D17S921 at 17p12 (lod = 2.42; BP-P2, dominant model), D18S851 at 18q21 (lod = 2.40; BP-P2, dominant model), and D20S480 at 20q13 (lod = 1.98; BP-P1, dominant model). More moderate lod scores were obtained for D5S820 at 5q33 (lod = 1.78), D6S474 at 6q21 (lod = 1.81), and D10S2327 at 10q22 (lod = 1.6).

The multipoint lod scores (same models as in the two-point analysis) were generally consistent with the two-point results. Although multipoint parametric analysis of complex traits may result in deflated lod scores,²⁵ four of the loci showed increased lod scores, including the two significant linkage results at 8p21 and 9q31.

As shown in Table 1, all the loci listed displayed two-point lod scores ≥ 1 across other configurations of diagnostic and genetic models.

The A-test did not reject the hypothesis of linkage homogeneity for the marker loci tested.

Nonparametric analysis

Table 2 shows the results of multipoint affected sib pair (ASP) analysis.

A lod score supportive of suggestive linkage using the Lander and Kruglyak's²² criteria for nonparametric analysis (lod ≥ 2.2) occurred on 15q25–26, in the D15S652–816 interval (lod of 2.62 with BP-P1). The corresponding lod score curve is shown in Figure 4.

As shown in Figure 4 and Table 2, this region also showed lod scores > 2 with other diagnostic models. Several other loci gave more modest lod scores (> 1 but < 2.2), and some of these loci also showed lod scores > 1 under diagnostic models other than those mentioned (Table 2). The two-point ASP lod scores (not shown) were smaller than the multipoint results.

Lod scores and familial load of psychosis

Table 3 shows the relation between our strongest results (significant or suggestive linkage) and familial

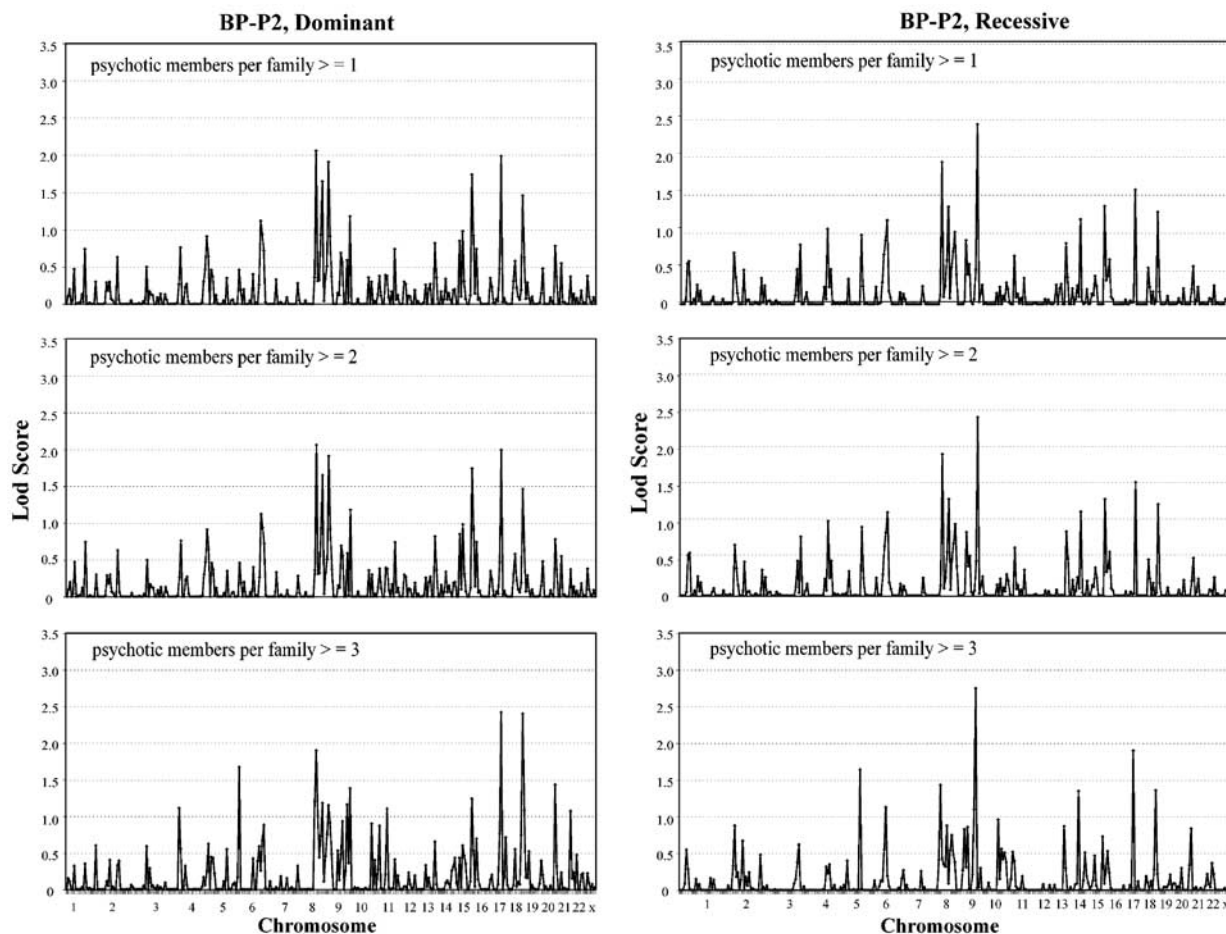


Figure 2 Genome-wide scan results for diagnostic model BP-P2. Other features as in Figure 1.

load of psychosis (the number of family members with psychotic BP). A graphical presentation (parametric results) appears in Figures 1–3.

We examined three subgroups of families. Eight of the 12 loci displayed their highest lod scores in families with the largest aggregation of psychosis (≥ 3 psychotic individuals per family). These are D5S820 at 5q33, D6S474 at 6q21, D8S382 at 8p21, D9S938 at 9q31, D13S779 at 13q32, D17S921 at 17p12, D18S851 at 18q21, and D20S480 at 20q13. Lod scores at the other four loci, although supportive of linkage, were either unchanged or somewhat reduced in these families. A similar pattern was observed for loci with more modest linkage signals (listed in Tables 1 and 2) (data not shown).

Discussion

Our results point to several chromosomal regions that may harbor susceptibility loci for psychotic BP: 5q33, 6q21, 8p12, 8p21, 8q24, 9q31, 13q32, 15q25–26, 17p12, 18q21, and 20q13. Regions 9q31 and 8p21 showed significant linkage (genome-wide $P < 0.05$); the other regions gave evidence of suggestive²² or near-suggestive linkage.

Most of our strongest results were obtained with a dominant model of transmission. As described,¹⁰ our pedigrees display primarily a ‘dominant-like’ pattern—as customary in studies of extended bipolar pedigrees, we sought families with unilineal transmission. Some studies suggest a role for dominant inheritance in BP,^{26–28} although the exact mode of transmission is unknown. The ASP results were generally less pronounced, consistent with the structure of our pedigrees, where most of the meioses connect family members across, not within sibships.

For most loci, support for linkage was observed under several configurations of diagnostic and genetic models. In addition, there was some correspondence between our parametric and nonparametric linkage results. Specifically, six of the regions with the highest parametric lod scores—8p, 9q, 10q, 13q, 15q, and 18q—were also supportive of linkage under ASP analysis. Most of our strongest results were obtained using narrowly defined disease phenotypes (BP-P1 or BP-P2). Compared to broader disease definitions, such phenotypes are thought to be more homogeneous, with a more predictable phenotype–genotype relationship.

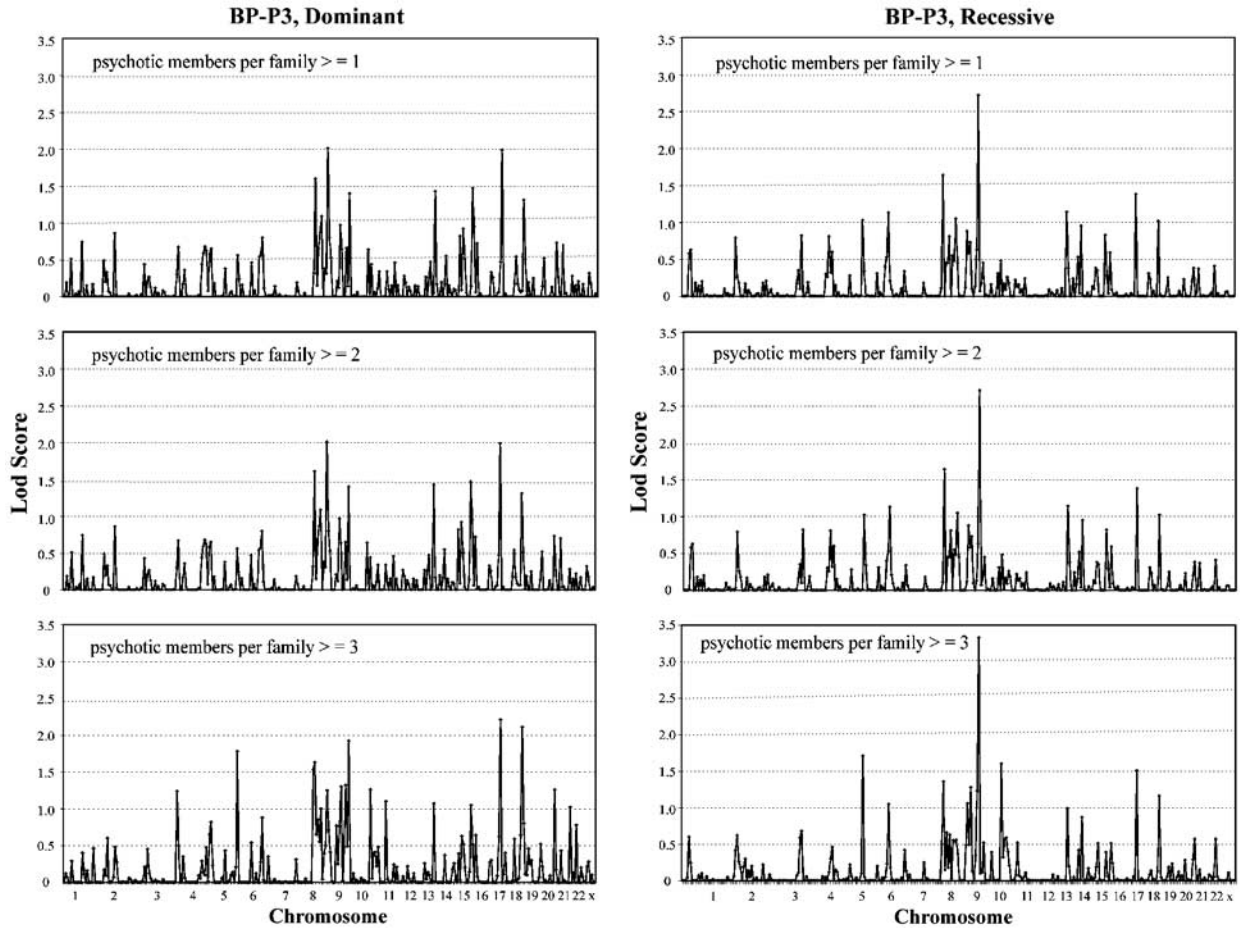


Figure 3 Genome-wide scan results for diagnostic model BP-P3. Other features as in Figure 1.

Table 2 Multipoint ASP lod scores > 1

Chromosome	Locus	Position (cM)	Maximum Diagnostic lod score	Diagnostic model
2p13	D2S1394	90.82	1.34	BP-P2
			1.04	BP-P1
8p12	D8S1477	60.34	1.80	BP-P1
			1.65	BP-P2
9q22	D9S910	104.48	1.22	BP-P3
10q22	D10S2327	100.92	1.51	BP-P3
10q26	D10S169	173.17	1.18	BP-P1
13q32	D13S779	82.93	1.55	BP-P1
			1.40	BP-P2
			1.15	BP-P3
14q32	D14S617	105.53	1.46	BP-P1
15q25–26	D15S652–816	94.25	2.62	BP-P1
			2.60	BP-P2
			2.45	BP-P3
18q21	D18S851	76.58	2.07	BP-P2
			1.70	BP-P3
			1.34	BP-P1

Six of the regions implicated in this study—5q33, 6q21, 8p12, 8q24, 15q26, and 18q21—did not show notable evidence of linkage in our previous genome scan.¹⁰ Two previously reported linkage signals were

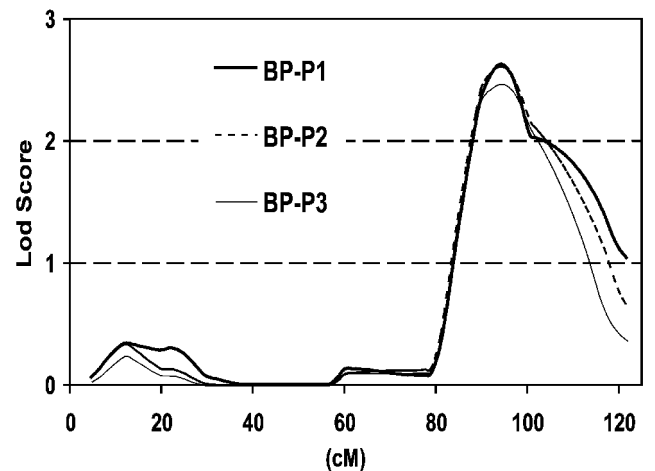


Figure 4 Multipoint ASP results with suggestive evidence of linkage; chromosome 15.

enhanced in the present study: D9S938 at 9q31 (a previous parametric lod of 2.07 vs 3.55 in the current analysis) and D18S851 at 18q21 (a previous ASP lod of 1.18 vs 2.07 in this study). Also, all regions but six—5q33, 6q21, 8p21, 8q24, 13q32 and 18q21—were

Table 3 Lod scores and familial load of psychosis

Chromosome	Locus	Position (cM)	Lod score		
			Psychotic members per family		
			≥ 1	≥ 2	≥ 3
<i>Two-point parametric analysis</i>					
8p12	D8S1477	60.34	2.06 (0.05)	2.06 (0.05)	1.90 (0.00)
8p21	D8S382	51.15	0.45 (0.15)	0.45 (0.15)	2.09 (0.00)
8q24	D8S1179	135.08	2.01 (0.10)	2.01 (0.10)	1.25 (0.15)
9q31	D9S938	110.93	2.72 (0.05)	2.71 (0.05)	3.33 (0.00)
13q32	D13S779	82.93	1.10 (0.10)	1.10 (0.10)	1.68 (0.00)
15q26	D15S652	90.02	1.96 (0.10)	1.96 (0.10)	1.50 (0.10)
17p12	D17S921	36.14	1.99 (0.10)	1.99 (0.10)	2.42 (0.05)
18q21	D18S851	76.58	1.46 (0.10)	1.46 (0.10)	2.40 (0.00)
20q13	D20S480	79.91	0.80 (0.15)	0.80 (0.15)	1.77 (0.05)
<i>ASP analysis</i>					
15q25–26	D15S652–816	94.25	2.62	2.62	2.16

Regions included in this table are those with suggestive or significant genome-wide linkage in any analytic configuration (Tables 1 and 2). The same analytic models that produced the highest lod score for a given locus were also used for comparison among family subgroups. The number of families in the three psychosis load categories (≥ 1 , ≥ 2 , ≥ 3) is 14, 25, and 36, respectively (see Subjects).

Numbers within parentheses, theta (recombination fraction).

not clearly supportive of linkage to BP in other published genome scans (reviewed in Baron,³ Dicks *et al*,²⁹ and Segurado *et al*⁴). The novel (or enhanced) linkages to BP in this study may be due to the fact that previous genome-wide linkage studies did not systematically target psychotic BP as the disease phenotype.

Our linkage finding on 13q is congruent with a previous report on linkage of psychotic BP to this region.⁹ The other region implicated in that report, 22q, did not appear linked in our study. Support of linkage on 2p was more pronounced in our previous genome scan:¹⁰ parametric lod = 3.2 vs 0.8 in this study (result not tabulated); however, the ASP results for 2p were similar in the two studies: lod = 1.59 (previous study) vs 1.34 (this study). These differences may be partly due to the smaller number of affected individuals in the current analysis, which was restricted to individuals with psychotic BP.

Lod scores for most of the regions with significant or suggestive linkage—8p21, 9q31, 10q22, 13q32, 17p12, 18q21, and 20q13—were most pronounced in families with the highest load of psychotic BP, reinforcing the potential genetic relevance of this disease phenotype. Similarly, Potash *et al*⁹ observed that linkage to BP in two of the regions they studied—13q (same general region as in our finding on this chromosome) and 22q—was stronger in families with the largest number of psychotic individuals. Lod scores for the other four regions included in our analysis—6q21, 8p12, 8q24, and 15q26—were either unaltered or reduced in these families, but remained supportive of linkage.

Four of the regions implicated in our study—5q33, 6q21, 8p21, and 13q32—are reportedly linked to schizophrenia (reviewed in Baron,³⁰ Lewis *et al*,³¹ and Owen *et al*³²). We also observed modest evidence of linkage on regions 2p13 and 10q26, previously implicated in BP^{3,10,29,33} and/or schizophrenia.^{30,31,34} Our findings are consistent with the notion that BP and schizophrenia have some genes in common. For some loci, this may be more pronounced when the BP phenotype is restricted to the psychotic form. Also of interest are regions 15q25–26 and 18q21, with suggestive linkage to both psychotic BP (this study) and schizophrenia (15q, reviewed in Baron;³⁰ 18q, reviewed in Lewis *et al*³¹), although at somewhat disparate locations, with uncertain overlap (BP, 15q25–26 and 18q21; schizophrenia, 15q15–24 and 18q22-qter). Similarly, region 17p12 showed suggestive linkage to both psychotic BP (this study) and schizophrenia,³² although the region implicated in schizophrenia spanned a large distance (17p11–q25). However, a linkage signal for a complex disease locus may occur at an interval up to 30 cM from the original finding.³⁵

Many of the loci thought to play a role in the susceptibility to BP (standard phenotype definition, combining psychotic, and nonpsychotic forms) or schizophrenia show no evidence of linkage in this study. This suggests only partial overlap in genetic predisposition between psychotic and nonpsychotic forms of BP and between BP and schizophrenia. Variability among studies in marker coverage and sample size (affecting power to detect linkage) may also explain the diversity in linkage results.

The pattern of linkage signals was similar in American and Israeli families (data not shown). The *A*-test failed to reject the hypothesis of linkage homogeneity. Given the likely heterogeneity of BP, we do not suggest that failure to reject the null hypothesis implies that it should be accepted. The *A*-test is not a powerful statistic for the analysis of disorders with complex inheritance because the model errors are confounded with the recombination fraction estimates. Larger samples are needed to assess linkage heterogeneity and differences among populations.

Several limitations are worth noting. First, we employed several diagnostic and genetic models, a common practice in studies of complex disorders. This may have led to inflated lod scores due to multiple testing. However, the fact that some of these models are correlated—for example, model BP-P1 is nested in model BP-P2, and model BP-P2 is nested in model BP-P3—partially obviates this problem because these tests are not truly independent. There is no clearcut, satisfactory method to adjust for multiple testing in these circumstances. Second, to render genotyping more efficient,³⁶ we did not genotype unaffected siblings and married-in spouses.¹⁰ This may cause an increase in the genome-wide false-positive rate. Third, the subset of families with the highest concentration of psychosis constitutes a small portion (about one third) of the genotyped sample. Small samples may lead to spurious linkage results, although it might also be argued that true linkage signals may be missed (or weakened) due to reduced statistical power. A measure of confidence in our results is offered by the strength of linkage signals compared to other regions in our genome scan, and by supporting evidence from other studies for some of the results. Fourth, using the number of psychotic relatives for subgrouping of families may leave out small-sized families where psychotic relatives are not present. This could potentially confound the analysis. However, the exclusion of small families would only reduce statistical power and would not bias the linkage results proper. Previous studies of familial breast cancer have found that using familial load of the disease can greatly increase the power to detect the BRCA1/BRCA2 genes in breast cancer families.³⁷ Therefore, the results from our heavily loaded families should be considered potentially interesting and in need of further investigation. Further study using large data sets is needed to confirm our findings and to examine the utility of this approach.

In conclusion, our findings speak to the potential merit of dissecting the BP phenotype based on the presence or absence of psychosis. This could enhance the detection of susceptibility loci, whether unique to BP or shared in common with schizophrenia.

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