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Affected-Sib-Pair Analyses Reveal Support of Prior Evidence for a Susceptibility Locus for Bipolar Disorder, on 21q

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Summary

In 22 multiplex pedigrees screened for linkage to bipolar disorder, by use of 18 markers on chromosome 21q, single-locus affected-sib-pair (ASP) analysis detected a high proportion (57%–62%) of alleles shared identical by descent (IBD), with *P* values of .049–.0008 on nine marker loci. Multilocus ASP analyses revealed locus trios in the distal region between D21S270 and D21S171, with excess allele sharing (nominal *P* values <.01) under two affection-status models, ASM I (bipolars and schizoaffectives) and ASM II (ASM I plus recurrent unipolars). In addition, under ASM I, the proximal interval spanned by D21S1436 and D21S65 showed locus trios with excess allele sharing (nominal *P* values of .03–.0003). These findings support prior evidence that a susceptibility locus for bipolar disorder is on 21q.

Introduction

Bipolar disorder is a common disease of unknown genetic etiology. The pattern of inheritance is complex, and early reports of linkage for this disease (Baron et al. 1987; Egeland et al. 1987) have not been substantiated by further analysis in these pedigrees (Kelsoe et al. 1989; Baron et al. 1993) or in other pedigrees (Detera-Wadleigh et al. 1987; Hodgkinson et al. 1987; Berrettini et al. 1990; Gejman et al. 1990). To identify loci that contribute to susceptibility to bipolar disorder, a global search of the genome was conducted. We have adopted a genomewide screening approach using 22 multiplex pedigrees, as described elsewhere (Berrettini et al. 1991, 1994, and in press; Detera-Wadleigh et al. 1992, 1994). Evidence of a susceptibility locus on the pericentromeric region of chromosome 18 was found (Berrettini et al. 1994). Detection was achieved by using nonparametric methods of linkage analysis. This initial finding has been strengthened by a recent replication in an independent panel of pedigrees (Stine et al. 1995).

In a study of an extended Finnish pedigree, linkage to bipolar disorder on Xq24-q27.1 was demonstrated by the LOD-score method (Pekkarinen et al. 1995). Evidence for another possible vulnerability locus for bipolar affective disorder, on 21q22.3—specifically, in the region of PFKL and D21S171—has been reported by Straub et al. (1994). In a series of 47 pedigrees, 1 family gave a LOD score of 3.41 with PFKL, under dominant inheritance and an affection-status definition that consisted of bipolar disorder and recurrent major depression. The maximum LOD score for the series was 2.8, and extended sib-pair analyses did not yield a significant result. However, the multilocus affected-pedigree-member (APM) method, using D21S171 and PFKL, gave significant values ($P < 10^{-6}$). Because of the difficulties associated with the genetic dissection of bipolar disorder, independent confirmation of an initial linkage is important. Gurling et al. (1995) analyzed an independent pedigree sample and found a three-point LOD score of 1.33, with PFKL and D21S171. In addition, an overall LOD score of 3.58 was found when a two-locus model with tyrosine hydroxylase (TH) on chromosome 11 and PFKL/D21S171 was used. In contrast, the chromosome 21 study by Byerley et al. (1995) yielded essentially negative results. We have attempted to replicate Straub et al.'s (1994) finding, in our panel of pedigrees. Here we report a confirmation of the evidence that a possible predisposing locus for bipolar disorder is on 21q, by affected-sib-pair (ASP) analysis.

Pedigrees and Methods

Pedigrees

A panel of 22 multiplex, unilineal bipolar pedigrees was genotyped in this linkage study. Diagnostic and as-

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certainment methods for 21 of these pedigrees have been described elsewhere (Berrettini et al. 1991). The 21 families consisted of ~365 informative persons (i.e., persons whose genotypes can be determined directly or indirectly), and the numbers of affected and unaffected individuals have been reported elsewhere (Berrettini et al. 1991). We also studied the "right extension" of the Old Order Amish pedigree 110 (Kelsoe et al. 1989), which appeared to have a unilineal pattern of illness comparable with that in our pedigrees. There were a minimum of four affected individuals per kindred, under affection-status model II (ASM II), which included bipolars (I and II, with major depression), schizoaffective illness, and recurrent unipolar depression. For the majority of the markers used in this study, we genotyped the same 22-pedigree panel, consisting of a reduced number of 223 individuals who included all with the affected phenotype, their parents, and other unaffected relatives who connect the affected subjects.

Genotyping

Genotyping was performed with short-tandem-repeat markers on chromosome 21q, all of which were found in published maps (Chumakov et al. 1992; NIH/CEPH Collaborative Mapping Group 1992; Lawrence et al. 1993; Cooperative Human Linkage Center [CHLC] 1994; Gyapay et al. 1994; CHLC human screening set/Weber, version 6). The order of and distances between some of the markers were checked in our pedigree panel composed of 365 individuals and were consistent with published maps (data not shown). The distances from D21S1432 to D21S1437, D21S1437 to D21S1435, D21S1435 to D21S1270, D21S1270 to D21S1440, and D21S1440 to D21S1446 were taken from the CHLC human screening set/Weber, version 6. The distances reported in the CHLC (1994) integrated map, from D21S1270 to D21S65, D21S65 to D21S1252, D21S1252 to D21S212, and D21S212 to D21S171, were used. The distances between D21S1252 and D21S267/D21S270 and between D21S267/D21S270 and D21S266 were taken from the Généthon map (Gyapay et al. 1994). The same map showed that D21S267 and D21S270 occupy the same genetic position, and, for multilocus calculations that included these markers, the distance between them was assumed to be 0.01 cM. The distances between D21S65 and HMG14 and between HMG14 and D21S212 were taken from the NIH/CEPH Collaborative Mapping Group (1992). The kainate type 1-glutamate receptor (GRIK1) has been mapped by Gregor et al. (1993), and its genetic distance from D21S65 was deduced from the latter study and the chromosome 21 map reported by Chumakov et al. (1992). For multilocus ASP analysis we used the map order reported by Chumakov et al. (1992) and Lawrence et al. (1993), which placed PFKL proximal to D21S171 and assumed a 0.05-cM distance between these loci. In contrast, Straub et al. (1994) reported the reverse order for PFKL and D21S171, with a distance of 4 cM. The composite map is shown in table 1.

Table 1

Analysis for Chromosome 21q and Bipolar Disorder

Between-Marker Distance[a] (cM)	Locus[b]	ASM I			ASM II		
			IBD	*P*		IBD	*P*
	D21S1432	68	.51	.4	128	.49	1
1.5	D21S11	57	.58	.016[c]	98	.54	.1
3.2	D21S1436	66	.55	.1	126	.51	.3
4.3	D21S1437	65	.53	.2	121	.52	.3
10	D21S1435	63	.59	.015[c]	122	.54	.1
1.5	GRIK1	61	.62	.0008[c]	117	.52	.2
3.5	D21S1270	64	.57	.049[c]	122	.50	1
7.5	D21S65	63	.56	.1	122	.55	.033[c]
1.5	D21S1440	69	.52	.3	126	.49	1
.7	D21S1252	64	.55	.1	124	.51	.3
2.99	D21S267	67	.57	.013[c]	126	.54	.08
.01	D21S270	67	.59	.017[c]	126	.53	.09
4.9	HMG14	59	.59	.0077[c]	113	.56	.0026[c]
6.1	D21S266	68	.59	.0096[c]	125	.55	.019[c]
3	D21S212	64	.59	.016[c]	120	.56	.024[c]
5.8	D21S171	62	.50	.5	120	.50	.2
	PFKL	67	.54	.1	127	.52	.2
	D21S1446	67	.53	.2	127	.50	1

NOTE.—Single-locus ASP analyses were performed to evaluate genotype data derived from 22 multiplex pedigrees screened with 18 marker loci on 21q.

[a] Taken or deduced from published maps, as described in Pedigrees and Methods. The distances of PFKL and D21S1446 from the other loci are not shown. PFKL has been shown to be proximal to D21S171 by Chumakov et al. (1992); and Lawrence et al. (1993) but in the reverse order by Straub et al. (1994); and D21S1446 is 23 cM distal to D21S1440, according to Research Genetics Mapping Panel/Weber, version 6.

[b] Arranged from the most centromeric (D21S1432) to the most telomeric on 21q (D21S171).

[c] $P < .05$.

PCR amplification conditions and analysis of PCR products were as described elsewhere (Detera-Wadleigh et al. 1994). The thermocyclers used were the Perkin Elmer Cetus GeneAmp System 9600 and the Bio Therm BioOven III. During electrophoresis M13 sequencing ladders and 123-bp ladders were used as size standards. In addition, samples from 2 control CEPH individuals were run with each set of 30 DNA samples. All genotype readings were blind to diagnosis and were done in duplicate.

Linkage Analysis

Two diagnostic affection-status models were used in linkage analysis: model I (ASM I) included bipolars (BPI and BPII, with major depression) and schizoaffectives

Table 2

Loci with Positive LOD Scores for Entire Pedigree Series, under a Recessive, 85%-Penetrance Model

Locus	LOD Score at θ = .2	
	ASM I	ASMII
D21S65		.44
D21S267	1.57	.41
HMG14	.63	.59
D21S266	.80	.99
D21S212	1.79	1.10

as ill, and model II (ASM II) included those in model I and recurrent unipolars. LOD-score calculations were done as previously described, by using the program LINKAGE version 5.10, for θ = .01, .05, .10, .20, and .30, under both a dominant mode of inheritance (85% and 50% penetrance) and a recessive mode of inheritance (85% penetrance) (Detera-Wadleigh et al. 1994). ASP (Blackwelder and Elston 1985) statistics were computed by using the SIBPAL program in Statistical Analysis for Genetic Epidemiology, release 2.2 (1994). APM analysis was done according to the method described by Weeks and Lange (1988). Multilocus ASP analysis was performed as described by Goldgar (1990), Goldgar and Oniki (1992), and Goldgar et al. (1993).

Results

LOD-Score Data

A total of 18 densely spaced markers covering ~60 cM of the long arm of chromosome 21 were used for genotyping 22 unilineal, multiplex bipolar pedigrees (table 1). Of these loci, HMG14, D21S266, D21S212, PFKL, and D21S171 were also employed in the linkage study by Straub et al. (1994). LOD scores were computed under both dominant and recessive modes of inheritance. Although the total LOD scores for the entire pedigree series failed to reach 3 for all 18 marker loci, some yielded LOD scores >1. Under a stringent affected-phenotype classification, ASM I, the highest cumulative LOD scores (θ = .2) were 1.79 and 1.57 (recessive, 85% penetrance) for D21S212 and D21S267, respectively (table 2), and 1.02 (dominant, 50% penetrance) for D21S266. We found that, under both affected-phenotype models and a recessive mode of disease transmission, there was a cluster of markers with positive LOD scores for the pedigree sample as a whole (tables 1 and 2). These markers—D21S267, HMG14, D21S266, and D21S212—are located in the distal portion of 21q (tables 1 and 2).

A number of individual pedigrees yielded LOD scores >1, with the highest values being 1.74 and 1.65 for D21S65 with pedigrees 0643 (ASM I, recessive) and 0068 (ASM I, dominant, 85% penetrance), respectively. For PFKL, the highest LOD score for a single pedigree (0068) was 1.19 (ASM I, dominant, 85% penetrance). For D21S171, the highest LOD score was 1.03 (recessive, 85% penetrance), for pedigree 9002. For both PFKL and D21S171, the overall LOD scores for the entire series were highly negative under different genetic models (data not shown).

Linkage with heterogeneity was not detected by the HOMOG program (Ott 1991). These results indicate that the parametric method of analysis failed to detect evidence of linkage between 21q and bipolar disorder in this pedigree series.

Single-Locus ASP

ASP analysis was performed by using the two definitions of the affected phenotype, ASM I and ASM II, where the number of affected pairs was 57–69 and 98–128, respectively (table 1). Under ASM I, an excess proportion (57%–62%) of alleles shared IBD, with *P* values of .049–.0008, was found with nine loci: D21S11, D21S1435, GRIK1, D21S1270, D21S267, D21S270, HMG14, D21S266, and D21S212 (table 1). GRIK1 yielded the highest IBD allele sharing, 62%, under ASM I, with a corresponding *P* of .0008. Under ASM II, only four markers—D21S65, HMG14, D21S266, and D21S212—yielded increased allele sharing, with *P* values <.05 (table 1).

The marker loci D21S267, D21S270, HMG14, D21S266, and D21S212 form a distal cluster spanning ~14 cM. Of these, as shown earlier (table 2), D21S212, D21S267, and D21S266 yielded LOD scores >1 for the entire data set. The most telomeric of these loci, D21S212, is located ~6 cM proximal to PFKL/D21S171 (table 1). Centromeric of this cluster were the four markers D21S11, D21S1435, GRIK1, and D21S1270. On the basis of the single-locus ASP analysis, under the restrictive diagnostic classification (ASM I), it appears that the increased IBD allele sharing on 21q covers ~30 cM, from the D21S1435–GRIK1–D21S1270 proximal cluster to the D21S267–D21S270–HMG14–D21S266–D21S212 distal cluster (table 1).

Multilocus ASP

To examine regions of 21q for linkage to bipolar disorder, overlapping three-marker multilocus ASP analyses were performed (Goldgar 1990; Goldgar and Oniki 1992; Goldgar et al. 1993). For the multipoint calculations the locus order and genetic distances between markers were taken and deduced from published maps and are shown in table 1. Under ASM I, the majority of chromosome 21q, spanning the proximal region from the locus trio D21S1436–D21S1437–D21S1435 to

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Table 3

Multilocus ASP for Chromosome 21q and Bipolar Disorder

	ASM I		ASM II	
Locus Trio[a]	IBD[b]	*P*	IBD[b]	*P*
D21S11 D21S1436 D21S1437	.56	.07	.53	.2
D21S1436 D21S1437 D21S1435	.56	.03[c]	.53	.09
D21S1437 D21S1435 GRIK1	.56	.027[c]	.53	.06
D21S1435 GRIK1 D21S1270	.62	.0003[c]	.54	.08
GRIK1 D21S1270 D21S65	.56	.027[c]	.53	.07
D21S1270 D21S65 D21S1440	.55	.08	.53	.2
D21S65 D21S1440 D21S1252	.57	.011[c]	.54	.028[c]
D21S1440 D21S1252 D21S267	.57	.013[c]	.53	.1
D21S1252 D21S267 D21S270	.57	.0096[c]	.54	.038[c]
D21S267 D21S270 HMG14	.59	.0044[c]	.55	.023[c]
D21S270 HMG14 D21S266	.59	.0011[c]	.56	.0024[c]
HMG14 D21S266 D21S212	.63	.0002[c]	.59	.0001[c]
D21S266 D21S212 PFKL	.60	.0057[c]	.57	.0086[c]
D21S212 PFKL D21S171	.57	.0095[c]	.55	.0053[c]

[a] Order for PFKL and D21S171 is as reported by Chumakov et al. (1992) and Lawrence et al. (1993), and the distance between them is assumed to be 0.5 cM.

[b] Calculated under two affection-status definitions. The marker distances and map order are as shown in table 1.

[c] $P < .05$.

GRIK1–D21S1270–D21S65 and the distal region from the locus trio D21S65–D21S1440–D21S1252 to D21S212–PFKL–D21S171 showed excess allele sharing in ASPs (table 3). Marker trios in these regions gave multipoint *P* values of .03–.0002. Under ASM II, a smaller region of 21q, which included D21S65–D21S1440–D21S1252 and the interval between D21S1252–D21S267–D21S270 and D21S212–PFKL–D21S171, yielded excess allele sharing, with multipoint *P* values of .038–.0001 (table 3). We also performed multipoint analysis for the distal locus trio, HMG14–D21S266–PFKL, where the distances between loci were >5 cM, which revealed the following results: ASM I, IBD = .61 (*P* = .0013); and ASM II, IBD = .57 (*P* = .0011). These data were consistent with multilocus scores for trios where markers were separated by smaller distances (table 3).

For the multilocus calculations that included PFKL and D21S171, we assumed a genetic distance of 0.5 cM, following the map order published elsewhere (Chumakov et al. 1992; Lawrence et al. 1993). We also assigned a 4-cM distance between these loci, on the basis of Straub et al.'s data (1994), but this did not produce a substantial change in the *P* values (data not shown). This distal portion of 21q contains the region where evidence for a possible susceptibility locus for bipolar disorder in another pedigree series has been found (Straub et al. 1994).

APM Analysis

We also performed APM analyses, but no significant results for all 18 markers were obtained (data not shown). This is not necessarily surprising, since the APM method has been shown to have lower power than is shown by other nonparametric tests (Goldin and Weeks 1993). This is because APM evaluates whether relatives are identical by state (IBS) rather than IBD. In addition, cautious interpretation of results from the APM test is required, since it is sensitive to misspecifications of marker-allele frequencies (Babron et al. 1993). We estimated marker-allele frequencies by using all of the data on our families, which we believe is a conservative approach.

Discussion

Because the genetics of bipolar disorder is complex, it is likely to be caused either by multiple interacting susceptibility genes or by different genes acting independently. Environmental factors might help trigger the disease by altering the activity of these genes. Genome-scanning strategy has provided evidence for three possible susceptibility loci for this disease (Berrettini et al. 1994; Straub et al. 1994; Pekkarinen et al. 1995). In a complex trait, however, replication must be demonstrated in independent pedigree series, to validate the initial finding.

We have conducted genotype analyses on 22 kindreds with bipolar disorder, using 18 markers on chromosome 21q. Under a stringent affected-phenotype definition,

single-locus ASP analyses show a proximal and a distal cluster of loci, separated by 13 cM, with excess IBD allele sharing between ASPs. When recurrent unipolar depression is included as affected, excess allele sharing is restricted to the distal cluster. The addition of recurrent major depression to the affected category might introduce phenocopies, since this phenotype is more prevalent in the population; but this issue remains to be resolved.

Multilocus sib-pair analysis was conducted in order to extract maximal linkage information between markers and to determine whether a region can be excluded. Under the stringent affection-status definition, most of 21q, which includes the interval from D21S1436 to PFKL/D21S171, spanning ~50 cM, shows excess allele sharing. This finding represents the first demonstration that excess allele sharing extends to the proximal region of 21q. The proximal and distal regions with increased allele sharing are separated by an interval of 9 cM covered by the marker trio D21S1270–D21S65–D21S1440, which yields no evidence of excess allele sharing. As in the single-locus ASP analysis, under the relaxed affected-phenotype classification (ASM II), multipoint analysis reveals increased alleles shared IBD only in the more telomeric interval. This phenotype definition (ASM II) is equivalent to model III used by Straub et al. (1994), for which the highest LOD score for PFKL was found. It is interesting that, in our study, multilocus ASP analyses that included either PFKL or D21S171 or both revealed excess allele sharing, which single-locus ASP analyses on either marker failed to detect. Gurling et al. (1995) reported a single-locus ASP *P* of .001 for D21S171 when unipolar cases were included in the affected phenotype, and this is consistent with our multilocus ASP data that include this particular marker. More important, the distal region that shows excess allele sharing between ASPs overlaps with the region proposed by Straub et al. (1994) to contain a possible susceptibility locus for bipolar disorder.

In a genome scan for a complex trait, our finding, by itself, might be considered suggestive but not significant for linkage, on the basis of Lander and Kruglyak's (1995) proposed guidelines for interpreting results. However, our data are consistent with the hypothesis that a susceptibility locus for bipolar disorder is on 21q (Straub et al. 1994), although this previous finding does not strictly meet the criteria for significance for linkage.

Lander and Kruglyak (1995) have suggested that a "*P* of 0.01 should be required to declare confirmation at the 5% level." Several of the markers used in this ASP study that are within a 15-cM range from PFKL and D21S171 have single-locus *P* values of $\leq .01$. In addition, a number of multipoint *P* values in the marker trios that included PFKL or D21S171 or both are $<.01$. Our data coupled with those of Gurling et al. (1995) represent two independent supporting studies, implying that the initial finding on 21q is not likely to be a random phenomenon. We therefore believe that the data presented here provide support for a second susceptibility gene for bipolar disorder in our pedigree series, the first being that on chromosome 18 (Berrettini et al. 1994). This might suggest that bipolar disorder is oligogenic.

It would be interesting to determine whether the susceptibility loci on chromosomes 18 and 21 are interacting or whether they exert independent effects. We note that the pedigrees with the highest LOD scores for chromosome 21 loci (i.e., pedigrees 643, 68, and 9002) are different from those with the highest LOD scores for chromosome 18 loci (Berrettini et al. 1994). Since the LOD scores in these studies have been computed on a large number of markers and by using several genetic models, we cannot draw conclusions about the likelihood that these two loci are independent. Ideally, the relative likelihoods of different types of two-locus models (heterogeneity, epistatic, etc.) should be compared in our pedigree sample. This approach has been applied to a large set of nuclear families with insulin-dependent diabetes mellitus (Cordell et al. 1995), and this has permitted conclusions on the joint effects of HLA and other susceptibility loci. However, the proposed susceptibility loci on chromosomes 18 and 21 appear to exert relatively small effects, since their relative-risk values (Risch 1987) are low. The largest relative-risk value for both chromosomes 18 and 21 is 1.6, given by D18S45 (un-

Table 4

Relative Risk of Chromosome 21q Loci

Locus	Relative Risk (λ^a) ASM I	ASM II
D21S1432	.934	.872
D21S11	1.522	1.152
D21S1436	1.156	1.069
D21S1437	1.141	1.107
D21S1435	1.498	1.241
GRIK1	1.647	1.027
D21S1270	1.112	.858
D21S65	1.253	1.184
D21S1440	1.149	.991
D21S1252	1.117	.996
D21S267	1.265	1.178
D21S270	1.362	1.178
HMG14	1.327	1.186
D21S266	1.267	1.173
D21S212	1.499	1.338
D21S171	.958	1.004
PFKL	1.081	1.104
D21S1446	.993	.933

[a] .25/*P* (IBD = 0), from Risch (1987).

published results) and GRIK1 (table 4), respectively. Given the predicted small-gene effects, our sample of families is not large enough to allow us to differentiate among possible complex modes of inheritance.

The chromosome 18 linkage has been demonstrated in paternal pedigrees (Stine et al. 1995) and in mixed maternal/paternal families in our family series (Gershon et al., in press), but not in exclusively maternal pedigrees. In contrast, excess allele sharing on chromosome 21 appears to be more impressive in the maternal pedigrees than in the mixed maternal/paternal pedigrees (S. D. Detera-Wadleigh, J. Badner, T. Yoshikawa, A. Sanders, W. H. Berrettini, and E. S. Gershon, unpublished data). These studies suggest a parent-of-origin effect on the transmission of bipolar illness.

The region proposed to contain a susceptibility locus covers a large portion of 21q, and our study as well as previous reports (Straub et al. 1994; Gurling et al. 1995) fail to narrow it down. Similarly, the chromosome 18 linkage region is large (Berrettini et al. 1994; Stine et al. 1995). Although strategies for fine resolution mapping of a predisposing locus for a complex phenotype have been suggested (Lander and Schork 1994), achieving this for both chromosomes is difficult, since the highest relative risk in each is <2 (table 4 and authors' unpublished data). Also, because the combined relative risk for these chromosomes is small, we speculate that additional susceptibility genes for bipolar disorder remain to be identified.

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