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Convergent linkage evidence from two Latin-American population isolates supports the presence of a susceptibility locus for bipolar disorder in 5q31–34

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We performed a whole genome microsatellite marker scan in six multiplex families with bipolar (BP) mood disorder ascertained in Antioquia, a historically isolated population from North West Colombia. These families were characterized clinically using the approach employed in independent ongoing studies of BP in the closely related population of the Central Valley of Costa Rica. The most consistent linkage results from parametric and non-parametric analyses of the Colombian scan involved markers on 5q31–33, a region implicated by the previous studies of BP in Costa Rica. Because of these concordant results, a follow-up study with additional markers was undertaken in an expanded set of Colombian and Costa Rican families; this provided a genome-wide significant evidence of linkage of BPI to a candidate region of ~10 cM in 5q31–33 (maximum non-parametric linkage score = 4.395, $P < 0.00004$). Interestingly, this region has been implicated in several previous genetic studies of schizophrenia and psychosis, including disease association with variants of the enthoprotin and gamma-aminobutyric acid receptor genes.

INTRODUCTION

Bipolar disorder (BP) is a psychiatric condition characterized by alternating episodes of mania and depression (MIM 125480 and MIM 309200). Despite strong evidence for a genetic contribution to BP risk (1), and genome-wide linkage studies suggesting multiple possible chromosomal localizations for BP genes (2,3), there is no convincing evidence yet of specific BP susceptibility loci.

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Variability in the definition and assessment of the affected phenotype and heterogeneity of study samples are two factors that are likely to have contributed to the disappointing results of BP mapping studies. The use of standardized ascertainment and phenotyping procedures should enhance the probability that different samples will yield concordant results, as should the joint investigation of samples from populations with shared genetic backgrounds (4). We describe here the linkage mapping of BP in similarly phenotyped pedigrees from two genetically related Latin-American populations: the Central Valley of Costa Rica (CVCR) and the province of Antioquia in Northwest Colombia.

The founder populations of the CVCR and Antioquia have similar and related demographic histories. Both populations were established around the 16–17th centuries mainly by the admixture of male immigrants from Southern Spain and Native American females, most likely from the Chibchan-Paezan linguistic group (5,6). Subsequent to founding, these two populations grew dramatically and in relative isolation fuelled, until recently, by an elevated fertility rate (5,6). A study of 2486 SNP markers on chromosome 22, genotyped in 200 unrelated individuals from both Antioquia and the CVCR, confirmed the close genetic relatedness between these two populations as evidenced by very similar allele frequency distributions and linkage disequilibrium patterns (7).

Genetic studies of BP in the CVCR have focused on individuals with BPI, a diagnosis requiring at least one episode of full mania and representing the most severe and heritable form of mood disorder (8). A genome scan for BPI in two large CVCR pedigrees pointed to the presence of BP susceptibility loci in 18q23 and 5q31–33 (9–11). However, follow-up of these results has been limited by the difficulty of further extending these two pedigrees.

Here, we report results for a whole genome linkage scan for BPI in six extended multiplex pedigrees from Antioquia. These pedigrees were ascertained and characterized clinically using the procedures established in the CVCR study and focusing on the BPI phenotype (8). The most consistent linkage finding in this scan implicates markers on 5q31–34, the same region highlighted in the previous genome scan of CVCR pedigrees (11). We followed up this concordant signal by genotyping additional microsatellite markers in an expanded set of pedigrees from Antioquia and the CVCR. In the combined analysis, we observe linkage to markers in 5q31–34 that is significant at a genome-wide level.

RESULTS

Microsatellite genome scan of Antioquian pedigrees

Six Antioquian pedigrees were selected for a microsatellite genome screen (CO3, 4, 7, 14, 18 and 27; Fig. 1). A total of 91 individuals were genotyped, including 50 BPI cases (29 females and 21 males), representing a range of 5–13 cases per family. The average age of onset of these cases was 23 years (range 12–39). Results for two-point parametric and multipoint non-parametric linkage (NPL) analysis for all markers typed are displayed in Figure 2A and 2B, respectively. The most significant results from these analyses have been extracted into Tables 1 and 2. In parametric linkage analysis, seven markers produced heterogeneity lod-scores ≥ 1.3 (Table 1) with the highest lod-score (2.28) obtained with marker D21S1914. This marker and marker D3S1580 produce lod-scores >2 in family CO7. Non-parametric analysis resulted in seven markers with *P*-value of <0.05 in the combined set of six families (Table 2). Three of these markers are also included in the most significant set identified in the parametric analysis: D3S1580, D5S410 and D21S1914; these three markers produce the highest NPL scores. A second marker on chromosome 5 (D5S422), located ~ 8 cM away from D5S410, also results in an overall non-parametric *P*-value of <0.05. These two markers are in the 5q31–34 region highlighted previously in the NPL analysis of the genome scan of CVCR BPI pedigrees CR001 and CR004 (11). Because of this concordant evidence across populations, this region was chosen for follow-up genotyping studies, as described subsequently. For individual families, the most significant non-parametric *P*-values were obtained for markers D3S1580 (family CO7, NPL score = 2.52) and D21S1914 (family CO14, NPL score = 3.05).

Follow-up of the 5q31–34 region

An additional eight Antioquian pedigrees, including 35 BPI subjects, were studied in follow-up genotyping. These pedigrees were, on average, smaller than the six pedigrees used in the genome screen and included a range of 3–6 cases per family (see Pedigree Structures in Supplementary Material). Follow-up analyses also included three CVCR pedigrees. Pedigrees CR001 and CR004 have been described in Freimer *et al*. (9). Together, these pedigrees include 30 BPI individuals. These two pedigrees can be linked via numerous inbreeding loops into one large kindred. A third CVCR pedigree, CR201, has been described in Service *et al*. (12) and includes 25 BPI subjects. Genotype data were generated for 18 markers in 5q31–34 in this expanded Antioquian and CVCR family set. The highest two-point parametric linkage result was a heterogeneity lod score of 2.53 at D5S1971 (Table 3). Figure 3 shows the result of NPL analyses. The highest combined NPL scores (>4) were obtained between markers D5S673 and D5S403, representing a region of ~ 7 cM and peaking at marker D5S2049 (NPL score = 4.395, corresponding to a *P*-value of 0.00004).

DISCUSSION

The results of linkage studies carried out so far on BP are consistent with the view that substantial genetic heterogeneity underlies susceptibility to this disorder (13). Our approach of studying patients with a narrowly defined phenotype (BPI), ascertained from two closely related population isolates, and characterized with standardized clinical protocols, is an attempt to reduce the etiological heterogeneity of the study sample. From this perspective, it is noteworthy that non-parametric linkage analyses of genome scans in Antioquian and CVCR pedigrees have independently identified 5q31–34 as displaying the most consistent and among the strongest linkage signals to BPI. Our follow-up work in this region,

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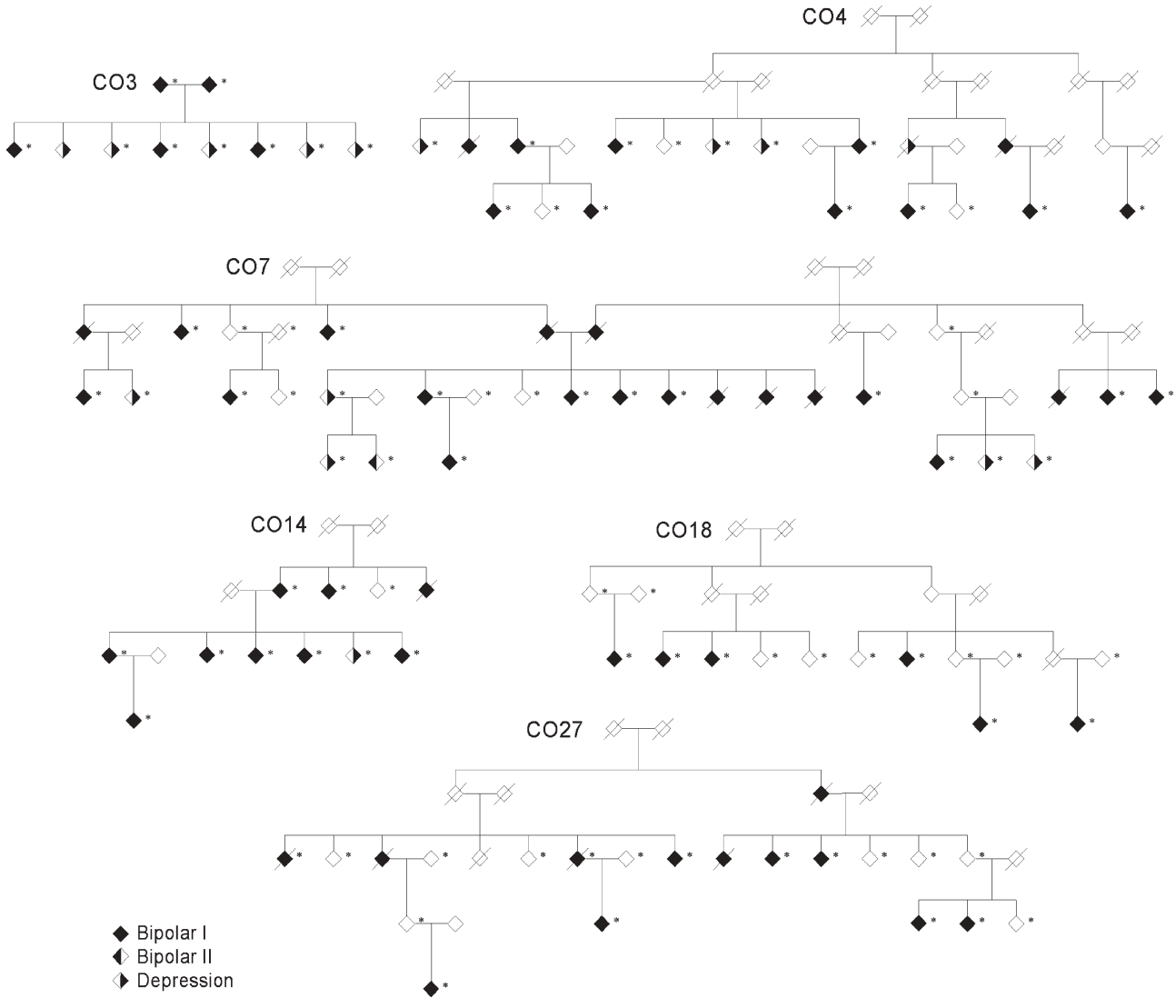

Figure 1. The six Antioquian pedigrees included in the genome scan. Filled symbols indicate individuals with a diagnosis of BPI: right half-filled symbols major depressive disorder and left half-filled symbols BPII. Asterisks indicate genotyped individuals. For linkage analysis, only living, genotyped individuals with a diagnosis of BPI were considered affected. All other individuals were considered to be phenotype unknown.

with additional markers and pedigrees, strengthened the linkage signal and narrowed the most probable location of a BPI susceptibility gene.

There are several possible explanations for the fact that we have observed stronger linkage evidence for 5q using non-parametric analysis compared with parametric analysis. In particular, the model employed in the parametric analysis may not be exactly correct, and this may be true to different extents for different loci. The same observation has been made previously with respect to 5q in the analyses of the original two CR pedigrees; this region was highlighted in the non-parametric analysis reported by Garner *et al*. (11) but not in the prior parametric analysis reported on by McInnes *et al*. (10). Additionally, the parametric analysis was a two-point analysis, whereas the NPL analysis was a multipoint analysis (with evidence evaluated at each marker, but including information from other markers).

The previously reported non-parametric analysis of the genome screen of CVCR pedigrees CR001 and CR004 had shown evidence of linkage to five consecutive markers covering a region of ~15 cM centromeric to marker D5S410 (11). Follow-up of this linkage with additional microsatellite markers identified haplotype sharing in this region among most of the BPI affected members of this CVCR kindred; maximal haplotype sharing occurred ~7 cM telomeric to D5S410 (14). The genome scan data from the Antioquian BPI families examined here also provided evidence of linkage for marker D5S410 as well as for marker D5S422, located ~8 cM telomeric to D5S410. The 18 markers examined here for follow-up cover the region in which the evidence of linkage was detected in the respective genome scans of Antioquian and CVCR pedigrees and also examined in the prior follow-up study restricted to family CR001/CR004 (14). The joint analysis of all pedigrees available to us from

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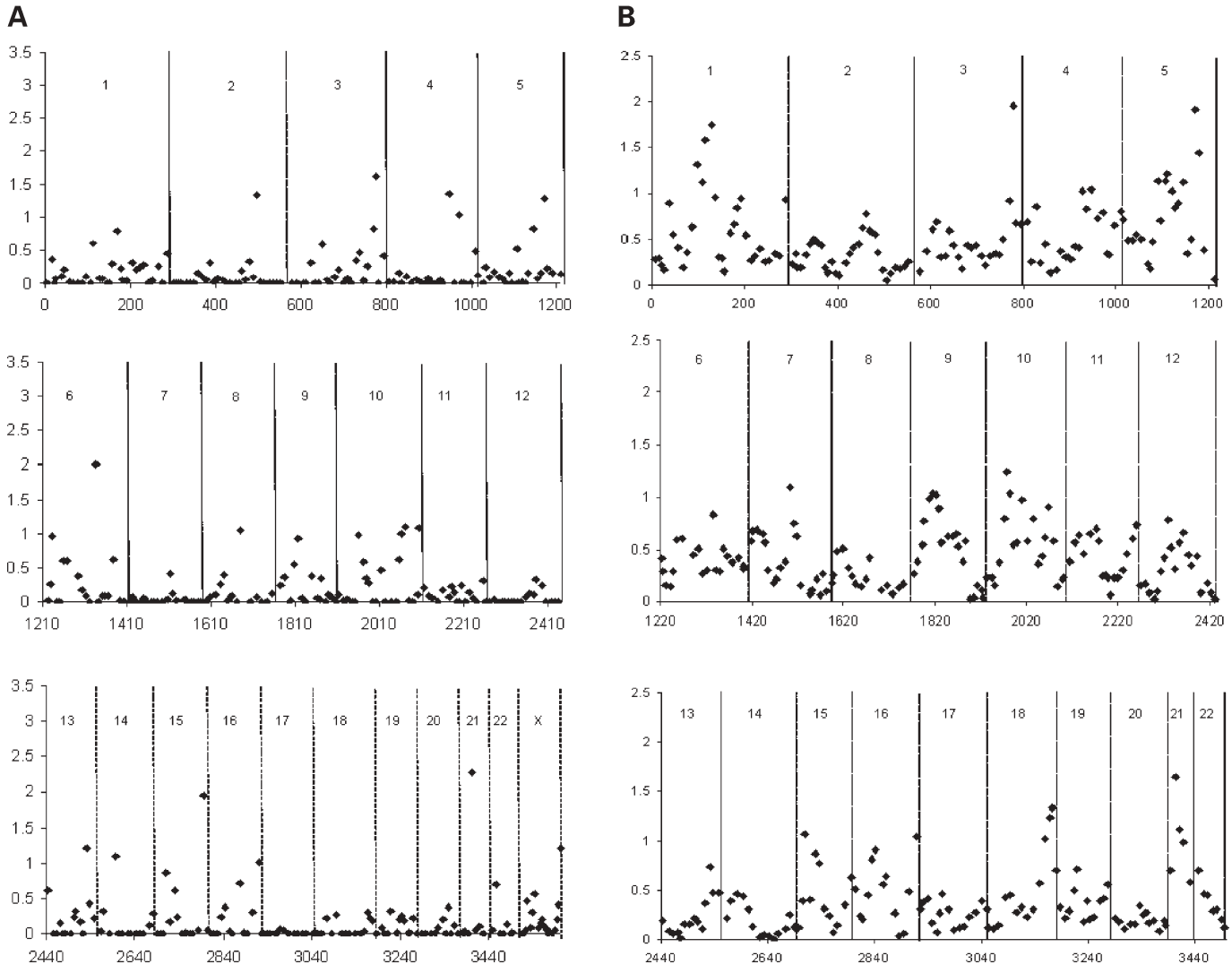

Figure 2. Linkage results for the genome screen of six Antioquian BPI families. (**A**) Maximum two-point heterogeneity lod-scores (the *y*-axis represents the lod score) and (**B**) Combined NPL scores [the y-axis represents $-\log(P)$]. Dotted vertical lines separate individual chromosomes. X-axis: cumulative genetic distance from 1 pter.

these two populations strengthened the evidence for linkage, achieving a genome-wide level of significance and identifying a narrow region (<10 cM) on which to focus the search for BPI susceptibility variant(s). The search for such variants should be aided considerably by the high probability of remote shared ancestry (from either European or Amerindian lines of descent) among sets of BPI affected individuals in the CVCR and Antioquia. The recent observation (7) that these two populations share remarkably similar patterns of LD, demonstrate considerably greater LD than more heterogeneous European-derived populations, and display comparable SNP allele frequencies over extended genome regions suggests that LD analyses in these populations of this candidate region using dense sets of SNPs should have high power to detect associations to BPI.

The well-described advantages of conducting genetic investigations of complex diseases within relatively homogeneous populations are at least partially offset by the difficulty in obtaining adequately powered samples within single, small populations (15,16). The approach that we have employed here—combining comparably phenotyped pedigree samples from genetically closely related populations—may be a useful strategy for enhancing the power of genetic investigation of complex diseases in general. The combination of samples across such populations may also provide an advantage for fine-mapping studies; shared ancestry among affected individuals from two such populations is likely more remote than in a single population, and therefore, haplotypes across the two populations will be observed in narrower segments surrounding a common disease susceptibility gene (5,17).

The linkage peak observed in these BP families overlaps strikingly with the regions linked in several previous studies to schizophrenia or to psychosis, broadly defined (18–22)

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Table 1. Markers with heterogeneity lod scores ≥1.3 in two-point parametric linkage analysis of genome scan data from six Antioquian BPI pedigrees

Chromosome	Marker	Position (cM)	HLOD	θ[a]	α[b]	Family[c]					
						CO3	CO4	CO7	CO14	CO18	CO27
2	D2S325	204.5	1.33	0.18	1.00	0.00	0.05	0.38	0.41	0.00	1.01
3	D3S1580	207.7	1.61	0.00	0.24	0.03	0.00	2.59	0.39	0.00	0.00
4	D4S424	144.6	1.35	0.15	1.00	0.00	0.43	0.11	0.00	0.00	1.88
5	D5S410	156.5	1.30	0.12	1.00	0.28	0.48	0.54	0.64	0.45	0.02
6	D6S287	122	2.01	0.00	0.47	0.00	1.69	0.22	0.07	1.57	0.03
15	D15S120	112.6	1.96	0.03	0.49	0.21	0.65	0.00	0.40	2.43	0.00
21	D21S1914	19.4	2.28	0.00	0.51	0.00	0.00	2.06	1.42	0.11	0.18

HLOD, heterogeneity lod scores.
[a]Recombination fraction at maximum HLOD.
[b]Proportion of linked families.
[c]Two-point lod scores for each individual family.

Table 2. Markers with the highest combined NPL scores ($P < 0.05$) in the genome scan of six Antioquian BPI pedigrees

Chromosome	Marker	Position (cM)	All[a]	Family[b]					
				CO3	CO4	CO7	CO14	CO18	CO27
1	D1S207	113.7	1.33	0.35	0.76	0.87	0.59	0.08	0.74
1	D1S2868	126.2	1.53	1.05	0.25	1.09	0.39	0.72	0.41
3	D3S1580	207.7	1.96	0.35	0.66	2.52	0.66	0.20	0.18
5	D5S410	156.5	1.92	1.19	0.65	1.54	0.24	0.44	0.35
5	D5S422	164.2	1.44	1.22	0.66	0.99	0.22	0.09	0.59
18	D18S462	120	1.34	0.36	0.33	0.91	0.92	0.22	0.70
21	D21S1914	19.4	1.65	0.32	0.12	1.20	3.05	0.13	0.34

[a]NPL scores for the combined family set.
[b]NPL scores for each individual family.

Table 3. Heterogeneity LOD scores (HLODS) for 18 microsatellite markers in 5q31–34 in the combined set of 17 pedigrees (Antioquia + CVCR)

Marker	Position (cM)	HLOD	θ[a]	α[b]
D5S436	147.49	0.6157	0.3201	1
D5S2033	148.63	0.075	0.365	1
D5S2090	150.34	0.073	0.4309	1
D5S2015	152.62	0.3437	0.3706	1
D5S2014	153.17	0.0002	0.4936	0.9874
D5S673	155.92	0.4595	0.3369	1
D5S410	156.47	0.7099	0.2864	1
D5S2012	157.21	1.7392	0.2740	1
D5S487	158.12	1.3385	0.2664	1
D5S1403	159.77	1.0346	0.2597	1
D5S2049	160.87	0.2204	0.3370	1
D5S2060	161.00	0.9519	0.2909	1
D5S1971	161.94	2.5269	0.0794	0.5078
D5S403	162.47	1.9832	0.1930	1
D5S422	164.19	0.5884	0.3151	1
D5S2066	165.13	0.6199	0.3067	1
D5S2040	168.68	1.4655	0.2175	1
D5S415	169.45	0.6408	0.3148	1

[a]Recombination fraction at maximum HLOD.
[b]Proportion of linked families.

including one study of pedigrees ascertained in the CVCR for schizophrenia (18). Somewhat weaker linkage evidence to 5q31–35 was obtained for the broadly defined phenotype of BPI, BPII, recurrent unipolar depression and schizoaffective disorder (23). Psychosis (the experience of hallucinations or delusions) is a prominent feature of both schizophrenia and severe mood disorders, including BPI. Given the focus of our studies on individuals with BPI, most of whom have experienced at least one episode of psychosis, our results provide further support for the hypothesis that a locus on 5q may predispose to psychosis rather than to either disorder *per se* (3,24,25). In the past several years, association has been reported between schizophrenia and several candidate genes located in the linkage region defined here (Fig. 3). A set of gamma-aminobutyric acid receptor subunit genes (*GABRA1*, *GABRA6*, *GABRB2* and *GABRG2*) in 5q34 has been found to be associated with schizophrenia in Portuguese and German samples (26) and in samples of Han Chinese (27). The enthoprotin gene (Epsin 4, *ENTH*) in 5q33.3 has been associated with schizophrenia in both an outbred sample from the UK (28) and in a sample of Han Chinese (29) (a recent study however failed to replicate the association in an additional sample of Han Chinese) (30). As shown in Fig. 3, these genes lie near the peak of the linkage region described here, and therefore, they must also be considered interesting candidate genes for BPI susceptibility.

Other potential candidate genes in the region include *GR1A1* and *HTR4*. *GRIA1* encodes the glutamate receptor 1 (GluR1) subunit of the ionotropic receptor AMPA. This receptor is widely expressed in human brain, shows decreased expression in brains of patients with schizophrenia (31) and was recently associated with schizophrenia in an Italian population (32).

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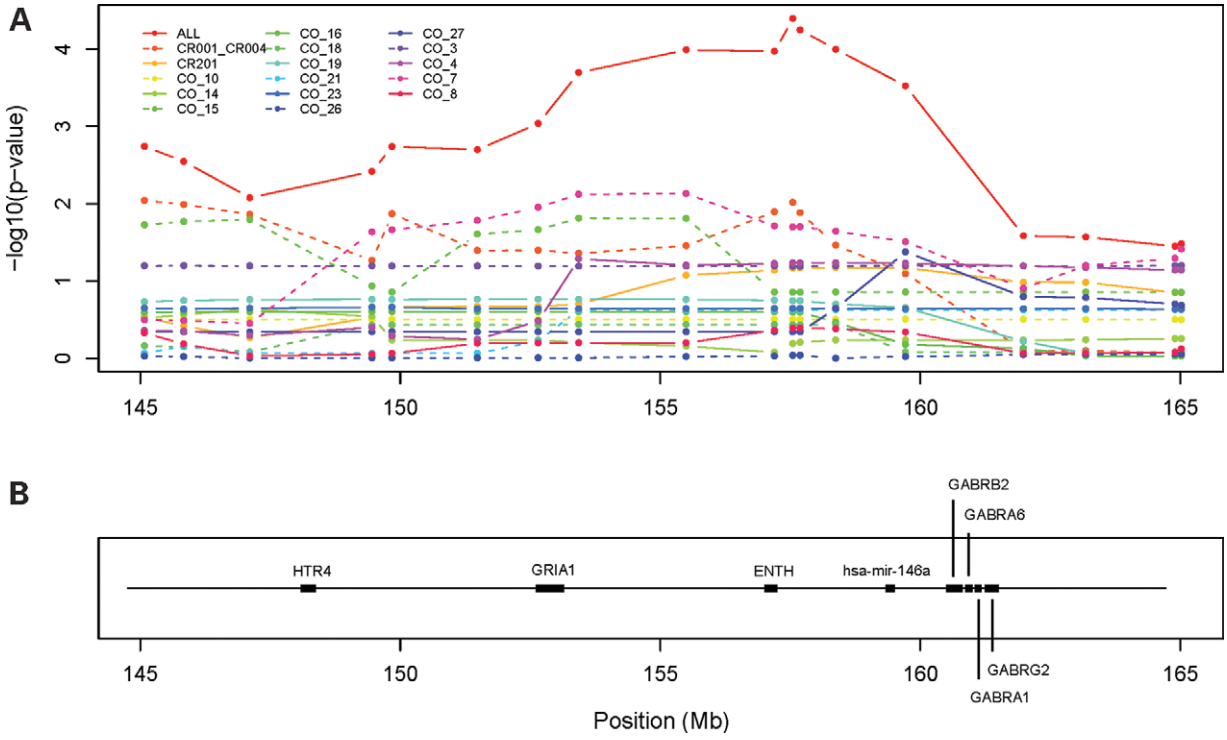

Figure 3. Follow-up of the 5q31–34 region. (**A**) NPL pair scores for 18 markers in 5q31–34 in 14 Antioquian (CO) and three CR pedigrees. All = NPL pairs score for the combined family set. (**B**) Location of some of the strongest candidate genes found within the 5q31–34 linkage region defined above. Genes are represented as black boxes drawn approximately to scale and positioned on a physical map based on information from the March 2006 human reference sequence (NCBI Build 36.1).

The serotonin 4 receptor gene *HTR4* lies within the follow-up region and has been associated with BP in a Japanese sample (33) but is located several megabases away from the linkage peak. Finally, a microRNA (hsa-mir-146a) having *GABRA1* as one of its predicted targets, maps near the 5q linkage peak, making it another interesting candidate for BP susceptibility in our sample.

Our strategy for identifying BP susceptibility variants in 5q rests on the genetic homogeneity and close relationship of the CVCR and Colombian populations. Through high-resolution SNP genotyping (approximately 1000 SNPs) across the 9.3 Mb segment including the peak NPL score and the surrounding NPL −1 (equivalent of LOD −1) region, we aim to identify a minimal candidate interval by assessing haplotype sharing among the affected individuals in the pedigrees and by linkage disequilibrium-based association analysis of several hundred independently ascertained BPI trios from the CVCR and Antioquia. As this SNP set includes all previously identified genic variants within the region, we will also test directly for association of all the candidate genes that have been highlighted in prior studies.

MATERIALS AND METHODS

Antioquian pedigrees

The families characterized here were collected as part of an ongoing psychiatric genetics research program in the population of Antioquia. This research has been approved by the Ethics Committee of Universidad de Antioquia, University College London and UCLA. Index cases were identified mainly at Hospital Mental de Antioquia and Hospital Universitario San Vicente de Paúl, both in the city of Medellín. All index cases included in the study had at least six great-grandparents born in Antioquia. Families with at least three individuals with a clinical diagnosis of BP were selected for pedigree extension by a social worker or psychiatric nurse using the Family Interview for Genetic Studies (34). Clinical assessments aim at identifying individuals with a clear-cut diagnosis of BPI, on the basis of the DSM-IV-TR criteria (35). Family members were assessed by an experienced psychiatrist trained in the application of a Spanish translation of the Diagnostic Interview for Genetic Studies (DIGS version 3) validated in Colombia (34,36). Final diagnosis was reached by consensus between two clinical experts who independently reviewed all the available clinical information, following the best estimate procedure described in Freimer *et al*. (8). Reliability of the best estimate diagnoses was achieved with the raters from the CVCR study ($\kappa = 0.8$). During pedigree extension, Family members unavailable for interview (including deceased individuals) were considered affected with BPI if they underwent at least two hospitalizations and clinical records allowed confirmation of symptomatology in the best estimate process.

Genome screen genotyping

DNA from the Antioquian samples was extracted from whole blood using a phenol/chloroform extraction method.

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The samples for Antioquian pedigrees CO3, 4, 7, 14, 18 and 27 were genotyped for the 398 markers included in the ABI LIMS v.2.5 panels (Applied Biosystems), using standard PCR protocols. The fluorescent PCR products were electrophoresed on ABI 377 and ABI 3700 genetic analyzers (Applied Biosystems). Raw data were collected and analysed using Genescan software (Applied Biosystems). Genotypes were scored independently by two individuals, blinded to affection status and relatedness between subjects, using the Genotyper software (ver 3.7). Mendelian segregation was checked using the Pedcheck program (37). Genotypes were ignored if allele scoring was found to be repeatedly inconsistent.

Follow-up genotyping in 5q31–34

An additional 17 microsatellite markers were genotyped within a 22 cM interval on chromosome 5q31–34, in the entire set of Colombian and CVCR pedigrees. These markers are located ~11 cM on either side of marker D5S410, which showed evidence of linkage in both parametric and non-parametric analyses in the genome screen of the Colombian pedigrees and had also showed evidence of linkage in non-parametric analyses of the genome screen of CVCR pedigrees CR001 and CR004 (11). These markers had an average spacing of 1.2 cM. All markers were amplified using standard PCR conditions and PCR products were subjected to electrophoresis on an ABI 3700 Genetic Analyzer. Genotypes were scored as described earlier.

Data analysis

The microsatellite genome screen data of the six Antioquian pedigrees were analysed using both parametric and NPL methods. Mendel version 5.5.2 (38) was used to perform two-point parametric linkage analysis for the 398 markers included in the genome scan. We employed essentially the same genetic model used in the previous genome scan of families from the CVCR (10). The frequency of the disease allele was 0.003, the penetrance for persons without a disease allele was set to be 0.01 and the penetrances for one and two copies of the disease gene were 0.81 and 0.90, respectively. Marker allele frequencies were estimated from the pedigrees using Mendel, with correction for dependencies due to family relationships (39). The genetic model used results in a population prevalence of ~1.5%, which is consistent with local epidemiological surveys (40,41). Multipoint NPL analysis was conducted using SimWalk2 (42), using the NPL pairs statistic; the same NPL analysis had previously been conducted in the CVCR pedigrees (11). For all analyses, only individuals with the best estimate diagnosis of BPI were considered affected. All other pedigree members were considered to be of unknown phenotype. Data files were converted between various formats, as required, using Mega2 v. 3.0 R4 (43).

Data from follow-up genotyping in the Antioquian and CVCR pedigrees were analysed using both parametric linkage and NPL analyses, in the same manner as described for the genome screen. Note that, for the parametric analyses only, 16 elderly individuals in CVCR pedigrees CR001 and CR004 were considered unaffected; this was to maintain consistency with the previously published parametric analyses of these pedigrees (9). Allele frequencies were estimated using all 17 pedigrees. CR001 and CR004 were combined into one kindred for the NPL analysis, as had been done in the genome-wide NPL analysis of these pedigrees (11).

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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Conflict of Interest statement. None declared.

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