Evidence of Linkage and Association on 18p11.2 for Psychosis

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The genetic basis of bipolar disorder (BPD) and schizophrenia (SCZ) has been established through numerous clinical and molecular studies. Although often considered separate nosological entities, evidence now suggests that the two syndromes may share some genetic liability. Recent studies have used a composite phenotype (psychosis) that includes BPD, SCZ, psychosis not otherwise specified, and schizoaffective disorder, to identify shared susceptibility loci. Several chromosomal regions are reported to be shared between these syndromes (18p, 6q, 10p, 13q, 22q). As a part of our endeavor to scan these regions, we report a positive linkage and association finding at 18p11.2 for psychosis. Two-point linkage analysis performed on a series of 52 multiplex pedigrees with 23 polymorphic markers yielded a LOD score of 2.02 at D18S37. An independent set of 159 parent offspring trios was used to confirm this suggestive finding. The TDT analysis yielded support for association between the marker D18S453 and the disease allele ($\chi^2 = 4.829$, $P < 0.028$). This region has been implicated by several studies on BPD [Sjoholt et al. (2004); Mol Psychiatry 9(6):621–629; Washizuka et al. (2004); Biol Psychiatry 56(7):483–489; Pickard et al. (2005); Psychiatr Genet 15(1):37–44], SCZ [Kikuchi et al. (2003); J Med Dent Sci 50(3):225–229; Babovic-Vuksanovic et al. (2004); Am J Med Genet 124(3):318–322] and also as a shared region between the two diseases [Ishiguro et al. (2001); J Neural Transm 108(7):849–854; Reyes et al. (2002); Mol Psychiatry 7(4):337–339; Craddock et al. (2005); J Med Genet 42(3):193–204]. Our findings provide an independent validation of the above reports, and suggest the presence of susceptibility loci for psychoses in this region.

KEY WORDS: psychosis; linkage and association; chromosome 18

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INTRODUCTION

Bipolar disorder (BPD) and schizophrenia (SCZ) are common psychiatric syndromes with variable clinical expression. The worldwide prevalence of both these diseases is ~1%. Several families, twin and adoption studies [Tsuang et al., 2001; Smoller and Finn, 2003] suggest evidence of a genetic contribution to these disorders. However, the precise mechanism of inherited liability is not well understood, thus complicating the process of gene identification. Linkage studies from different populations have yielded putative loci for BPD and SCZ. Moreover, like other complex disorders, BPD and SCZ are characterized by the presence of incomplete penetrance, non-mendelian inheritance, genetic heterogeneity, and phenocopies, thus making interpretation of linkage reports difficult. Following up a linkage finding with association analysis is recommended as an useful strategy for fine-mapping disease genes and has resulted in positive findings for other complex traits like Alzheimer's disease [Corder et al., 1993], non-insulin-dependent diabetes mellitus [Horikawa et al., 2000], and asthma [Van Eerdewegh et al., 2002]. This systemic approach complements the power of linkage analysis localizing the region of interest with evaluation of association between the disease and a marker at the allelic level.

Although several researchers treat BPD and SCZ as separate syndromes, a review of the epidemiological and molecular genetics research suggests a partial overlap between the two nosologic entities, and a 'continuum hypothesis' was suggested. The proponents of this hypothesis suggest that psychosis is a continuum extending from unipolar, through bipolar affective illness and schizoaffective (SA) psychosis, to typical SCZ [Crow, 1986; Taylor, 1992; Maier et al., 1992; Wildenauer et al., 1999; Valles et al., 2000; Bramon and Sham, 2001; Tsuang et al., 2004]. However, given the complex interactions of the brain network underlying these disorders, the degree of genetic overlap between BPD and SCZ may be difficult to quantify on a linear scale. Changes in one gene with a small contribution to risk of disorder may result in

a dramatic shift in the non-linear dynamics of a complex system, which are unpredictable [Cloninger, 2002]. Thus, it can be assumed that a shared liability with complex rather than additive (continuum) effect may underlie these two disorders.

Further support for shared liability comes from family-based segregation studies and genetic linkage reports. Relatives of patients with BPD or SCZ are at an increased risk of developing similar symptoms, as well as other syndromes like SA [Berrettini, 2003]. Dunayevich and Keck [2000] reported that 50% of BPD patients experience at least one psychotic episode in their lifetime. In a detailed analysis Potash et al. [2001] demonstrated that psychotic symptoms like hallucination and delusion show familial aggregation in bipolar pedigrees. Anti-psychotics (including atypical anti-psychotics like olanzapine) are successful in reducing symptoms of both BPD and SCZ [Tohen et al., 2003].

In view of the above, researchers have scanned the genome for identifying regions harboring putative loci for both BPD and SCZ. Several promising overlapping susceptibility regions (18p11, 13q32, 22q11, 10p14, and 8p22) have been identified [Berrettini, 2003]. Variant analyses of several genes (*IMPA2*, *c18orf1*, *DLGAP1*, *G72*, *G30*) localized to these regions show association with both BPD and SCZ [Yoshikawa et al., 2001; Hattori et al., 2003; Kikuchi et al., 2003; Addington et al., 2004; Sjoholt et al., 2004; Pickard et al., 2005]. It may thus be suggested that analysis of composite phenotypes like psychosis that includes clinical diagnosis of BPD, SCZ, SA, and psychosis not otherwise specified (psychosis NOS) may be a more appropriate phenotype for identification of genes for these complex traits.

Chromosome 18 was one of the first chromosomes reported to harbor genes for mental illness [Richards et al., 1970]. Berrettini et al. [1994], Berrettini [1997] and Detera-Wadleigh et al. [1999], using non-parametric analysis were the first to report a susceptibility locus for BPD on 18p11.2, which has been validated by several investigators [Stine et al., 1995; Nothen et al., 1999; Turecki et al., 1999]. The region is also shown to harbor putative loci for SCZ [Schwab et al., 1998]. A review of linkage and chromosomal aberration studies on chromosome 18 suggests susceptibility loci for BPD and SCZ [McMahon et al., 2001]. Segurado et al. [2003], in a rank-based meta-analysis conducted on all the published genome scans also reported that there exists a nominally significant locus for both narrow definition of BPD (BPI and SA) as well as broad definition of BPD (BPI, BPII, SA, and recurrent unipolar disorder) on chromosome 18.

As an initial step to assess the implicated regions of shared susceptibility between BPD and SCZ, this study presents our investigation with 23 polymorphic STRs on the short and the long arm of chromosome 18 to identify a susceptibility region for psychosis.

MATERIALS AND METHODS

Family Ascertainment

The genotyped sample consisted of 780 individuals collected from 211 families (52 nuclear pedigrees and 159 parent offspring trios). All families were from southern India, identified from the clinical services of the National Institute of Mental Health and Neurosciences (NIMHANS), India. Clinical information was available on a total of 893 individuals of which 489 (54%) could be assigned a lifetime diagnosis. All the remaining family members who either were not ill at the time of interview or could not be assigned a diagnosis due to incomplete information were treated as unknown phenotype for all statistical analysis. The mean age at onset of the affected individuals was 19.66 (years) SD 4.98 (years). Table I provides the profile of the samples used for this study. Clinical information was based on personal interview using standard diagnostic instruments; SCAN-2.1 (Schedule for Clinical Assessment for Neuropsychiatry) [WHO, 1999] and OPCRIT-3.1 (Operational Criteria checklist for psychosis) [McGuffin et al., 1991]. This was supplemented with family history information using FIGS (The Family Interview for Genetic Studies) and all other available medical records to reach the best estimate diagnosis by raters blind to the genotypic information. All diagnosis was in accordance with the ICD-10 criteria. Sample collection was initiated after approval by the Institutional Review Board (IRB). Informed consent was taken from all participating individuals prior to sampling. Clinical information was maintained in the database.

TABLE I. Description of Sample Used for the Linkage and the Association Study

	Linkage	TDT	Total
Number of families	52	159	211
Number of individuals	416	477	893
Number of affected individuals	173	316	489
Number of genotyped samples	303	477	780
Number of affected individuals genotyped	146	316	462
Number of BPAD	121	178	299
Number of SCZ	16	138	154
Number of psychoses NOS	7		
Number of SA	2		

Genotyping

High-molecular weight DNA was isolated from peripheral leukocytes using the modified salting out protocol [Miller et al., 1988]. Fluorescence-based genotyping was performed using 23 dinucleotide repeat markers spanning a region of 126 cM (Table II). The average heterozygosity and the polymorphic information content of the markers was 0.70 and 0.67, respectively. Amplification was done by PCR assay in a total volume of 15 μl using standard protocol. Briefly, genomic DNA was aliquoted into 96-well plate and amplified using the Perkin Elmer thermocycler. Amplified products were resolved on a 4% sequencing gel in ABI 377 platform and alleles scored using the GENESCAN v 2.1 (Perkin Elmer). Allele calling was confirmed by two independent raters blind to clinical information.

Statistical Analysis

Mendelian inconsistencies of genotypes were checked using PEDCHECK [O'Connell and Weeks, 1998]. In case of an inconsistency the PCR was re-performed and the process repeated. Allele frequencies were calculated using RECODE (http://watson.hgen.pitt.edu/register/docs/recode.html). Linkage was estimated using three diagnostic models: BPD (specific phenotype), BPD and SCZ (BPD + SCZ phenotype), and severe psychiatric disease (BPD, SCZ, psychosis NOS, and SA disorder) as the psychoses phenotype. The MLINK program from the LINKAGE [Lathrop and Lalouel, 1984] package was used to compute the two-point LOD score between each of the markers and the disease allele. Due to ambiguity in the mode of inheritance of these diseases, we computed two-point LOD score under both dominant and recessive inheritance models. Multiple genetic models were tested prior to arriving at the model definition which best fitted the pedigrees used on this analysis.

TABLE II. Summary of the Linkage Analysis Performed on the Dataset

Marker	Position from pter (cM)	Het	Highest two-point LOD	Diagnostic model	Genetic model
D18S59	0.0	0.85	−14.8998	Psychoses	Dominant
D18S476	2.34	0.75	−10.25	Psychoses	Dominant
D18S54	8.30	0.65	−0.8592	Psychoses	Dominant
D18S1138	8.30	0.79	−2.42	Psychoses	Dominant
D18S63	8.30	0.83	−3.12	Psychoses	Dominant
D18S1154	8.30	0.82	−5.14	Psychoses	Dominant
D18S452	18.70	0.82	0.43	Psychoses	Dominant
D18S843	28.10	0.62	−0.06246	Psychoses	Dominant
D18S464	31.17	0.71	−0.2752	Psychoses	Dominant
D18S1153	35.46	0.65	−7.282	Psychoses	Dominant
D18S1150	37.15	0.57	−1.242	Psychoses	Dominant
D18S1158	38.92	0.68	−1.42	Psychoses	Dominant
D18S1116	41.24	0.56	−0.14	Psychoses	Dominant
D18S53	41.24	0.67	0.67	Psychoses	Dominant
D18S453	43.49	0.77	1.9	Psychoses	Dominant
D18S37	43.49	0.63	2.02	Psychoses	Dominant
D18S40	43.49	0.65	−0.4	Psychoses	Dominant
D18S71	43.49	0.75	−2.14	Psychoses	Dominant
D18S478	52.86	0.68	−2.42	Psychoses	Dominant
D18S1102	62.84	0.62	−0.317	Psychoses	Dominant
D18S474	71.32	0.74	−0.2752	Psychoses	Dominant
D18S462	120.05	0.74	−5.12	Psychoses	Dominant
D18S70	126.00	0.62	−7.12	Psychoses	Dominant

Dominant model was defined as $P = 0.007$, and genotype-dependent penetrance f = 0.009 (aa), 0.8 (Aa), and 0.9 (AA).

To verify the significance of the linkage results we performed an independent test of association [Spielman et al., 1993] on a set of 159 parent offspring trios. For this analysis, the extended transmission disequilibrium test ETDT [Sham and Curtis, 1995] was used.

RESULTS

Parametric Linkage Analysis

Table II shows the highest two-point LOD score obtained at each of the marker loci. LOD scores were evaluated using the Lander and Kruglyak's criterion for suggestive linkage (LOD = 1.9, chromosome wise). Two microsatellite markers showed evidence of suggestive linkage in this cohort: D18S37 (LOD = 2.02, psychosis phenotype, dominant model) and D18S453 (LOD = 1.9, SCZ + BPD phenotype, dominant model). D18S453 is 0.28 Mb distal to D18S37. We computed the power of these pedigrees to yield suggestive LOD score. The SLINK program of the LINKAGE package was used to perform the simulation studies. The pedigree structure was simulated 1,000 times to estimate the expected LOD score (ELOD) = 2.95. This is close to the observed LOD (2.02), which strengthens our belief that our linkage finding is not a false positive result. Two more markers yielded positive LOD score: D18S452 (LOD = 0.43, SCZ + BPD, dominant model) and D18S53 (LOD = 0.67, psychoses phenotype, dominant model). These two markers are 9.29 and 1.71 Mb distant from the highest LOD score marker, D18S37.

Phenotype specific LOD scores are presented in Figure 1. D18S453 (LOD = 0.77) and D18S37 (LOD = 0.4) yielded positive but not statistically significant LOD score for the BPD phenotype. Including the other psychosis syndromes yielded suggestive LOD score at D18S453 (LOD = 1.9) and D18S37 (LOD = 2.02) for the BPD + SCZ phenotype and the psychoses phenotype, respectively.

Family-Based Association Study

The above result prompted us to investigate loci D18S453 and D18S37, in a family-based association study, based on transmission distortion. This does not require specification of the mode of inheritance at the disease locus and hence is more robust. A preferential transmission of the 168 bp allele at D18S453 from heterozygous parents was observed with the complete parent offspring dataset ($\chi^2 = 4.654$, $P = 0.03$). Analysis was further performed by subdividing triads based on the diagnosis of the affected probands (BPD = 82; SCZ = 77). The details of the family-based association study are provided in

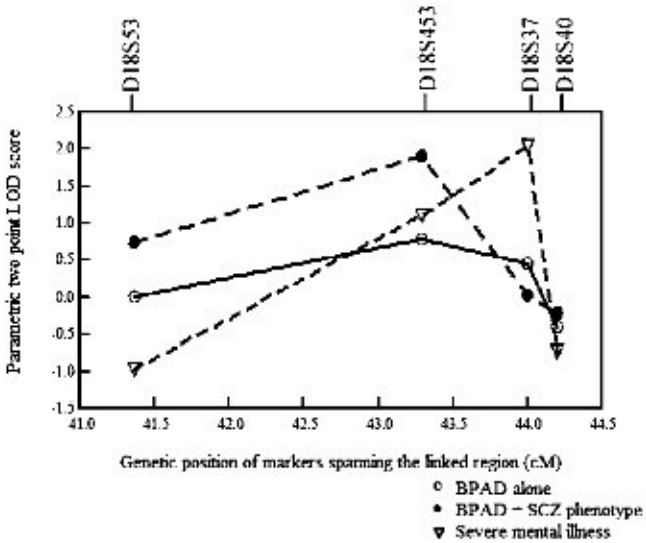

Fig. 1. Genetic position of markers spanning the linked region (cM). ○, BPAD alone; ●, BPAD + SCZ phenotype; ▽, severe mental illness.

TABLE III. Transmission of Alleles at the D18S453 Marker Locus

Allele in bp	Triads complete (n = 159)				BPAD triads (n = 82)				SCZ triads (n = 77)				Triads from linkage families (n = 52)			
	T	NT	$\chi 2$	*P*	T	NT	$\chi 2$	*P*	T	NT	$\chi 2$	*P*	T	NT	$\chi 2$	*P*
166 bp	28	33	0.267	0.6065	11	13	0.167	0.6831	17	20	0.243	0.6219	28	36	1.0	0.3174
168 bp	**64**	**41**	**4.654**	**0.0310**	**34**	**19**	**4.245**	**0.0394**	**30**	**22**	**1.231**	**0.2673**	**40**	**24**	**4.0**	**0.0456**
170 bp	65	68	0.069	0.7932	36	42	0.462	0.4969	29	26	0.164	0.6858	14	22	1.778	0.1825
172 bp	33	31	0.063	0.8026	20	18	0.105	0.7456	13	13	0.0	1.0	6	6	0.0	1.0

Global allele specific *P*-values are 0.094, 0.513, and 0.22 for the complete triads, BPAD triads, and SCZ triads, respectively.

Table III. Positive association with the 168 bp allele at D18S453 was observed in the BPD trios ($\chi^2 = 4.245$, $P = 0.039$). Analysis of the SCZ trios with respect to the same allele and the disease phenotype; however, was not significant ($\chi^2 = 1.231$, $P = 0.267$). The same allele was found to be overtransmitted when the analysis was performed separately on random trios from the 52 linkage families (Table III). Taken together the above result indicates positive association between this allele and the major disease allele. Alleles at D18S37 did not reveal positive association with any of the phenotypes tested. To correct for multiple testing, empirical *P*-values were generated using the ETDT program. The program uses Monte–Carlo simulations to generate random tables having the same total as the observed and calculates chi-square values for each of these tables. From these values, the level of significance of the observed chi-square value is empirically estimated ($\chi^2 = 4.245$, $P = 0.0125$). This value is not significantly different from the observed value suggesting it to be a true value rather than a chance effect.

DISCUSSION

We adopted a parametric search for identifying loci shared by families diagnosed with BPD, SCZ, and related phenotypes.

Meta-analysis of all the published genome scans of BPD and SCZ suggests that there may be multiple loci perhaps attributable to the complex modes of inheritance of both these disorders [Gershon and Badner, 2002]. Overlap between psychotic BPD and SCZ has been proposed at symptom definition, family, genetic, cytoarchitectural, and neuropsychological levels [Potash et al., 2001; Berrettini, 2003; Sklar et al., 2004; Craddock et al., 2005; Ishiguro et al., 2001; Reyes et al., 2002; Faraone et al., 2003; Babovic et al., 2004; Washizuka et al., 2004]. Our result with BPD specific phenotype model gave a maximum LOD score of 0.77 at $\theta = 0.15$ for D18S453. A significant increase in the LOD score (1.9 at $\theta = 0.15$) was observed for the same marker when analysis was performed using the BPD + SCZ phenotype. The psychoses phenotype, which included all severe syndromes, yielded the highest two-point LOD score (2.02 at D18S37, $\theta = 0.15$). This marker is 0.28 Mb distal to D18S453. These results are consistent with several previous findings [Stine et al., 1995; Collins and Go, 1997; Lin and Bale, 1997].

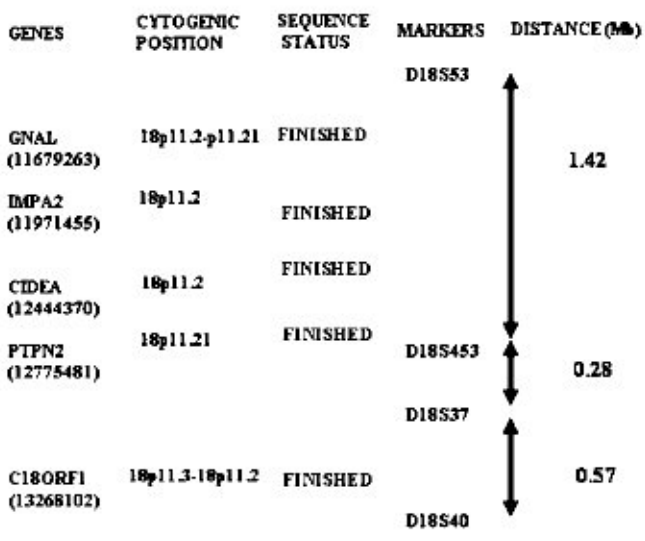

Fig. 2. Location of known genes in the linked genomic region. (NCBI database May 2005).

The TDT analysis with marker D18S453 provided further support of linkage between this marker and the disease locus as well as a positive association between the 168 bp allele of D18S453 and the major disease allele. The association observed with the 168 bp allele is not likely to be influenced by variation in allele frequency across populations, since this is a family-based analysis.

The linkage approach used as well as the TDT analysis involve only affected individuals, and hence statistical problems due to variable age at onset encountered when both affected and unaffected individuals are used, do not arise in our analysis. Additionally, TDT is robust with respect to population stratification, thereby increasing the possibility that our significant TDT result is a true positive association.

The close proximity of the two positive markers observed in this analysis in a previously implicated region, followed by the confirmation using TDT analysis strengthens the linkage findings on chromosome 18, for liability shared by BPD and SCZ.

There may be certain limitations to this study. Like many previous studies on complex traits; we have examined multiple genetic models to arrive at the best model yielding the highest LOD score. It is possible that the LOD score obtained using this approach may be an overestimate of the true value. However, validation of the linkage finding in an independent dataset using family-based association method (corrected for multiple testing) indicates that our linkage finding is not a false positive result.

Equivocal linkage reports for complex traits are attributed to genetic heterogeneity, inadequate knowledge about the mode of inheritance and unknown biological basis underlying these disorders. In spite of these weaknesses, linkage analysis is the preferred mapping approach for the initial localization of putative loci. The two positive markers (D18S453 and D18S37) lie within a very small region of 0.28 Mb harboring several brain-expressed transcripts (Fig. 2). Genetic variation in some of these genes is reported to be associated with disease pathology, encouraging a detailed mapping of the region.

In conclusion, our finding along with other reports on this region, suggests the presence of a locus with moderate effect loci at 18p11.2 shared by BPD and SCZ.

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