SPECIAL ARTICLE

Bipolar disorder and schizophrenia: not so distant relatives?

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Bipolar disorder (BPD) and schizophrenia (SZ) may have some susceptibility genes in common, despite the fact that current nosology separates them into non-overlapping categories. The evidence for shared genetic factors includes epidemiologic characteristics, family studies and overlap in confirmed linkages. Review of these data indicates that there are five genomic regions which may represent shared genetic susceptibility of BPD and SZ. As the genes underlying these confirmed linkages are identified, the current nosology must be changed to reflect the new knowledge concerning the shared etiologies of BPD and SZ.

Key words: Bipolar disorder, schizophrenia, genetics, linkage

Epidemiological, family and molecular genetic linkage studies of bipolar disorder (BPD) and schizophrenia (SZ) will be reviewed. BPD and SZ share multiple epidemiological characteristics, consistent with the hypothesis that the two groups of disorders share some risk factors. Consideration of the family and genetic linkage studies indicates that BPD and SZ share some genetic susceptibility.

EPIDEMIOLOGY OF BIPOLAR DISORDER AND SCHIZOPHRENIA

If narrow diagnostic criteria are employed, lifetime risks for SZ and BPD are estimated at about 1% (1). Recent evidence suggests that broader diagnostic criteria, especially for hypomania, will yield much higher estimates of lifetime risk for BPD (2,3), especially the BPD II subtype, which may be the most common form of BPD. Both syndromes affect men and women equally. Although BPD and SZ are common in young adulthood (onset of illness typically occurs between ages 15-25), these disorders are uncommon in the prepubertal period, and it is unusual for either disorder to arise *de novo* after age 50. Therefore, these groups of disorders have similar age-at-onset distributions. BPD and SZ are lifelong conditions: once diagnostic thresholds for BPD or SZ are met, the disorder persists through life. Spontaneous, lifelong remissions in either type of disorder are uncommon. Increased risk for suicide is another epidemiologic characteristic shared by BPD and SZ.

While acute symptoms and course of illness may distinguish these groups of disorders in more classical cases, there are no pathognomonic signs or symptoms on which the clinician can rely. Treatments for BPD and SZ now show overlap in the case of atypical antipsychotics, which represent the first choice treatment for SZ, as they improve both positive and negative symptoms. Clozapine, the prototype of atypical antipsychotics, may have mood stabilizing properties (4-6). Olanzapine showed efficacy among BPD patients in preventing recurrences of both mania and depression (7). These data suggest that atypical antipsychotics may be mood stabilizers. In addition, atypical antipsychotics may treat depressive symptoms in schizophrenia and reduce risk for suicide, thereby (8). If SZ and BPD share some genetic susceptibility (see below), one might predict that some medications for one group of these disorders might be therapeutic for the other category of illness.

Twin, family and adoption studies of BPD and SZ are consistent with substantial genetic influences; estimates of heritability are about 50% for SZ and about 65% for BPD (for review see 9). With this evidence for heritability, it can be expected that gene mapping techniques will lead to identification of alleles which increase risk for BPD and SZ. However, this process of risk allele identification has been slow and difficult, as with other common complex traits (such as alcoholism, asthma, cardiovascular disease and diabetes). The difficulty is mostly due to the small effect sizes of individual BPD and SZ susceptibility genes and to genetic heterogeneity. Identification, from confirmed linkage regions, of susceptibility genes in non-insulin dependent diabetes mellitus (10) and inflammatory bowel disease (11,12) suggests that identification of disease risk alleles from confirmed linkage regions for complex traits can be accomplished.

SCHIZOPHRENIA AND BIPOLAR DISORDER FAMILY STUDIES

If BPD and SZ share some of the same susceptibility factors, it might be expected that family studies would reveal some overlap in risk for particular diagnostic entities. Among SZ family studies, an increased risk for schizoaffective (SA) and recurrent unipolar (RUP) disorders is found for the first-degree relatives of SZ probands (13-17).

Kendler et al (16) reported increased risk for psychotic affective illness among the relatives of SZ probands.

Increased risks for SA and RUP disorders are found among the first-degree relatives of BPD probands, compared to first-degree relatives of controls (18-20). An important conclusion follows: increased risk for SA disorders and RUP disorders occurs among relatives of BPD or SZ probands. Importantly, there is no increased risk for BPD among first-degree relatives of SZ probands (14,16,21-23), nor is there increased risk for SZ among first-degree relatives of BPD probands (14,18,19,24-28). The family study data are consistent with partial overlap in susceptibility for SZ and BPD, in that relatives of probands with these disorders are at increased risk for SA and RUP disorders.

MOLECULAR STUDIES

If BPD and SZ share some of the same susceptibility factors, it might be expected that molecular linkage studies of BPD and SZ would identify some linkage regions in common. In order to make the process of comparison of BPD and SZ linkage studies less susceptible to false positives, this comparison will be restricted to linkage regions which have been identified at a rigorous statistical level ($P \leq 0.0001$) and confirmed by two or more additional studies ($P < 0.01$). This level of statistical significance is required to limit false positives (29). In the sections which follow, five genomic regions may be implicated in shared genetic susceptibility for BPD and SZ.

SCHIZOPHRENIA AND BIPOLAR DISORDER MOLECULAR LINKAGE STUDIES: 18p11.2

Berrettini et al (30,31) and Detera-Wadleigh et al (32) reported evidence for a BPD susceptibility locus on 18p11 using affected sibling pair (ASP) and affected pedigree member (APM) methods ($P = 10^{-4}$ - 10^{-6}). Independent evidence ($0.01 \leq P \leq 0.0001$) for confirmation of this finding was reported by Stine et al (33), Nothen et al (34), Bennett et al (35) and Turecki et al (36). As part of Genetic Analysis Workshop no.10, independent BPD chromosome 18 linkage data sets, including about 1200 samples, were assembled for meta-analyses (37). An affected sibling pair (N=382 sibling pairs) meta-analysis yielded $p= 2.8 \times 10^{-8}$ at marker D18S37 (38).

In light of the family studies suggesting partial overlap in susceptibility for BPD and SZ (see above), it is of interest to determine whether confirmed BPD loci might overlap with reports of SZ susceptibility loci. Schwab et al (39) employed about twenty chromosome 18 markers in a linkage study of 59 multiplex German and Israeli SZ pedigrees, in which there were 24 affective disorder cases (two had BPD). When these data were analyzed by two-point parametric methods, using a broad affection status model (including affective disorders), the maximum LOD score was 3.1 at D18S53. A multipoint non-parametric analysis revealed P = 0.002 at D18S53. Evidence for SZ linkage disequilibrium at an 18p11.2 microsatellite was also noted (39). The data of Schwab et al (39) were most positive when a broad affection status model was employed, including SZ, SA disorders, RUP disorders and BPD.

This is the only SZ linkage report to identify the 18p11 genomic region. However, most SZ linkage reports do not include affective disorders in the affection status model. Thus, there may not be comparable methods in most SZ linkage studies. Given the results of Schwab et al (39), it is reasonable to consider the 18p11.2 region as one of potential susceptibility to both BPD and SZ.

A promising 18p11.2 candidate gene is an inositol monophosphatase gene (IMPA2), whose protein is an enzyme of the phosphoinositol triphosphate second messenger signaling cascade (40). Single nucleotide polymorphisms (SNPs) in IMPA2 were associated with SZ in a Japanese sample (40).

SCHIZOPHRENIA AND BIPOLAR DISORDER MOLECULAR LINKAGE STUDIES: 13q32

One genomic region of potential overlap in genetic susceptibility for SZ and BPD is 13q32. Lin et al (38) observed a LOD score of 2.58 (P = about 0.001) at 13q32 markers (D13S122 and D13S128) in a linkage study of SZ. In a genome scan of 54 SZ families, Blouin et al (41) reported a P value of 0.00002 (LOD = 3.6) at the 13q32 marker D13S174. Subsequently Brzustowicz et al (42) confirmed these reports in 21 Canadian SZ families, with a maximal LOD score of 3.92 at the 13q marker D13S793. Thus, there are several independent reports, with substantial statistical significance, consistent with a 13q32 SZ susceptibility locus.

Detera-Wadleigh et al (32) described linkage (P = 0.00003) to 13q32 markers (D13S1271 and D13S779) in 22 BP kindreds of European ancestry. One may be concerned that these kindreds were misclassified. However, they reveal evidence for linkage to 18p11.2 and 21q21 (32), which are confirmed BPD susceptibility loci. Kelsoe et al (43) reported linkage of BPD to 13q32 markers, with LOD = 2.4 at D13S154. Thus, in the 13q32 region, a confirmed SZ susceptibility locus, there are statistically impressive reports of linkage in BPD.

A promising candidate gene in this region is G72 (44), a gene of uncertain function. The G72 protein interacts with D-amino acid decarboxylase. SNPs in the G72 gene are associated with SZ (44) and BPD (45).

SCHIZOPHRENIA AND BIPOLAR DISORDER MOLECULAR LINKAGE STUDIES: 22q11

The velocardiofacial syndrome (VCFS) presents in childhood with variable clinical manifestations, including cardiac anomalies, typical facies, learning disabilities and, in about 30% of cases, psychosis. The form of the psy-

chosis is affective according to some authorities (46,47), although others describe it as schizophrenia-like (48). The VCFS is caused by microdeletions in 22q11. Although the exact boundaries of the critical region remain uncertain, most deletions are about 3 Mb in size. Stemming from an initial report by Pulver et al (49), a substantial multicenter effort to confirm a SZ susceptibility locus in this region resulted in evidence for linkage, at D22S278 (50).

Lachman et al (51) first reported evidence for BPD linkage in the VCFS region. Subsequent weakly positive reports include those by Detera-Wadleigh et al (32) and Edenberg et al (52). Kelsoe et al (43) report a LOD score of 3.8 at D22S278, while, at this same microsatellite locus, Mujaheed et al (53) reported evidence for linkage disequilibrium in BPD Arab Palestinian kindreds. Thus, this 22q11 region may be a locus for susceptibility to SZ and BPD.

Several promising candidate 22q11 genes have been described as explanations for the 22q11 linkage results in BPD and SZ. Proline dehydrogenase (PRODH2) variants are in linkage disequilibrium with SZ in some populations (54). A second candidate is a G-protein coupled receptor kinase (GRK3), whose gene is markedly upregulated in rat brain during chronic amphetamine exposure (55). A third promising candidate is catechol-O-methyltransferase (COMT), which has been associated with cognitive difficulties in SZ (56) and with SZ diagnosis (57).

SCHIZOPHRENIA AND BIPOLAR DISORDER MOLECULAR LINKAGE STUDIES: 8p22

There have been several reports of SZ susceptibility mapped to 8p22-24. In 54 extended SZ kindreds, Blouin et al (41) reported evidence for a SZ locus at 8p22: the heterogeneity LOD score was 4.5, and non-parametric analysis yielded P = 0.0001. Brzustowicz et al (42), in 21 extended Canadian SZ pedigrees with 8p markers, reported a maximum multipoint LOD score of 2.1 at D8S136. Levinson et al (58), in a multicenter collaborative effort, reported independent results (that did not include the pedigrees of Blouin et al [41]), yielding P = 0.00018 in this same region of 8p22. Gurling et al (59), in a study of 13 extended European SZ kindreds, reported a LOD of 3.6 for 8p22 markers. Thus, these reports constitute a confirmed SZ linkage.

Recently, Stefansson et al (60) described evidence from both mouse and human studies that neuregulin 1 (NRG1) is an 8p susceptibility gene for SZ. They found linkage disequilibrium with NRG1 haplotypes in Icelandic individuals with SZ. This has been confirmed in a Scottish SZ sample (61).

Recently Ophoff et al (62) described a linkage disequilibrium signal at 8p22 in distantly related BPD persons from a population isolate in the Central Valley of Costa Rica. Greater than expected sharing of a 5 cM three marker haplotype at D8S503 was observed. The significance level reported was 0.000057. Thus there is a statistically impressive report of BPD susceptibility mapped to this region.

SCHIZOPHRENIA AND BIPOLAR DISORDER MOLECULAR LINKAGE STUDIES: 10p14

A fifth region of potential BPD/SZ susceptibility is found at 10p14. Faraone et al (63), Straub et al (64) and Schwab et al (65) reported evidence for linkage of SZ to 10p14 markers. Faraone et al (63) reported P = 0.0004 for marker D10S1423 and P = 0.0006 for D10S582, in a study of 43 American SZ kindreds of European ancestry. Straub et al (64), in a study of Irish SZ kindreds, reported P = 0.006 for this region in a multipoint analysis. For marker D10S582, Schwab et al (65) reported P = 0.0058 for German SZ kindreds. These three groups of investigators studied independent sets of kindreds which were of general European ancestry.

Foroud et al (66) studied BP kindreds from the National Institute of Mental Health (NIMH) Genetics Initiative. They found LOD = 2.5 (P = 0.001) for marker D10S1423. Thus, the 10p14 region may represent another genomic region at which there is shared susceptibility for BPD and SZ.

META-ANALYSES

Badner and Gershon (67) analyzed complete genome scans for BPD and SZ. There were 11 BPD genome scans (about 1250 affected) and 18 SZ genome scans (about 1900 affected). The most promising regions of the genome for BPD were 13q32 and 22q11, while the most promising SZ regions were 8p24, 13q32 and 22q11. All of these regions have been implicated in shared BPD/SZ susceptibility, as noted above.

A rank-sum type of meta-analysis (68) was applied to SZ linkage data by Levinson et al (69). They concluded that 8p and 22q were among the most promising regions for SZ.

CONCLUSION

Family and linkage studies are consistent with the concept that SZ and BPD share some genetic susceptibility. Multiple regions of the genome, including 18p11, 13q32, 22q11, 10p14 and 8p22, represent areas with potential BPD/SZ shared genetic susceptibility. As susceptibility genes in these regions are identified, through the application of linkage disequilibrium mapping methods to large sample sizes, it will be necessary to develop a new, genetically-based nosology, in which this overlap is accurately represented.

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