Schizophrenia Bulletin vol. 32 no. 1 pp. 9–16, 2006
doi:10.1093/schbul/sbj033
Advance Access publication on November 30, 2005

Genes for Schizophrenia and Bipolar Disorder? Implications for Psychiatric Nosology

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It has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent Emil Kraepelin's traditional dichotomous classification of the so-called "functional" psychoses and form the basis of modern diagnostic practice. However, findings emerging from many fields of psychiatric research do not fit well with this model. In particular, the pattern of findings emerging from genetic studies shows increasing evidence for an overlap in genetic susceptibility *across* the traditional classification categories—including association findings at *DAOA(G72)*, *DTNBP1 (dysbindin)*, *COMT, BDNF, DISC1*, and *NRG1*. The emerging evidence suggests the possibility of relatively specific relationships between genotype and psychopathology. For example, *DISC1* and *NRG1* may confer susceptibility to a form of illness with mixed features of schizophrenia and mania. The elucidation of genotype-phenotype relationships is at an early stage, but current findings highlight the need to consider alternative approaches to classification and conceptualization for psychiatric research rather than continuing to rely heavily on the traditional Kraepelinian dichotomy. As psychosis susceptibility genes are identified and characterized over the next few years, this will have a major impact on our understanding of disease pathophysiology and will lead to changes in classification and the clinical practice of psychiatry.

Key words: schizophrenia/bipolar disorder/psychosis/nosology/diagnosis/classification/genetics

Background

It has been conventional for psychiatric research, including the search for predisposing genes, to proceed under the assumption that schizophrenia and bipolar disorder are separate disease entities with different underlying etiologies. These represent Emil Kraepelin's traditional dichotomous classification of the so-called "functional" psychoses[1,2] and form the basis of modern diagnostic practice as defined operationally in DSMIV[3] and ICD10.[4] However, there has been a long tradition of dissent against the validity of this view,[5–7] and the veracity and utility of the so-called Kraepelinian dichotomy have been increasingly challenged by emerging data from many fields of psychiatric research.[8–10] The most convincing challenges have come in recent years from genetic studies. These findings are of great potential for informing our understanding of nosology as well as delineating the biological mechanisms that contribute to the pathogenesis of the psychoses.

In this article we will first briefly review the key pieces of genetic evidence that support the existence of a genetic relationship between bipolar disorder and schizophrenia. We will then consider the current data for genes that have, to date, been implicated in both disorders. We will end by considering the implications.

Genetic Evidence Supporting Non-Independence of Schizophrenia and Bipolar Disorder

Most current genetic studies of schizophrenia and bipolar disorder have been based on the assumption of independence, with individual studies typically focusing on only one or the other disorder. Cases with a mix of mood and psychotic features, while common, have been ignored or subsumed into some broader category of either schizophrenia or bipolar disorder. Although there is a substantial body of family, twin, and adoption data that has been interpreted to support the dichotomous view,[11,12] some earlier studies and several more recent studies are inconsistent with this view, as are the data emerging from molecular genetic investigations. Although it is beyond the scope of this article to review the data in detail, key pieces of evidence include the following.

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Table 1. Summary of current weight of available evidence supporting several of the more promising genes implicated in the pathogenesis of categorically defined schizophrenia, bipolar disorder, and mixed bipolar-psychosis phenotypes*

Gene/Locus	Chromosomal Location	Evidence in Schizophrenia	Evidence in Cases with Mixed Bipolar-Psychosis Features	Evidence in Bipolar Disorder
Dysbindin	6p22	+ + + + +	+	
Neuregulin 1	8p12	+ + + +	+	+
DISC 1	1q42	+ + +	++	+
COMT	22q11	+		+
DAOA(G72)/G30	13q33	+ +		+ +
BDNF	11p13	+		+ +

*More + symbols indicate greater evidence. The scale is relative. Note that very few studies have been undertaken explicitly using cases with mixed phenotype (although many ''schizophrenia'' and bipolar disorder'' samples will include a substantial proportion of cases with a mix of mood and psychotic features). Note that the limitations of the current approach of examining diagnostic categories makes it difficult to determine whether overlaps represent a non-specific contribution to susceptibility across traditional categories or a relatively specific contribution to susceptibility to one or more domains of the phenotype (such as depression or paranoid ideation).

Family Studies

Although many family studies have demonstrated that schizophrenia and bipolar disorder tend to ''breed true,''[13–15] families are known in which there are multiple cases of schizophrenia, bipolar disorder, and cases in which both psychosis and mood disorder occur.[16] Further, some studies have shown statistically significant evidence that bipolar disorder occurs at increased rates in relatives of probands with schizophrenia,[17] and that schizophrenia occurs at increased frequency in relatives of probands with bipolar disorder.[18] Moreover, schizoaffective disorder has been shown to occur at increased rates both in families of probands with schizophrenia[19] and in those of probands with bipolar disorder,[20] and both schizophrenia and bipolar disorder have been shown to occur at increased rates in families of probands with schizoaffective disorder.[20]

Twin Studies

Only one twin study has used an analysis that was unconstrained by the diagnostic hierarchy inherent in current classification systems (i.e., the principle that schizophrenia ''trumps'' mood disorder in diagnosis). This study demonstrated a clear overlap in genetic susceptibility to syndromically defined mania and schizophrenia.[21] In addition to supporting the existence of some susceptibility genes that are specific to schizophrenia and others that are specific to bipolar disorder, it suggested that there are others that influence susceptibility to schizoaffective disorder, schizophrenia, and bipolar disorder. A graphic illustration of the varied expression of the same set of susceptibility genes is provided by the Maudsley triplets—a set of genetically identical triplets, two of whom had a lifetime diagnosis of schizophrenia and the third a lifetime diagnosis of bipolar disorder.[22]

Linkage Studies

Genetic linkage studies have identified some chromosome regions that show convergent or overlapping regions of interest in both schizophrenia and bipolar disorder—including regions of 13q, 22q, 6q, and 18.[23,24] There are, however, difficulties in interpreting overlaps in linkage findings from different phenotypes because of the poor localization of linkage signals for complex disorders and difficulties assessing statistical evidence for significant co-occurrence. However, the hypothesis that loci exist that influence susceptibility across the schizophrenia-bipolar divide receives further support from the observation that a genome scan using families selected on the basis of a member with DSMIV schizoaffective disorder, bipolar type, demonstrated genome-wide significance at 1q42 and suggestive linkage at 22q11, with linkage evidence being contributed equally by ''schizophrenia'' families (i.e., where other members had predominantly schizophrenia) and ''bipolar families'' (i.e., where other members had predominantly bipolar disorder).[25]

Studies of Individual Genes

Linkage studies can only provide at best indirect evidence for shared genetic effects. More direct evidence has come from reports implicating variation in the same genes as influencing susceptibility to both schizophrenia and bipolar disorder (see Table 1). In most cases the gene was first implicated in studies of schizophrenia, and the evidence in most cases is strongest for this phenotype. This could reflect the true contribution to the phenotype or may simply reflect the fact that substantially greater resources and samples have been used to date on studies of schizophrenia. We will consider the evidence for each gene in turn.

NRG1

NRG1 was first implicated in schizophrenia in the Icelandic population after a systematic study of 8p21-22 revealed association between schizophrenia and a multi-marker haplotype at the 5′ end of *NRG1*.[26] Strong evidence for association with the same haplotype was subsequently found in a large sample from Scotland,[27] with considerably weaker support in our own UK sample.[28] These and subsequent studies of *NRG1* in schizophrenia have been reviewed recently in *Schizophrenia Bulletin*.[29] Overall, there is strong evidence from several studies that genetic variation in *NRG1* confers risk to schizophrenia, but as yet, and in spite of extensive re-sequencing, specific susceptibility and protective variants have not been identified. *NRG1* has not yet been extensively studied in bipolar disorder. However, the one study published to date found significant evidence for association of the core Icelandic risk haplotype with susceptibility to bipolar disorder with a similar effect size to that seen by the same group in schizophrenia.[30] In the bipolar cases with predominantly mood-incongruent psychotic features, the effect was greater, as was the case in the subset of schizophrenia cases (n = 27) who had experienced mania. These findings should be treated with caution pending replication, but they suggest that *NRG1* plays a role in influencing susceptibility to both bipolar disorder and schizophrenia, and that it may exert a specific effect in the subset of functional psychosis that has manic and mood-incongruent psychotic features.

Dysbindin (*DTNBP1*)

Evidence implicating dystrobrevin binding protein 1 (*DTNBP1*), also known as dysbindin, in schizophrenia was first reported by Straub et al.,[31] and there is now quite impressive support from a number of studies reviewed recently in *Schizophrenia Bulletin*.[32] However, once again various markers and haplotypes have been associated, and the actual susceptibility variants have yet to be identified. Only one published study has so far examined SNPs from dysbindin in bipolar disorder. Raybould and colleagues[33] found no significant associations in bipolar disorder as a whole but found modestly significant evidence for association in the subset of bipolar cases with predominantly psychotic episodes of mood disturbance with a similar pattern of findings to that seen by this group in schizophrenia. This finding suggests that variation in dysbindin confers risk to psychosis rather than to mood disorders *per se*, although replication is required. Recent work in the Irish Study of High-Density Schizophrenia Families has shown that schizophrenic patients with negative symptoms were more likely to inherit the dysbindin risk haplotype,[34] raising the possibility that negative symptoms might also define the subgroup of psychotic bipolars that are particularly likely to carry the dysbindin risk haplotype.

G72(DAOA)/G30

This locus was first implicated in studies of schizophrenia by Chumakov and colleagues,[35] who undertook association mapping in the linkage region on chromosome 13q22-34. They found associations in French Canadian and Russian populations in markers around two novel genes, *G72* and *G30*, which are overlapping but transcribed in opposite directions. *G72* is a primate-specific gene expressed in the caudate and amygdala. Using yeast two-hybrid analysis, evidence for *physical* interaction was found between *G72* and D-amino-acid oxidase (*DAO*). *DAO* is expressed in the human brain, where it oxidizes D-serine, a potent activator of NMDA glutamate receptor. Co-incubation of *G72* and *DAO in vitro* revealed a *functional* interaction with *G72* enhancing the activity of *DAO*. Consequently, *G72* has now been named D-amino-acid oxidase activator (*DAOA*).

Associations between *DAOA* and schizophrenia have subsequently been reported in samples from Germany,[36] China,[37] Ashkenazi Jews,[38] and both the United States and South Africa,[39] as well as a small sample of very early onset psychosis subjects from the United States.[40] There is no consensus concerning the specific risk alleles or haplotypes across studies.

Currently this is the best-supported locus for bipolar disorder. At least five independent datasets contribute evidence that variation at the *DAOA*/*G30* locus on chromosome 13q influences susceptibility to bipolar disorder, including three US family samples,[41,42] a German case-control sample,[36] and a large UK case-control sample.[43] In all studies, evidence for association came from both individual SNPs as well as multilocus haplotypes, although there is variation between studies in the associated SNPs and haplotypes. No pathologically relevant variant has yet been identified, and the biological mechanism remains to be elucidated. The largest study to date was of 2831 individuals, of whom 709 had DSMIV schizophrenia, 706 had bipolar-I disorder, and 1416 were ethnically matched controls.[43] The authors identified significant association with bipolar disorder but failed to find association with schizophrenia. Analyses across the traditional diagnostic categories revealed significant evidence for association in the subset of cases (n = 818) in which episodes of major mood disorder had occurred. A similar pattern of association was observed in both bipolar cases and schizophrenia cases in which individuals had experienced major mood disorder. In contrast, there was no evidence for association in the subset of cases (n = 1153) in which psychotic features occurred. This finding requires replication, but the data as they stand suggest that, despite being originally reported as a schizophrenia susceptibility locus, variation in

DAOA/G30 does not primarily increase susceptibility for prototypical schizophrenia or psychosis. Instead, it appears that variation in *DAOA/G30* influences susceptibility to episodes of mood disorder across the traditional bipolar and schizophrenia categories. Importantly, these findings also imply that whether or not significant associations are seen in schizophrenia will depend upon the proportion of cases that have suffered from episodes of mood disorder, and remind us of the importance of sample differences in the replicability of genetic association studies.

Disrupted in Schizophrenia 1 (*DISC1*)

This gene was implicated through studies of an extended pedigree in which a balanced chromosomal translocation (1;11)(q42;q14.3) showed strong evidence for linkage to a fairly broad phenotype comprising schizophrenia, bipolar disorder, and recurrent depression.[44] The translocation was found to disrupt two genes on chromosome 1: *DISC1* and *DISC2*.[44,45] *DISC2* contains no open reading frame and may regulate *DISC1* expression via anti-sense RNA.[45] A small pedigree has recently been reported in which a 4bp deletion in exon 12 of *DISC1* cosegregates with schizophrenia and schizoaffective disorder.[46] Interestingly, *DISC 1* and *2* are located close to the chromosome 1 markers implicated in two Finnish linkage studies of schizophrenia.[47,48] The Edinburgh group that identified *DISC1* found no linkage evidence in their own schizophrenia sample but did find suggestive evidence for linkage in bipolar disorder.[49] More recently, Hamshere and colleagues reported genome-wide significant evidence for linkage at this locus in a linkage study of schizoaffective disorder, bipolar type.[50] *DISC1* is certainly an interesting candidate gene for mental disorder, but it is important to remember that translocations exert effects on genes other than those directly disrupted. For example, there are several mechanisms by which a translocation can influence the expression of neighboring genes. In order to unequivocally implicate *DISC1* and/or *2* in the pathogenesis of schizophrenia, it is necessary to identify mutations or polymorphisms that are associated with schizophrenia in non-deleted cases, and are not in linkage disequilibrium with neighboring genes. Negative studies were initially reported by the Edinburgh group with a small number of markers,[51] and by a group that focused on the 5' end of the gene in a large Japanese sample.[52] More recently, several groups have reported positive findings,[53–56] although in no case are the results compelling, and there is little agreement as to the specific markers or haplotypes showing association. Interestingly, in three of these studies, associations were observed with bipolar disorder as well as schizophrenia,[53–55] and in one, the strongest association was observed with schizoaffective disorder.[54]

While no consistent pattern of association has yet emerged and no pathogenically relevant variants have been established, the convergence of the linkage data are strongly suggestive that variation in *DISC1* or another gene in this region influences susceptibility to mood-psychosis phenotypes that cut across the traditional Kraepelinian divide.

COMT

COMT lies in the chromosome 22q11 region implicated in schizophrenia, bipolar disorder, and schizoaffective disorder bipolar type by linkage studies[23,28,50,57,58] and by its deletion in Velo-cardio-facial syndrome, in which adult sufferers frequently develop affective and psychotic disorders. *COMT* has been intensively studied because of its key role in dopamine catabolism. Most studies have focused upon a valine to methionine change at codon 158 of the brain-predominant membrane-bound form of *COMT* (*MB-COMT*) and codon 108 of the soluble form (*S-COMT*). The valine allele confers higher activity and thermal stability to both forms of *COMT*[59] and has been fairly consistently associated with reduced performance in tests of frontal lobe function.[60,61] The results in schizophrenia have been mixed, with recent meta-analyses[62–64] reporting no overall evidence for association with the valine allele. Some studies have found stronger evidence for association between haplotypes at *COMT* than for the Val/Met locus alone,[59,65–67] although a recent study found no evidence for association in a study of more than 2800 individuals, including almost 1200 schizophrenics.[68] Moreover, it is difficult to reconcile the stronger evidence for association with haplotypes at *COMT* with the observation that *COMT* activity, at least in peripheral tissues,[69] is largely dictated by the Val/Met locus, a finding that may also be true in the brain.[59] The evidence does not support a simple role for Val/Met 158 in susceptibility to schizophrenia, although a small effect on susceptibility cannot be excluded, nor can a role in phenotype modification. It also remains possible that variation elsewhere in *COMT*, or in a neighboring gene such as *ARVCF*[66,70] confers susceptibility.

COMT has been studied less in bipolar disorder, although some evidence for association at the Val/Met polymorphism was found in one meta-analysis[71] and modest haplotypic evidence in one Israeli study.[72] It is extremely likely that genetic variation in this *region* influences susceptibility across the psychosis spectrum, although it is not yet clear that *COMT* itself is the only (or the major) susceptibility gene at this locus. If it is, the mechanism is complex and the phenotype not yet adequately defined.

Brain Derived Neurotrophic Factor (BDNF)

A functional candidate gene that has attracted a great deal of recent interest in mood disorder is Brain Derived Neurotrophic Factor (*BDNF*).[73] *BDNF* plays

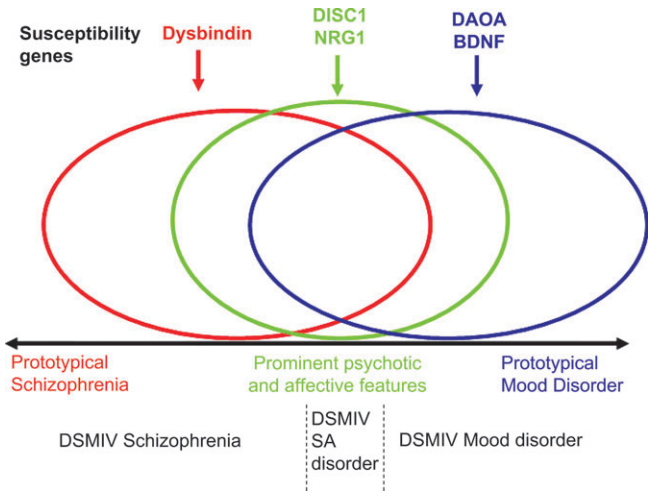

Fig. 1. Simplified hypothesized relationship between specific susceptibility genes (above the black line) and clinical phenotype (below the line) using the model outlined in Craddock and Owen[8] The overlapping ellipses represent overlapping sets of genes: red influencing susceptibility to phenotypes with prominent schizophrenia-like features, blue to prominent mood features, and green to phenotypes with a prominent mix of both types of feature. These assignments are based on current data and are likely to require revision as more data accumulate.

an important role in promoting and modifying growth, development, and survival of neuronal populations and, in the mature nervous system, is involved in activity-dependent neuronal plasticity,[74] processes that are prominent in the synaptic plasticity hypothesis of mood disorder, which focuses on the functional and structural changes induced by stress and antidepressants at the synaptic level. The *BDNF* gene lies on chromosome 11p13 and encodes a precursor peptide (pro*BDNF*), which is cleaved proteolytically to form the mature protein.[75] The 11p13 chromosomal location of *BDNF* has been implicated in some linkage studies of bipolar disorder but not in meta-analyses of linkage studies. Only one frequent, non-conservative polymorphism in the human *BDNF* gene has been identified, a single nucleotide polymorphism (SNP) at nucleotide 196 within the 5′ pro-*BDNF* sequence that causes an amino acid substitution of valine to methionine at codon 66 (Val66Met) and may have a functionally relevant effect by modifying the processing and trafficking of *BDNF*.[76]

There have been three positive reports using family-based association studies of Caucasian bipolar disorder samples of European-American origin and the Val66Met SNP: two are in adult bipolar samples,[77,78] and one is with a small childhood onset sample.[79] All have shown over-transmission of the common Val allele. Evidence with multilocus haplotypes was stronger in one study.[78] There have been four case-control association studies (of European,[80,81] Chinese,[82] and Japanese origin[83]) to date, in which there is no evidence for an allelic or genotypic association. In our own UK case-control study of over 1000 bipolar cases, we found no significant evidence for association of the Val allele (or multilocus haplotypes) with bipolar disorder but some evidence for association within the subset of cases in which rapid cycling of mood had occurred at some during illness.[84] This finding has been replicated in a re-analysis of one of the original family samples showing evidence for association.[85] *BDNF* has attracted less interest in schizophrenia, although there has been a positive report of association at Val66Met and a 2 locus haplotype including this polymorphism.[86] Of substantial interest is the recent finding of association with depression in schizophrenia as well as in unipolar disorder.[87] Such a finding has some consistency with the rapid cycling finding in bipolar disorder because depression is a prominent feature of such cases.

Substantial additional genetic and biological work will be required to confirm (or refute) the role of *BDNF* in influencing susceptibility to mood and psychotic illness. Systematic study of variation across the whole gene is required with study in further independent samples.

Conclusions

Current genetic findings are beginning to provide suggestive evidence that, as implied by the family and twin data, there are genetic loci that contribute susceptibility across the Kraepelinian divide to schizophrenia, bipolar disorder, and schizoaffective disorders (see Table 1). This work is in its early stages, and the findings should be treated with caution, especially given that for none of the genes implicated have specific risk variants been identified. Indeed, it may turn out that some, or all, of the genes discussed contain multiple risk (and protective) variants with effects on different aspects of psychopathology. However, the simplest interpretation of the current published data is that variation in *DISC1/2* and *NRG1* appears to predispose to both prototypical Kraepelinian illnesses, but there is suggestive evidence that the effects of both genes might be felt most strongly in disorders with features of both schizophrenia and bipolar disorder. Variation in *DTNBP1* predominantly predisposes to schizophrenia and possibly a form of illness characterized by prominent negative symptoms, with an effect on bipolar disorder confined to those cases with prominent psychotic features. In contrast, *DAOA/G30* and *BDNF* appear to be most strongly associated with mood disorder, and the extent to which associations with schizophrenia are seen is likely to depend upon the proportion of cases that have experienced mood disorder syndromes.

These findings have important implications for classification of the major psychiatric disorders because they suggest an overlap in the biological basis of disorders that have, over the last 100 years, been classified as distinct entities.[8] Thus, we can expect that over the

coming years molecular genetics will catalyze a reappraisal of psychiatric nosology as well as providing a path to understanding the pathophysiology that will facilitate development of improved treatments. For example, current genetic findings suggest that rather than classifying psychosis as a dichotomy, a more useful formulation may be to conceptualize alternative categories or a spectrum of clinical phenotypes with susceptibility conferred by overlapping sets of genes[8] (see Figure 1). It is important that researchers are willing to embrace and explore such alternative approaches to the clinical phenotype in order to interpret the accumulating data. This will be an iterative process with identified genetic signals allowing refinement of the phenotype and the refined phenotype allowing increased power to detect further genetic signals. To facilitate this approach, it will be important to use large samples that have a full representation of phenotypes across the mood-psychosis spectrum, and detailed, high-quality phenotypic assessments, preferably including dimensional measures[88,89]. Already it is possible to recognize some common biological features among the genes implicated by current studies, and tentative models have been advanced that postulate the key role of synaptic function.[90]

In conclusion, accumulating evidence supports the existence of an overlap in genetic susceptibility across the traditional Kraepelinian divide with studies of several genes providing the most compelling such evidence. This work is at an early stage but has the potential to change our conception of psychiatric nosology as well as our understanding of the pathogenesis of psychopathology.

Acknowledgments

The authors' work on the genetics of psychosis and mood disorders is funded through grants from the Wellcome Trust and the MRC. We are indebted to all the participants in our studies.

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