

Approaches for Unraveling the Joint Genetic Determinants of Schizophrenia and Bipolar Disorder

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Since Emil Kraepelin proposed in 1919 that dementia praecox (schizophrenia) be differentiated from manic depression (bipolar disorder), the concept of nosological dichotomy has greatly influenced the diagnosis, treatment, and research of pathogenesis of these 2 disorders. However, this concept has recently been challenged by increasing evidence showing biological overlap between schizophrenia and bipolar disorder. This article reviews some of the previous evidence for phenomenological and molecular overlaps between these 2 disorders. We then discuss approaches for examining shared etiological mechanisms with a concentration on genetic factors. We have put a particular emphasis on incorporating the concept of endophenotypes in research of shared genetic liability for these 2 disorders.

Key words: schizophrenia/bipolar disorder/genes/endophenotype

Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are regarded as separate disease entities according to most diagnostic classification schemes, including the DSM-IV (*The Diagnostic and Statistical Manual of Mental Disorders-IV*)¹ and ICD-10 (*International Statistical Classification of Diseases and Related Health Problems-10*),² despite their overlap in symptoms such as psychosis. The concept of SZ and BP as distinct entities stems from the work of Emil Kraepelin approximately 100 years ago.³ However, the distinction between these 2 disorders has received renewed consideration since the 1980s in light of a growing appreciation that SZ and BP may share some common determinants, or, at the very

least, share some common psychopathological elements.⁴ As a consequence, the “Kraepelin dichotomy” concept has been challenged.⁵ In this review, we first summarize the phenomenal and biological evidence supporting an overlap between SZ and BP and then describe some of the epidemiologic and genetic approaches used for establishing a shared liability between these 2 disorders.

Phenomenological and Biologic Evidence Supporting an Overlap Between SZ and BP

Phenomenological Overlap

The most marked clinical feature shared by patients with SZ and BP is psychosis. Psychotic symptoms, such as delusions, sensory hallucinations, disorders of forms of the thought, and grossly disorganized or catatonic behavior, are major components in clinical characteristics of SZ. Additionally, some schizophrenic patients also present negative symptoms, including anhedonia (loss of interest or pleasure in daily activities) and avolition (lack of desire, or motivation to pursue meaningful goals). The conventional diagnostic criteria for BP are established based upon mood disturbances, ie, mania and depression. According to DSM-IV criteria, BP can be classified into bipolar I disorder (BP-I), bipolar II disorder (BP-II), and bipolar disorder not otherwise specified (BP-NOS). BP-I is characterized by at least one manic episode (ie, elevated, expansive, or notably irritable mood lasting for at least 1 week) during the lifetime, while BP-II manifests with one or more major depressive episodes accompanied by at least one hypomanic episode (ie, milder symptoms of mood elation and irritability). BP-NOS is a variant of BP different from BP-I and BP-II in that BP-NOS is characterized by mood elation with rapid mood swings, recurrent hypomanic episodes without episodes of depression between them, delusions, and other psychotic symptoms. For individuals diagnosed with BP, their manic episodes may be dominated by psychotic symptoms. Previous studies have estimated that at least 50% of BP individuals have experienced at least one psychotic episode during their lifetime.^{6,7} Additionally, mood components may also be shared by individuals afflicted by SZ and BP.

Individuals affected by SZ may also present affective disturbances that mimic depression and mania.

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Schizophrenic patients may exhibit reduced emotional responses or experience overly active and exultant feelings. A study reported that the lifetime prevalence of depressive mood (lasting for at least 2 weeks) at first admission for schizophrenia is 83%; additionally, during the first psychotic episode 71% of schizophrenic patients presented clinically relevant depressive symptoms, and 23% were diagnosed with a depressive episode.⁸ In addition, anhedonia, one of negative symptoms inherent to schizophrenia, is also a symptom in depression. Romney and Candido examined clinical symptoms in schizophrenia and major depressive disorder using factor analysis and found that anhedonia pertains to the domain of depression.⁹ Hence, differential diagnosis between SZ and BP (particularly BP-II and BP-NOS) is required for individuals exhibiting negative symptoms such as anhedonia. Such overlap in symptoms has provided the first line of evidence for shared etiological components in SZ and BP.

Biological Overlap

Pharmaceutical treatments may reflect the pathological mechanism of a disease. A few same classes of pharmaceutical treatments are arguably considered to treat the 2 disorders. The mechanisms of actions of these treatments may shed some insights into the molecular basis for these 2 disorders. Atypical antipsychotics that target both the dopamine 2 (D2) and serotonin 5-HT_{2A} receptors can be used to treat SZ. Recently, anti-psychotic agents have been increasingly prescribed to BP patients. The effects of these pharmaceutical compounds on SZ and BP suggest that dopaminergic and serotonergic pathways are both involved in the pathogenesis of SZ and BP.¹⁰ It is of note that these anti-psychotics may have varying affinities for these receptors. The efficacy of these different anti-psychotics may also vary by diagnosis. Possibly, the pathogenesis of these 2 disorders may be influenced by heterogeneous mechanisms underlying dopaminergic and serotonergic pathways.

The most compelling line of support for a common biological pathogenesis shared by SZ and BP is provided by genetic studies suggesting that some of the same genes influence risk for both disorders. For example, one study has recently reported altered expressions of oligodendroglia-related genes in multiple brain regions to be associated with both SZ and BP.¹¹ Linkage studies have provided another line of support. In genome-wide linkage analyses of these disorders, at least 5 distinct genomic regions have been implicated as being linked to susceptibility for both SZ and BP (reviewed in Berrettini¹²). Among the chromosomal regions identified as possibly harboring putative risk genes for both SZ and BP are 4p,¹³ 6q, 18p, 13q, and 22q.^{14,15} Candidate gene-based association studies have also implicated several risk genes that may contribute to susceptibility to both SZ and BP. Among these implicated genes that may influ-

ence susceptibility to both disorders are dysbindin (*DTNBP1*), *G72 (DAOA)*, disrupted in schizophrenia (*DISC1*), catechol-O-methyl transferase (*COMT*), and brain-derived neurotrophic factor (*BDNF*), and others, as reviewed elsewhere.^{16,17} These findings have provided potentially useful leads for efforts to disentangle the shared liability for SZ and BP. In the next section, we describe some of the epidemiological and statistical approaches for such efforts.

Craddock et al.¹⁸ postulated a formulation to conceptualize a spectrum of clinical phenotypes associated with SZ, schizoaffective disorder, and mood disorders. In this putative spectrum of symptoms, psychotic symptoms, mixed psychotic-affective features, and mood symptoms (particularly mania) are modulated by 3 clusters of susceptibility genes; these 3 clusters of genes are partially overlapped with each other. Owen et al.¹⁷ pointed out that these 3 subsets of genes are represented by the *DTNBP1*, *DISC1*, and *DAOA* genes, respectively. Based on this model, one may infer that different genes may influence the risk of SZ or BP to the different extents.

Approaches to Studying the Shared Genetic Liability Between SZ and BP

Despite the overlapping phenomenological and biological features shared by SZ and BP, the epidemiologic and statistical evidence supporting a shared liability is uneven. Many of the efforts targeted towards identifying a common etiology between these 2 disorders have focused on identifying common genetic factors. Indeed, there is some evidence that these 2 disorders co-aggregate in the same families. While some studies have identified specific risk alleles potentially influencing joint susceptibility to SZ and BP (eg, see above), these associations have not been consistently replicated in multiple studies so that the specific genes influencing susceptibility of both SZ and BP remain largely unknown.

Familial Co-aggregation of SZ and BP

A common pathological mechanism for 2 diseases may be reflected by comorbidity in the same individual. However, the current hierarchical diagnostic systems for psychiatric diseases do not allow dual diagnoses for SZ and BP in the same individual (with BP-NOS as an exception) and thus pose a challenge for assessing shared etiology for SZ and BP at the individual level. As an alternative, familial co-aggregation, which reflects excessive occurrence of 2 disorders within the same family, can provide evidence for common genetic pathways for SZ and BP. Familial co-aggregation and co-segregation differ in that the former indicates that the clustering of 2 diseases within families, which does not necessarily result in the occurrence of 2 diseases in the same individual; the latter can lead to the occurrence of 2 diseases in the same

individual. One common approach for testing for the presence of familial co-aggregation is to determine if the risk for one disease (eg, SZ) is elevated in relatives of an individual affected with a second disease (eg, BP). “Excess” familial risk can be assessed either by contrasting disease prevalence (eg, of SZ) in relatives of case (eg, BP) probands with disease prevalence in either the relatives of control probands or with overall population prevalence rates. In fact, evidence for familial co-segregation of SZ and BP has been provided by Valles et al.¹⁹, who reported that first-degree relatives of BP patients had a 4-fold higher risk of SZ compared with relatives of healthy individuals. In familial co-segregation studies, various statistical approaches can be used for the comparisons to take into account such issues as the ages of the family members, other disease risk factors, and the correlations in measurements due to the family members being related to each other (eg, see Hudson et al.²⁰). One caveat of co-aggregation studies is that they may provide spurious evidence for familial co-aggregation if the 2 diseases being studied are easily misdiagnosed or can be confused with each other due to resemblances of clinical features of these 2 disorders.

The clustering of a disease within families alone does not permit one to distinguish between the effects of genetic factors and environmental factors in the etiological pathway of disease because relatives who share genes in common are also more likely to share similar lifestyles and/or environmental risk factors. In the same way, the presence of familial co-aggregation of 2 diseases within the same family alone cannot distinguish between the role of shared genetic factors and environmental factors in a shared etiological pathway. One conventional approach used to clarify the relative impact of genetic variants versus environmental factors on a single disorder is to parse out the variance in trait susceptibility to that attributable to genes and that attributable to nongenetic (or environmental) risk factors using statistical approaches akin to analysis of variance. In such approaches, the variation in the trait due to genetic factors is modeled as a function of trait similarity among related individuals, and the heritability of the trait is defined as the proportion of the total trait variance due to genetic effects.

The standard variance decomposition procedures can be extended for the joint study of 2 diseases to tease apart genetic and environmental influences of 2 disorders using a bivariate extension of the variance component approach. This method partitions the joint variation in the 2 traits into their trait-specific genetic components, trait-specific environmental components, shared genetic effects, and shared environmental effects. The shared genetic effects represent effectively the “co-heritability” of the 2 traits. One can use bivariate variance component method to study the genetic relationship between 2 continuous traits. One application of this approach is described

by Mitchell et al.²¹, who reported strong genetic correlations between serum concentrations of insulin and body mass index and between insulin and plasma levels of high-density lipoprotein-cholesterol, suggesting that one or more genes influences joint variation in these sets of traits. This bivariate analysis method has been extended for analysis of binary phenotypes using variance component models or generalized linear mixed models.^{22–24}

The analysis of twin studies represents a subtype of family analysis that can be used to differentiate between genetic and environmental contributions to familial aggregation. In principle, one can evaluate whether genes play an important role in susceptibility to disease by comparing disease prevalence in the monozygotic (MZ) twin siblings of affected probands to disease prevalence in the dizygotic (DZ) twin siblings of affected probands. Higher disease prevalence in the MZ twin pairs is generally interpreted to indicate a genetic basis for disease if one assumes that environmental risk factors are shared equally among DZ twin pairs as among MZ twin pairs (an assumption that can be challenged in some situations). By extending the framework of twin studies from one disorder to 2 disorders, one can further test whether the MZ twin siblings of SZ probands have higher risk of BP compared with DZ twin siblings of SZ probands (or vice versa) to provide insights into the relative impact of genes on familial co-aggregation of these 2 disorders. Cardno and colleagues examined genetic correlations between SZ, schizoaffective disorder, and BP in 77 monozygotic and 89 same-sex dizygotic twin pairs using relaxed diagnostic criteria. They found evidence for both common and syndrome-specific genetic contributions to the variance in liability to SZ and manic syndromes, but the genetic liability to the schizoaffective syndrome was entirely shared in common with the other 2 syndromes. In contrast, environmental liability to the schizoaffective syndrome was not shared with the other syndromes.²⁵

Identifying the Shared Risk Genes

Conventional approaches used to identify risk alleles for single disorders include linkage and association studies. Linkage analysis is based on using recombination frequencies to infer physical distance between a genetic marker and target risk locus, while association studies directly measure the correlation between the genetic polymorphism at a locus and the disease endpoint. Association analyses are more powerful to detect causal variants, provided there is linkage disequilibrium (ie, correlation between a paired of genetic loci) between the genetic marker and disease loci; however, linkage analyses are more powerful in the absence of such disequilibrium.²⁶ Excellent reviews of both approaches have been published elsewhere.^{27–29}

The introduction of high-throughput, low-cost genotyping technologies has recently generated great

enthusiasm in the field of complex disease genetics by making possible the conduct of large-scale genetic association studies that use 500,000 or more single nucleotide polymorphisms (SNPs) scattered throughout the genome. Such studies have rapidly gained popularity and complement traditional candidate gene studies that are based on measurement and analysis of only a single SNP or set of SNPs within a single gene. Identification of disease susceptibility genes using the genome-wide association approach has proven remarkably successful, with novel genes already reported for complex traits such as cardiovascular diseases^{30,31} and diabetes³²⁻³⁴. These studies have employed either single- or multistage designs to generate evidence for association in an initial original sample and have then replicated these associations in other populations. An important lesson learned from the GWAS scans of diabetes and cardiovascular disease is that the associations detected have tended to be in novel genes rather than in previously studied candidate genes.

It is possible that approaches such as genome-wide association analysis may identify single SNPs that will turn out to be associated with both SZ and BP or may even reveal different SNPs in the same gene to be associated with each disorder. Other studies have explored the genetic underpinnings for disorders characterized by a mix of mood and psychotic features, such as schizoaffective disorder.¹⁶ The pathological processes in schizoaffective disorder are thought to be correlated with those in SZ and BP, although some investigators have questioned the validity of the independent diagnostic entity of schizoaffective disorder.³⁵ It thus remains to be seen whether susceptibility genes for schizoaffective disorder will turn out to be, at least in part, involved in the shared genetic liability of SZ and BP.

Common Endophenotypes for SZ and BP

According to Gottesman and Gould,³⁶ endophenotypes are neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological components associated with the target disorder. From a genetic perspective, endophenotypes can be very attractive targets for study if they are easily and reliably measured, co-aggregate with the target disorder within families, and are also present in unaffected relatives. A desirable endophenotype is also one that is more proximal to a causative gene than the end-stage disease state and thus may be more amenable to genetic study than the downstream disease.

Many candidate endophenotypes in SZ and BP are neurophysiological markers. Other endophenotypes that should be explored extensively include drug response and metabolism, RNA expression, and protein levels.³⁷ Studies of other neurocognitive functions related to information processing also reveal the biological resem-

blances of SZ and BP. For instance, impaired performance in span of apprehension has been shown in both SZ and BP.³⁸ Other abnormalities in information processing associated with these 2 disorders include P300-evoked response latency³⁹ and amplitude,⁴⁰ P50 auditory-evoked response suppression,^{41,42} prepulse inhibition,⁴³ facial scanpath patterns,⁴⁴ and a mismatch negativity paradigm.⁴⁵ Additionally, other cognitive function impairments, such as executive deficits, can be demonstrated in psychotic and bipolar disorder.⁴⁶ These biomarkers related to neurocognitive functions may hence serve as common endophenotypes upstream to pathological pathways to SZ and BP.

If an endophenotype is influenced more directly by genetic factors, one may expect to observe a higher heritability of an endophenotype compared with its end-point disease (although a high heritability may not necessarily result from a smaller number of genes involved in the pathological mechanism). Take smooth pursuit eye movement (SPEM) as an example. SPEM refers to the movement of the eyes as they track a slowly moving target, a process that is initiated by visual processing of motion signals (ie, extraretinal motion). One of the major SPEM submeasurements, predictive pursuit gain, is highly heritable (heritability estimate = 0.90),⁴⁷ indicating that this trait is under substantial genetic control. Additionally, both schizophrenic patients and their unaffected relatives are more likely than healthy individuals to have deficits in SPEM, suggesting that this trait co-segregates with SZ and that deficits in SPEM are not secondary sequelae occurring as a result of SZ. Moreover, individuals affected with BP and their relatives are also more likely to have deficits in SPEM compared with healthy individuals.⁴⁸ Genetic analysis of SPEM-related phenotypes has provided further insights into shared genetic influences that might cut across different psychiatric diagnoses, including SZ and BP. For example, 2 studies have reported evidence for linkage of SPEM phenotype to 6p23-21, suggesting that this chromosomal region may harbor one or more genes influencing variation in SPEM.^{49,50} Interestingly, the same region also harbors 2 genes previously associated with risk of schizophrenia, *ATXN1* (*SCA1*) and *NOTCH4*.⁵¹ Other candidate genes associated with SPEM include dopamine D3 receptor gene (*DRD3*),⁵² *DISC1*,⁵³ and *COMT*.⁵⁴ All these genes have also been hypothesized to play a role in the pathogenesis of SZ and BP.¹⁶ Taken together, these findings suggest that the study of common endophenotypes for SZ and BP, such as SPEM, may reveal insights into alleged etiologic factors linking these 2 disorders.

Studying common endophenotypes may circumvent the limitation of hierarchical diagnostic system posed on SZ and BP. Meanwhile, the conceptualization of endophenotypes does not contradict the putative hierarchical pathological relationship between SZ and BP. Furthermore, endophenotypes can allow the investigator

to examine the genotype-phenotype relationship in the same population. Conventional studies focusing on SZ and BP in different populations separately may produce findings that cannot be transferred to each other. Therefore, deciphering the genetics of common endophenotypes may serve as an alternative and effective approach to untangling the mechanism of shared genetic liability for these 2 disorders.

The success of endophenotype-based approaches hinges on the assumption that endophenotypes are modulated by less complex genetic factors than the disease syndrome itself. Hence, the identification of genetic variants that yield a larger effect on endophenotypes than the end-point disease will benefit from such an approach. Goldman et al.⁵⁵ discovered a number of loci with a greater impact on endophenotypes compared with related psychiatric disorders, such as BP and alcoholism. However, one recent study compared the effects of genetic variants on several endophenotypes and end-point diseases using the meta-analysis technique and did not produce supportive evidence for this assumption. The investigators examined 7 different endophenotypes, such as “circadian rhythm” and prefrontal cognitive function, etc., as the endophenotypes for BP, and “spatial and verbal working memory” and “ventricular enlargement,” etc., as endophenotypes for SZ. Their findings suggest that genetic contributions of the COMT gene Val/Met polymorphism to endophenotypes were not significantly different from those effects on SZ or BP.⁵⁶ Therefore, one needs to carefully evaluate the locus-specific genetic effect size of the endophenotype in order to unravel the joint genetic determinants for SZ and BP.

Alternatively, investigators can use an endophenotype to select a more clinically homogeneous subgroup of subjects for genetic studies. SZ and BP characterized by a shared endophenotypic feature may be regarded as subtypes of SZ and BP, respectively. Such an endophenotype-based approach may not only overcome the problem of genetic heterogeneity in each individual disorder but also enhance clinical resemblances for these 2 disorders and hence help identify the shared genetic variant of a possibly larger effect. This approach may allow investigators to avoid the concern that an endophenotype is not modulated by less complex genetic factors than those associated with the risk of SZ or BP.

Conclusions

To summarize, the conventional nosological distinction between SZ and BP has been challenged by research showing a phenomenological and biological overlap of these 2 disorders. Genetic research suggesting that common genes may be involved in both SZ and BP has lent additional support for the presence of shared etiological pathways between these 2 disorders, although specific genes associated with SZ and BP jointly have yet to be

identified. Just as the long-standing “Kraepelin dichotomy” has become subject to reevaluation, the diagnostic systems for other disorders centered on psychotic symptoms, such as schizoaffective disorder, may also need to be reexamined.

The hierarchical diagnostic system for SZ and BP precludes the usual approaches for assessing their being associated with each other because the 2 diagnoses usually cannot be assigned to the same individual. However, assessment of familial co-aggregation may provide very useful insights into whether these 2 disorders share common etiologies. Although previous evidence has suggested a number of susceptibility genes shared by SZ and BP, most of these studies have focused on one disorder at a time in independent populations. Alternatively, mapping genes for schizoaffective disorder, which shares symptoms related to both SZ and BP, may help unravel shared genetic mechanisms for these 2 disorders. Finally, identifying the genes modulating common endophenotypes, such as SPEM, provided that they are influenced more directly by genetic factors, may unveil the shared genetic pathways for SZ and BP.

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