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Comparing Genes and Phenomenology in the Major Psychoses: Schizophrenia and Bipolar 1 Disorder

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Classifying Psychotic Disorders

For the last several decades, diagnosis in psychiatry has been rule based, related to phenomenology and standardized. It has given psychiatry an unearned advantage in communicating about its illnesses, unearned because the molecular basis for this standardization has remained elusive. However, it has provided a language for successful communication about psychiatric syndromes and supported practical functions for which categorization is helpful; functions as disparate as insurance reimbursement and drug development have been enabled with this language. Moreover, this standardization has had additional practical advantages beyond communication and labeling, specifically in terms of public familiarity.

Further, these standardized categories have been postulated without any real knowledge about the biological nature of the underlying brain disturbances or their mechanisms. Imagine categorizing diabetes by phenomenology before 1922 or infectious disease before the microscope and antibiotics. It is hard to intuit how one might successfully use nonspecific illness descriptors of phenomenology to sort affected individuals into homogeneous enough categories to discover molecular disease mechanisms, whether the diseases involve disorders of the pancreas, heart, or brain.

In psychiatry, despite the practical importance of the *Diagnostic and Statistical Manual of Mental Disorder* (*DSM*) nomenclature, the diagnostic system remains a hypothesis of disease categories, awaiting a refinement of categorization based on mechanisms and molecules. Not that we should be persuaded to discard this current system, until another one, more biologically based, is in place. But, because this current system may not provide the final correct illness categories, it may be time to experiment with other systems, within research indications. In this context, scientists and clinicians alike have developed an informed skepticism, whose goal is to promote mechanism-oriented research into the major psychoses with the goal of defining the mechanistic basis of the brain diseases with cognitive and affective expression.

There is consistent evidence that genes contribute to the etiology of psychosis. Recent findings from genetic studies provide evidence for an overlap in genetic susceptibility across the traditional psychosis categories. Candidate genes show strong associations with component symptom complexes, such as psychosis, that are not projected directly onto Kraepelinian disease entities. Genetic studies suggest that psychosis may be conceptualized as a clinical phenotype with specific genetic etiologies. Hypothetically genes or sets of genes, interacting with environmental factors, may predetermine vulnerability to psychosis. Depending on additional syndrome-specific genetic influence and environmental interactions, psychosis may coexist with other clinical phenotypes, eg, mood symptoms or cognitive dysfunction, composing categorical diagnoses. This conceptualization of psychosis is well illustrated by epidemiological and molecular genetic studies. In this chapter, we will review the phenomenology and genetics of psychosis, across different diagnoses. Other aspects of the psychosis overlap will be presented in other articles in this volume.

The Bipolar Disorder-Schizophrenia Distinction

Kraepelin divided insanity into a bipolar type and a schizophrenia type in the 1890s, distinguished by symptom profile and by overall outcome. Since that time, clinical scientists have discussed whether this is a useful division or a false dichotomy. Whether this categorization conforms to a biological distinction between these 2 syndromes likely to be molecularly based, remains a question. Formulating answers to this question highlights the current controversy of whether it more advantageous to utilize traditional diagnostic categories or to pursue dimensional constructs. To advance this controversy, we explore here the dimension of "psychosis" from a practical point of view, as a representative dimensional

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construct, using phenomenologic and genetic data as they address this question. Other perspectives are presented elsewhere in this issue.

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (*DSM-IV*), distinguishes between schizophrenia and psychotic mood disorders, mainly based upon psychosis being the core-defining feature of the schizophrenia diagnosis, whereas in mood disorders it is considered a secondary clinical phenomenon. In fact, there is no *DSM-IV* diagnostic category for psychotic bipolar disorder, although psychosis is included as a specifier for severe mood episodes. While in the current diagnostic system psychosis in mood disorders is treated as a secondary feature, recent research has suggested that there is a subpopulation of patients with bipolar disorder, in which psychosis appears to be a consistent syndrome which may have a genetic basis.[1]

Therefore, a dimensional approach to categorization has emerged, driven by clinical observations and research need. It has been recently directed toward facilitating novel drug development in schizophrenia for symptoms domains without treatments, specifically for cognition. It is applicable more broadly for research in pathophysiology and etiology. The idea is clinically based and practical, taking "component symptom complexes" and targeting these for evaluation, disease hypotheses, and drug development.[2] Component symptom complexes (or clinical domains) are groups of symptoms which associate in an illness and appear to have a common pharmacology, neural basis, and putative pathophysiology. Purportedly, eg, the symptom construct psychosis could be supported by a common disease mechanism across different psychiatric diagnoses, a concept which is important for clinical prediction, mechanistic research, and drug development. We will discuss the similarities and distinctions in phenomenology across the 2 psychotic illnesses, schizophrenia and psychotic bipolar 1 disorder (BD-1) as illustrative of developing this formulation further.

The Phenomenology of Psychosis as a Component Symptom Complex

Psychosis receives a range of definitions in the *DSM-IV*. The narrowest definition is restricted to "delusions and prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature." In a less restrictive formulation, it includes "prominent hallucinations that the individual realizes are hallucinatory experiences." This definition uses insight into the phenomenon to distinguish the symptoms. Another broader psychosis definition also includes "other positive symptoms of schizophrenia (ie, disorganized thought process, grossly disorganized or catatonic behavior)." Finally, the most generalized, conceptual definition of psychosis is "a loss of ego boundaries or a gross impairment of reality testing."

Schizophrenic psychosis is distinguished more by its course than by the nature of the psychotic symptoms. Usually the course of psychosis is chronic with either continuous or episodic psychotic symptoms, mostly without full interepisode recovery. Although courses of schizophrenia with a good prognosis are described in *DSM-IV* (eg, a single episode with partial or full remission), they are uncommon. In contrast, the course of psychosis in other psychotic illnesses can be fleeting, with relatively short episodes of hallucinations and delusions manifest at the peak of severe depression or mania, decompensated medical conditions, or episode of illicit substance use. Over the full course of schizophrenia, psychotic symptoms tend to become less severe with time, whereas cognitive function worsens and negative symptoms become more apparent. A further deterioration in the patient's baseline functioning can follow each relapse of schizophrenia psychosis. This failure to return to baseline functioning after each relapse is commonly taken as the major distinction between schizophrenia and psychotic mood disorders. However, recent studies report that 20%–25% of patients with affective illnesses show considerable long-term impairment in daily functioning.[3–5] Without treatment, psychosis in schizophrenia is incapacitating and contributes, along with negative symptoms and cognitive dysfunction, to an overall poor prognosis.

Comparative studies across diagnoses, contrasting predictions of clinical course based on dimensional composites compared with traditional diagnostic categories, have shown that the use of component symptom complexes have an advantage; moreover, demand for psychiatric care, treatment outcome, social adaptation, and global prognosis for the illness seem also to be facilitated by dimensional categorization.[6,7] Recently, the use of component symptom complexes has been applied in research, as well as clinical, paradigms to inform genetic and intermediate phenotype studies, and as novel symptom targets for drug development. Dimensional composites of schizophrenia are, at least partially, pharmacologically independent and may have independent etiologies and mechanisms. Psychotic symptoms are satisfactorily treated with first- and second-generation antipsychotic drugs; however, no effective treatments exist either for cognitive deficits or for negative symptoms.[8] Clinical experience and research data show that psychosis in different diagnostic categories shows a similar pharmacological response to antipsychotic drug treatment, including psychosis in schizophrenia, bipolar disorder, depression, substance-induced psychoses, and organic psychoses.[9] One of the current goals of drug development for schizophrenia is treatment for cognitive dysfunction, with hypothetical treatment targets focused on glutamatergic, cholinergic, and serotoninergic neurotransmitter systems.[8–16]

The course of schizophrenia varies across individuals but is generally described as starting with premorbid signs and symptoms followed by a prodromal phase of

illness, as the illness evolves. However, in practice, it is not always possible to distinguish these 2 periods precisely; several reasons account for this failure, including the presence of schizophrenia spectrum personality disorders, traits, or the presence of minor psychotic symptoms appearing long before the onset of the diagnosis. In the typical, although not invariable premorbid picture of schizophrenia, affected probands have schizoid or schizotypal personality features and are characterized as quiet, introverted, emotionally aloof, and seclusive. They prefer solitary activities, seem content by themselves, and are unattached to family members. When schizotypal features are predominant, thinking, perception, and behavior may be odd. Various psychotic-like symptoms, such as magical thinking, peculiar beliefs, ideas of reference, perceptual illusions, odd fantasies, and derealization-depersonalization symptoms, are commonly present. Especially during the adolescent period, they may have poor communication skills and distorted social judgment. This often leads to feelings of isolation, ''not fitting in,'' and withdrawal from social interactions. Although different types of personalities (including paranoid, avoidant, obsessive-compulsive, and borderline) are also seen in the premorbid period in individuals with schizophrenia, schizoid and schizotypal personality traits are the most common. Still, the presence of these symptoms does not inevitably develop into schizophrenia.

The presence of prodromal symptoms for BD-1 with psychosis is unclear. Although clinical observations suggest that symptoms like mood lability, impulsivity, destructibility, and physical hyperactivity are often present long before the development of affective psychosis, the phenomenology of the BD prodrome is not well characterized. A recent study suggested that there are unique prodromal characteristics distinguishing psychotic and nonpsychotic mania. This study was conducted with early onset BD-1 individuals.[17] Specifically, attenuated late psychotic symptoms during the prodrome accompanied by increased energy and goal-directed activity were more common in individuals with eventual psychotic mania. The phenomenology of prodromal symptoms in schizophrenia and affective psychosis revealed considerable overlap, including such symptoms as suspiciousness, hallucinatory experiences, anxiety, and insomnia. On the other hand, depressed mood, suicidality, mood lability, difficulty communicating clearly, lack of energy, obsessions, and physical agitation were more prevalent in the mania prodrome.[17]

At present, the prodromal syndrome is a hypothetical construct; its actual existence can only be confirmed after the diagnosis of schizophrenia or BD-1 has been made. During the prodromal phase, patients characteristically lack insight about their developing symptoms, although some individuals experience a sense of change. In clinical situations, information about the prodrome is developed from the history of events proximal to illness onset; often this information is more reliable from relatives than from the patient. In the area of research, studies are focused on large samples of individuals who are at increased risk for developing schizophrenia (eg, offspring of ill parents or members of high density families, especially, those with mild psychotic symptoms). These populations are being studied for the rate of conversion of these individuals to a diagnosis of schizophrenia (approximately 30%–35%) and predictive factors for illness onset.[18,19]

Family studies of schizophrenia and affective psychoses show that psychosis aggregates in families.[1,20–23] Having a relative with schizophrenia or bipolar disorder is a single most powerful risk factor for developing psychosis. A familial liability to psychosis is not disorder specific, in that many pedigrees show familial aggregation of various functional psychoses, including schizophrenia, schizoaffective disorder, psychotic bipolar and major depressive disorder, substance-induced psychoses, delusional disorder, and other psychoses.[24–26] Certain clinical phenotypes or psychopathological dimensions seem to predict familial risk of psychosis across the *DSM-IV* categorical diagnoses.[27–29] Overall, studies suggest that familial liability for psychosis crosses *DSM-IV* categories of schizophrenia and mood disorders. From a dimensional perspective, psychosis may represent a shared phenotype with unique genetic etiologies, running through family generations.

Psychosis Genetics

Family Studies

Family studies of schizophrenia and affective psychoses show that psychosis aggregates in families.[1,20–23] The lifetime risk for developing schizophrenia increases approximately 8- to 12-folds in first-degree biological relatives of schizophrenic probands. Although the results of genetic studies in affective psychoses are less consistent, the familial aggregation of bipolar disorder and major depressive disorder has been observed. First-degree relatives of individuals with BD-1 have elevated rates of BD-1 (4%–24%), bipolar II disorder (1%–5%), and major depressive disorder (4%–24%). A familial liability to psychosis is not disorder specific, in that many pedigrees show familial aggregation of various functional psychoses, including schizophrenia, schizoaffective disorder, psychotic bipolar and major depressive disorder, substance-induced psychoses, delusional disorder, and other psychoses. Although there are a few studies that note coaggregation of bipolar disorder and schizophrenia in families of bipolar disorder or schizophrenia probands,[24,25] the vast majority of studies carried out in large epidemiological samples show that the familial risks for schizophrenia and bipolar disorders are mostly independent of each other.[30,31] On the other hand, bipolar disorder has been associated with increased risk of schizophrenia in relatives. In one family study in Spain, it was reported

that relatives of women with early onset of bipolar disorder had the highest morbid risks for both bipolar illness and schizophrenia.[26] In this study, the presence of more than one patient with bipolar disorder in a family increased the risk for schizophrenia nearly 4-fold. In a different study, it was shown that affective disorders are more frequently inherited from the same parental side of the family as schizophrenia psychosis,[25] consistent with the hypothesis that in some cases the same genes could contribute to susceptibility to both schizophrenia and affective psychoses. Schizoaffective disorder occurs at similarly increased rates both in families of probands with schizophrenia and bipolar disorder. Both schizophrenia and bipolar disorder have been shown to occur at increased rates in relatives of probands with schizoaffective disorder.[32]

Certain clinical phenotypes or psychopathological dimensions seem to predict familial risk of psychosis across the *DSM-IV* categorical diagnoses.[27–29] Consistently between the studies, presence of negative symptoms and insidious early onset of illness in probands are predictive of schizophrenia in their first-degree relatives, whereas familial morbid risk of affective psychosis is specifically predicted by history of mania in probands.[28,29] The syndrome characterized by bizarre behavior, inappropriate affect, catatonia, and poor rapport was reported to be predictive of psychosis independent of *DSM-IV* categories in biological relatives of psychotic probands.[29] Overall, studies suggest that familial liability for psychosis crosses *DSM-IV* categories of schizophrenia and mood disorders. From a dimensional perspective, psychosis may represent a shared phenotype with unique genetic etiologies, running through family generations.

Twin Studies

Twin studies show that the concordance rate for schizophrenia is higher in monozygotic twins (47%–56%) than in dizygotic twins (12%–16%), suggesting a strong heritability component for the illness. Some studies reported the concordance rates for monozygotic twins over 80% in cases of severe schizophrenia with typical core symptoms.[33] Further, twin studies suggest that a schizophrenia diagnosis in one twin increases risk for both schizophrenia and affective psychosis in the cotwin.[34,35] An overlap in genetic risk for schizophrenia, schizoaffective, and manic syndrome is also suggested by a report, based on the Maudsley twin series: the maximum monozygotic/dizygotic concordance ratio was produced by a combination of schizophrenia, affective disorder with mood-incongruent psychotic features, schizotypal personality disorder, and atypical psychosis.

Genetic Linkage Studies

In the past decade, numerous genetic studies have implicated chromosomal loci and candidate risk genes associated with schizophrenia.[36–38] Several large meta-analyses have found strong evidence of numerous genetic linkages of which 6p24-22, 1q21-22, and 13q32-43 are the best supported.[38,39] Highly suggestive linkages have been identified in 8p21-22, 6p22, 6q21-25, 22q11-12, 5q21-33, 10p15-11, and 1q42.[36,38–41] Genome-wide scans of bipolar disorder have produced inconsistent evidence for specific linkage, despite interesting leads in earlier studies (eg, chromosomes 2,[42] 11,[43] 18,[44] and "X."[45] Several meta-analyses of bipolar disorder data sets indicated no significant linkages by a priori criteria, but the most promising linkages were to 18q22, 21q21, 4p16, and 12q24[40,41] and 13q and 22q.[46]

Recent large meta-analyses of linkage studies based on the clinical phenotype have identified several loci that overlap between schizophrenia and bipolar disorder including 1q32, 10p11-15, 13q32, 18p11.2, and 22q11-13.[36,40,46–48] Interestingly, Park et al [49] identified several putative loci associated with psychosis in bipolar disorders pedigrees (with significant linkage to 9q31 and 8p21 and suggestive linkage to 5q33, 6q21, 8p12, 8q24, 13q32, 15q26, 17p12, 18q21, and 20q13). This study supports that psychosis is a potentially useful phenotype informative for future exploring of schizophrenia- and bipolar disorder–shared genetics markers. A recent genome-wide linkage scan in schizoaffective disorder confirmed the existence of loci that influence susceptibility across the functional psychosis spectrum.[50] This study demonstrated genome-wide significant linkage at chromosome 1q42 and suggestive linkages at 22q11 and 19p13. Noteworthy, 2 candidate genes, *Disrupted in Schizophrenia* 1 *(DISC1)* and *catechol-O-methyltransferase (COMT)*, which have been consistently implicated in schizophrenia and, more recently, in bipolar disorder, map to 1q42 and 22q11, respectively.

Studies of Individual Genes

Association studies have identified several putative candidate genes involved in etiology of schizophrenia. Some of these risk genes include *DISC1* on 1q42,[51–53] *COMT* on 22q11,[54–56] *dystrobrevin-binding protein 1 (dysbindin)* on 6p22.3,[57–62] *neuregulin 1 (NRG1)* on 8p12,[63–67] *d-amino acid oxidase activator (G72)/G30) (DAOA (G72)/G30)* on 13q33,[64,68–70] brain-derived neurotrophic factor (BDNF),[71–73] and *regulator of G protein signaling (RGS4)* on 1q23,[74–77] although the reports vary considerably. Recent functional candidate gene studies have specified that several candidate genes for schizophrenia may also be associated with bipolar disorder, including *DAOA (G72)/G30,*[69,78–80] *BDNF,*[48,81,82] *DISC1,*[83] *and NRG1.*[84] Of these, association with *G72* may be most robust; however, *G72* haplotypes and polymorphisms associated with bipolar disorder are not consistent. In the recent comprehensive review in genetics of bipolar disorder,[85] additional associations between bipolar disorder

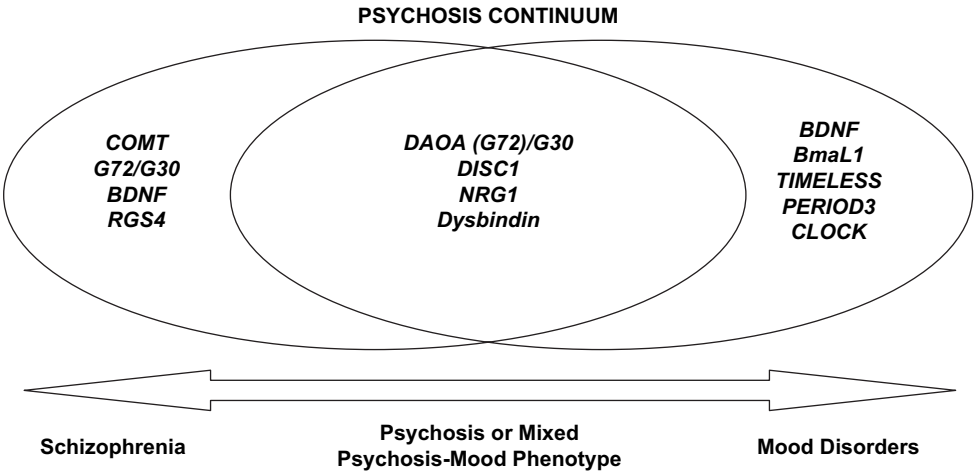

Fig. 1. Candidate Genes in Schizophrenia—Bipolar Disorder Boundary.

and *TRPM2* (21q22.3),[86] *GPR50* (Xq28),[87] *Citron* (12q24),[88] *CHMP1.5* (18p11.2),[89] *GCHI* (14q22-24),[90] *MLC1* (22q13),[91] *GABRA5* (15q11-q13),[92] *BCR* (22q11),[93] *CUX2, FLJ32356* (12q23-q24),[94] and *NAPG* (18p11)[95] have been suggested, although future replicating studies are warranted. From gene expression analysis, *PDLIM5, somatostatin, and the mtDNA 3243* mutation were found to be related to bipolar disorder.[85] Additionally, recent reports have suggested *BmaL1,*[96,97] *TIMELESS*,[96] *PERIOD3*,[97] and *CLOCK*[98–101] as candidate loci associated with the circadian rhythm phenotype in bipolar disorder, although not all reports are consistent.[97,102,103]

Several recent reports on candidate genes implicate variation at the same loci influencing susceptibility to both schizophrenia and bipolar disorder[104]; most notably these are association findings at *DAOA (G72)/G30,*[64,68–70,74,78,79] *DISC1,*[51–53,83,105] *NRG1,*[66,84] *and dysbindin*[106] (figure 1). For instance, a recent study found the association of *NRG1* with a clinical phenotype of bipolar disorder with mood-incongruent psychotic symptoms, as well as with schizophrenia with lifetime manic episodes.[84] This suggests that *NRG1* may confer susceptibility to a specific clinical phenotype with combined features of psychosis and mania. A number of independent genetic linkage and association studies in diverse populations support the formulation that variation in *DISC1* gene influences susceptibility to disorders of psychosis spectrum, including schizophrenia, schizoaffective disorder, and bipolar disorder.[107] Although dysbindin has been extensively implicated in schizophrenia, a recent preliminary report has also suggested an association between polymorphism in this gene and a clinical subtype of bipolar disorder with recurrent psychotic episodes.[106] Overall, these findings implicate variations in *NRG1, DISC1, and dysbindin* in the susceptibility to psychosis or mixed phenotype with features of both psychosis and mood symptoms rather than to the *DSM-IV* schizophrenia phenotype. A large recent study from the United Kingdom implicated a genetic variation in *G72 (DAOA)/G30* in susceptibility for major mood episodes across the traditional bipolar disorder and schizophrenia categories.[108] This report suggests that even though this locus was originally described as a schizophrenia risk gene, it appears to be more strongly associated with mood symptoms domain than with psychosis; future replication studies are warranted.

Conclusions

Epidemiological and genetic studies support the hypothesis that psychosis is a clinical phenotype with multiple etiologies and a genetic component. Psychosis strongly aggregates in families. Twin studies have suggested high heritability estimates for psychosis and a complex mode of transmission. Whole-genome linkages studies have identified chromosomal loci that influence susceptibility to psychosis, independent of diagnostic categories. Detailed studies of linked genomic regions have identified several putative candidate genes *(NRG 1, dysbindin, DISC 1, COMT, G72/G30, BDNF, RGS 4)*, which appear to be involved in schizophrenia and affective psychoses. Understanding the biological effect of risk genes is complex. Even though several such genes have been implicated, it is difficult to determine the disease mechanism of each risk gene. Interactions between risk genes add to the complexity of the picture. In addition, environmental factors, interacting with risk genes, contribute to psychosis susceptibility.

While originally the candidate risk genes were implicated in schizophrenia, recent findings provide evidence that many show strong associations with symptom dimensions, such as psychosis *(NRG1, DISC1, and dysbindin)* or mood symptoms *(G72/G30, BDNF)*, across the schizophrenia-mood disorder continuum. A growing

number of reports suggest that psychosis may be a clinical phenotype with a unique genetic background from categorical diagnoses. Although intriguing, these observations are preliminary in establishing evidence for genetic associations in complex, polygenetic illnesses. Future genetic studies, focusing on the symptom dimensions across the functional psychosis continuum, are urgently needed. Dimensional approach may provide more direct clues to understanding the mechanisms of psychotic illnesses.

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