Published in final edited form as:
Harv Rev Psychiatry. 2010 ; 18(1): 67–74. doi:10.3109/10673220903523532.

A New Role for Endophenotypes in the GWAS Era: Functional Characterization of Risk Variants

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Keywords

endophenotypes; genomewide association studies (GWAS); psychiatric genetics

The field of psychiatric genetics is highly interdisciplinary, with roots in human genetics, psychiatry, statistics, and epidemiology. A primary goal in psychiatric genetics is to clarify how genes influence psychiatric illnesses—that is, the pathway from genotype to phenotype.[1] Such knowledge about the etiology and pathogenesis of illnesses should provide a basis for improving treatment and prevention. While genetic epidemiological studies have confirmed that clinically defined psychiatric disorders are familial and heritable, identifying the actual susceptibility genes involved has been a difficult, often frustrating endeavor. One explanation for this difficulty has been that the syndromes defined by the *Diagnostic and Statistical Manual of Mental Disorders* comprise heterogeneous phenotypes and were defined by expert consensus, making them suboptimal as phenotypes for genetic analyses. In addition, evidence to date suggests that common psychiatric illnesses are complex disorders that reflect the influence of many genes of individually small effect. This combination of phenotypic and genetic complexity has led some to conclude that the discovery of susceptibility genes will be a difficult proposition. In this context, some investigators have advocated the use of *endophenotypes* (also called *intermediate phenotypes*) in genetic studies.[2] The idea is that by defining neurobiological (e.g., neuroimaging) or psychological (e.g., temperament and personality) traits that are more direct expressions of gene effects, we might reduce heterogeneity and improve effect sizes in a way that would facilitate the search for susceptibility genes.

But the situation has changed. Over the past two years, advances in genomic and statistical methods, coupled with the availability of large sample sizes, have created a new opportunity for gene discovery that has proven remarkably effective for identifying susceptibility genes for complex diseases. Genomewide association studies (GWAS) using DNA microarray ("gene chip") technology have successfully identified loci influencing a broad range of medical disorders, including autoimmune, cardiovascular, metabolic, and neoplastic diseases.[3] These methods have begun to be applied to psychiatric illness, and early results are promising. Several specific variants have now been associated with bipolar disorder[4,5]

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

(BPD), schizophrenia[6,7] (SCZ), and autism.[8] Notably, these findings were achieved using DSM-defined disorder phenotypes rather than endophenotypes. These developments do not necessarily mean that the endophenotype strategy for gene mapping is flawed. For one thing, the intensity and cost of "endophenotyping" is high, so that GWAS using large samples have not yet appeared. We believe, however, that the GWAS era provides a new and important role for endophenotypes: the functional characterization of newly discovered genetic variants that increase the risk of disease (or what are commonly referred to as "disease risk variants").

Finding a statistically significant association between a genetic polymorphism and a clinical disorder is only the first step in understanding the role that genetic variants play in disease pathogenesis. The next step is to understand the functional effect of such variants and how they act to produce disease. As we argue below, we believe that endophenotypes can play an essential role in this project.

PSYCHIATRIC GENETICS: CHALLENGES AND COMPLEXITIES

Early psychiatric genetic research focused on whether and to what degree genetic factors influence psychiatric disorders. Family, twin, and adoption studies have consistently shown that major psychiatric illnesses like SCZ and BPD are familial and among the most heritable disorders in medicine.[1]

The evidence that genes influence risk for SCZ and BPD has motivated molecular genetic research aimed at identifying the specific genetic basis of these disorders.[9] Until recently, these efforts have relied on linkage analysis (which examines the cotransmission of illness and genetic markers within families to map disease genes to specific chromosomal locations) or candidate gene–based association analysis (which requires specifying genes of interest based on a hypothesized biological link with a disorder and then examining whether variants in those genes are more common among affected versus unaffected individuals).[10]

Progress in mapping risk genes for SCZ and BPD, as well as for other psychiatric illnesses, has been slow.[9,11] Recent evidence suggests that this difficulty can be explained by the complexity of these disorders, which likely involve a combination of common small-effect polygenes and rare moderate-effect variants.[12] That is, genetic risks may be the result of many relatively common variations in the genome, each conferring modest effects (e.g., relative risks in the range of 1.1–1.5)[3,4,6] along with multiple rare, but more highly penetrant, mutations or structural variations (e.g. duplications, deletions, or other copy-number variations).[13,14] In this article, we use SCZ and BPD as especially instructive examples since a large number of molecular genetics studies have been carried out in these illnesses.

Beyond this genetic complexity, psychiatric disorders like SCZ and BPD are phenotypically complex. While the constellations of symptoms used as diagnostic criteria in the most recent *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) have been useful for clinical practice, it is unlikely that they are the optimal phenotype definitions for genetic analyses. Valid phenotype definition is a prerequisite to successful genetic studies. The diagnoses enumerated in DSM-IV, however, are descriptive syndromes and categorical in nature. Within each diagnostic category, individuals may be phenotypically and genetically heterogeneous. Clinical boundaries between diagnoses are often blurred. One of the most unexpected and important dividends of psychiatric genetic research has been the growing evidence that genetic influences transcend the DSM categories. For example, evidence from family, twin, and molecular genetic studies suggests that genetic influences on SCZ and BPD overlap.[15,16]

"ENDOPHENOTYPES" IN PSYCHIATRIC GENETICS

To address uncertainties about phenotype definition, the use of endophenotypes in genetic analyses has been proposed as an alternative strategy to more directly assay the effect of disease risk variants and thus accelerate gene identification. Endophenotypes are heritable, disease-associated neurophysiological, cognitive, or neurobiological traits that are believed to be in the etiological pathway (i.e., intermediate) between risk genotype and the clinical syndrome but to be more proximally related to the genetic substrate than is the higher-order construct of a "disorder."[2,17,18]

Over the past decade, a large number of studies have tried to define intermediate endophenotypes for psychiatric disorders. In SCZ and BPD, results suggest that a number of neurocognitive processes and brain functions are robustly impaired in patients with these illnesses and in their unaffected relatives—including attention, learning, memory, language, sensory-input processing, inhibition, and emotional perception and regulation (see text box).[52–54] Direct assessment of the neurocognitive processes and brain functions associated with illnesses may provide phenotypes that are more strongly influenced by disease-related susceptibility variants, thereby enhancing the power of genetic-association studies.[2,17,18] This alternative gene-mapping strategy has had some success. The Collaborative Study on the Genetics of Alcoholism (COGA) project[55] and genetic studies of SCZ using the neurophysiological P50 sensory-gating endophenotype[56] (see below) are two examples. Linkage analyses of the COGA project using neurophysiological endophenotypes in addition to clinical diagnoses have strongly implicated two genes—*GABRA2* and *CHRM2*—with alcohol dependence.[55] The P50 sensory-gating endophenotype for SCZ has been linked with a genetic marker at the α-7 nicotinic receptor subunit gene *CHRNA7* that was not initially seen when the categorical phenotype of SCZ was used.[56] Recently, this gene region was implicated in two large-scale, genomewide surveys of copy-number variants deletions in patients with SCZ[13] and related psychosis.[14]

Illustrated Classes of Endophenotypes Relevant to Psychiatric Diseases

Alzheimer's disease

- Neurocognitive measures of memory performance[19]
- Reduced brain electrophysiological EEG activity[20]

Attention-deficit/hyperactivity disorder

- Structural brain imaging: reduced right prefrontal gray matter and left occipital gray and white matter[21]
- Functional brain imaging: prefrontal cortex and cerebellum deficits[22]
- Neuropsychological measures of inhibition[23] and processing speed[24]

Autism

- Neuropsychological measures of social cognition[25,26]

Anxiety disorder

- Functional brain imaging: greater amygdala and insula activation to emotional faces[27]
- Temperament traits: negative affectivity/neuroticism, positive affectivity, behavioral inhibition, effortful control[28,29]
- Neuropsychological measures of attentional bias toward stimuli relating to threats and negative emotions[28]

Bipolar disorder

- Structural brain imaging: alterations in gray and white matter[30,54]
- Neurophysiology: auditory P300; P50 sensory gating[31,32,69]
- Neuropsychological measures of executive function, verbal learning and memory,[33] facial-emotion processing,[34] deficits in ventral prefrontal cortex– related inhibitory processes,[35] attention[36]
- Temperament traits: affective temperament[37]

Major depression

Neuropsychological measures of cognitive function[38]

Temperament trait: neuroticism[28,39]

Clinical characteristics: number of episodes, duration of episodes, high levels of impairment, recurrent thoughts of death or suicide[40]

Obsessive-compulsive disorder

Structure brain-imaging: structural variation in brain systems related to motor inhibitory control;[41] white matter abnormalities in parietal and frontal regions[42]

Neuropsychological and functional MRI measures of cognitive flexibility and motor inhibition[43]

Schizophrenia

Structural brain imaging: smaller intracranial volumes,[44] frontal and temporal gray matter reductions,[45] hippocampal volume reduction[46]

Neurophysiology: auditory P300, sensory-gating, eye-movement deficits[31,47,70,80]

Functional brain imaging: dorsolateral prefrontal cortex dysfunction[18]

Neuropsychological measures of attention, executive function, working memory, processing speed[47]

Clinical features: thought disorder,[48] schizotypal personality disorder[49]

Substance-related disorders

Neurophysiology: resting EEG, visual P300 event-related potential[50,51]

GENOMEWIDE ASSOCIATION STUDIES

Within the past two years, the advent of GWAS has begun to have a major impact on our understanding of the genetics of complex diseases.[3] Instead of focusing on candidate gene–based association analysis, GWAS methods survey the whole genome using up to one million or more genetic markers (typically single nucleotide polymorphisms). The ultimate aim of the GWAS design is "to capture all common genetic variation across the genome and to relate this variation to disease risk."[57] This strategy has been made possible through a combination of advances in technology (microarray genotyping), population genetics (the cataloguing of genetic variation through the International HapMap project), and advances in statistical methods.

GWAS has provided a powerful tool for identifying common modest-risk variants and has already proven effective in many areas of medicine.[3] Very large samples of cases and controls (on the order of thousands or even tens of thousands) are typically required. A critical advantage of GWAS strategy is that it provides a *systematic* and *relatively unbiased* screening of the entire human genome that can lead to the discovery of previously unsuspected susceptibility variants.[58] This type of screening is especially valuable in the case of psychiatric disorders for which our understanding of pathogenesis remains limited.[59]

In the past year, compelling results from large case-control samples have emerged using this strategy for BPD and SCZ.[60] The recently established Psychiatric GWAS Consortium (PGC: https://pgc.unc.edu/pgc/index.php)[61] is combining GWAS data across multiple studies to identify convincing genotype-phenotype associations for major psychiatric disorders (including BPD, SCZ, attention-deficit/hyperactivity disorder, autism, and major depressive disorder). Statistical power of the PGC meta-analyses will be superior to any prior study in psychiatric genetics, offering hope that many common disease risk variants will be uncovered in the next few years.

Identification of validated susceptibility variants is a crucial step, but it is only the first step. Once statistical evidence of associations between disease risk variants and psychotic diseases is established, the work of defining the functional effects of these variants becomes

critically important.[12,62] Association analyses by GWAS can identify susceptibility genes but do not address *how* risk variants affect alterations in brain function that characterizes the disease. Dissecting the effects of risk genes on distinct domains of brain function can provide essential biological insights into the mechanisms by which these genes may produce illness.

ENDOPHENOTYPES AS A TOOL FOR CHARACTERIZING RISK GENES

As we noted above, the primary application of the endophenotype strategy to date has been to facilitate the identification of risk genes for particular diseases. However, the success of large-scale GWAS studies suggests another important role for endophenotypes—namely, to characterize how risk variants are related to neurobiological and neurophysiological phenotypes that underlie psychiatric disorders. That is, the application of endophenotypes can move the focus of research from the realm of gene discovery to the realm of functional characterization. Follow-up association analyses of risk alleles with one or more endophenotypes offer a strategy for elucidating the neurobiological or pathophysiological characteristics of risk variants and the mechanisms by which specific variants contribute to disease.

For example, GWAS analyses have revealed that variations in the *ANK3* (ankyrin G) and *CACNA1C* (alpha 1C subunit of the L-type voltage-gated calcium channel) genes are associated with susceptibility to BPD.[4,5] Although these results are among the most statistically strong to date, neither of these genes was previously even considered as a candidate risk gene, and their role in the neurobiology and neurophysiology of BPD remains unclear. One resource for characterizing such effects is well-validated endophenotypic measures of brain dysfunction in mood and psychotic disorders. We suggest that "endophenotype mapping" of susceptibility genes for BPD and SCZ may help elucidate the specific domains of brain function influenced by the relevant disease risk variants. As noted above, a substantial effort has been made in the past two decades to characterize neurophysiological and psychological endophenotypes for BPD and SCZ. In neurophysiology, evidence indicates that a number of cognitive processes and brain functions are robustly impaired in patients with psychotic illnesses. For example, altered P50 sensory-gating responses, reduced amplitude and delayed latency in auditory P300 event-related potentials, and reduced neural oscillations in the gamma frequency band are robust findings in patients with SCZ and common in BPD.[63–67] Twin and family studies have indicated that these neurophysiological alterations in the brain are heritable traits.[68–71] In addition, these traits appear to capture dissociable components of neurocognitive function:[72] auditory P50 suppression is an index of sensory gating and inhibitory mechanisms;[73] P300 amplitude and latency reflect attention-directed information processing;[74] and gamma band response appears to reflect cortico-cortical neuronal communication, synchronization, and integration processes.[75] Because the cognitive domains of these (and other) endophenotypes have been well characterized, they provide a resource for mapping confirmed disease risk alleles onto specific brain functions. In addition, they allow us to examine whether a disease risk variant is related to single or multiple (pleiotropic) cognitive processes that underlie psychiatric diseases. In other words, association analyses of multiple endophenotypes could clarify which risk variants have effects that transcend different cognitive and affective processes, and which variations contribute uniquely to specific brain functions.

In addition to indexing the function of specific brain processes, endophenotype mapping could also help illuminate the neurobiological mechanisms or neural circuits by which novel risk genes exert their pathogenic effects. For many endophenotypes, the underlying mechanisms and brain circuits have been well studied by drug challenge investigations,

animal models, and genetic quantitative trait linkages.[2,17,18,53] Findings emerging from these studies have implicated various neurobiological mechanisms in the etiology of psychotic and affective disorders. For example, dopaminergic hypofunction has been linked to working-memory deficits of the dorsolateral prefrontal cortex in SCZ[18] and to abnormal temporaparietal P300 amplitude;[76] dysregulation between glutamate receptor–mediated excitation and the GABAergic neuron–mediated inhibition feedback loop is proposed as one of the neurobiological mechanisms responsible for abnormal gamma oscillations in SCZ;[77,78] and disturbances in hippocampal cholinergic circuits are considered one of the main contributory mechanisms to P50 gating deficits in SCZ and BPD.[79,80] Thus, evidence of associations between novel disease risk genes such as *ANK3* or *CACNA1C* and endophenotypes would suggest a possible connection between risk genes and the biological mechanisms that are known to mediate altered endophenotypes.

Finally, we suggest that endophenotype mapping of disease risk genes could inform the evolution of psychiatric nosology. It has been argued that the canonical diagnosis classification system of DSM-IV does not reflect the underlying etiology of psychiatric disorders.[15,81] For example, growing evidence from family, twin, and molecular genetic studies suggests that genetic influences on mood and psychotic disorders transcend DSM-based categories.[15] Psychosis is a core feature of SCZ and is common in BPD; many patients with SCZ exhibit symptoms of depression and mania;[82] schizoaffective disorder, which has prominent symptoms of both psychosis and mood disorder, occurs at similarly increased rates in SCZ[83] and BPD[84] families; and molecular genetic studies have highlighted a number of candidate loci and genes influencing both SCZ and BPD.[15,85,86] These findings have led some investigators to propose that SCZ and BPD share some risk genes and that these shared genes predispose individuals to psychosis in general.[15,81,87] We suggest that endophenotype mapping may shed light on such questions. At the clinical level, studying multiple endophenotypic traits within a patient sample may help identify homogeneous bio-cognitive subtypes across diagnostic categories by classifying patients based on similar neuropsychological/cognitive functional-deficit profiles (e.g., deficits in frontal working memory, executive functioning, inhibitory control, and selective attention). These profiles, in turn, can be examined in relation to formal diagnoses, clinical phenotypes, genetic loading, and other variables that may optimize the usefulness of these classifications. Evidence that endophenotypes are associated with susceptibility genes specific to either SCZ or BPD would suggest that the diagnostic categories reflect distinctive etiologies, whereas evidence of association across disorders would suggest an overlapping pathogenesis. Thus, endophenotypes in this context could be used to test the validity of the clinical classification of the disorders.

CONCLUSION

The search for the genetic causes of psychotic illnesses has been a focus of psychiatric genetics research. GWAS has provided a powerful tool for gene identification, and progress in gene discovery is accelerating rapidly. The functional characterization of newly discovered risk variants now becomes a key project for psychiatric genetics. Successes in susceptibility gene identification have created a new and important role for endophenotypes studies, moving beyond the realm of gene identification to the realm of functional characterization of risk variants and etiological profiling of psychiatric disorders. As the number of validated disease genes increases and as our understanding of the neurophysiology underlying endophenotypes improves, these new uses for endophenotypes should become increasingly important. The processes of elucidating the functional effects of disease risk variants will provide essential insights into the mechanisms by which these genes may produce illness—and, as a consequence, into the means for improving treatment and prevention.

Acknowledgments

Supported, in part, by the National Alliance for Research on Schizophrenia and Depression (NARSAD) Sidney R. Baer, Jr. Foundation Young Investigator Award and NIMH grant no. 2T32MH016259-29A1 (Dr. Hall); NIMH grant nos. MH079799 and MH085542 (Dr. Smoller).

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