# Putting Genetics to Work in the Psychiatric Clinic

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The rapid progress in psychiatric genetics over the past 10 years, while exciting from a research perspective, has not yet had an impact on clinical practice. How will we really be able to put genetics to work in the psychiatric clinic? This overview will attempt to answer this question. A survey of widely used methods and major study designs highlights key findings that have emerged so far. These findings inform a broad conceptual model of how genetic risk may act to influence dimensions of psychopathology and clinical presentations. The overview concludes with highlights of some of the most clinically relevant findings to date and their implications for psychiatric practice in the near future.

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Many psychiatrists regard genetics with a mix of fascination and suspicion. Genetics *is* fascinating as a powerful tool for getting at the causes of mental illness and their well-known tendency to run in families. At the same time, we are justifiably suspicious of reductionist approaches that have sometimes seemed to promise to deliver "the gene for" each of the complex social and emotional problems that trouble patients and their families and are the focus of our professional attention. The steady stream of genetic findings in recent years has been exhilarating to specialists in the field, but at times it may resemble stamp collecting, with no obvious clinical relevance. How will we really be able to put genetics to work in the psychiatric clinic? This issue of the *Journal*, which focuses on genetics, provides an opportunity to address this question while providing an overview of the field accessible to non-geneticists.

I will begin with a brief overview of the widely used methods and major study designs, highlighting key findings that have emerged so far. Then I will present a broad conceptual model of how genetic risk may act to influence dimensions of psychopathology and clinical presentations. I will close with highlights of some of the most clinically relevant findings to date and their implications for psychiatric practice in the near future.

## GENOME-WIDE ASSOCIATION STUDY (GWAS)

In this study design, unrelated case subjects and unaffected control subjects are genotyped using arrays that carry up to a million common variants, known as single-nucleotide polymorphisms (SNPs), spread all over the genome. SNPs are sites in the DNA where two possible variants, or alleles, occur. Association analysis is used to detect alleles that are more or less common in case subjects and may thus alter illness risk. GWASs make no assumptions as to which genes are most important, and in fact most SNPs fall outside the regions of genes that encode proteins. Because so many SNPs are tested, statistical significance needs to be corrected for many independent tests. SNPs found by GWAS usually do not tag specific genes but tend to affect expression of one or more nearby genes, thus providing some level of biological information. GWASs tend to identify common alleles present in at least 20% of the population. Accordingly, the risk conferred by such alleles is low, with odds ratios typically less than 1.2. However, since some patients may carry a large number of risk alleles, taken together the cumulative risk is more substantial, explaining up to 30% of the risk for disease. A large set of SNPs can be used to score genetic risk in independent samples. This polygenic risk score (PRS) is thus a useful metric of individual risk for research purposes, although the PRS alone accounts for a very small proportion of the variance (<2%) and has little predictive value in clinical settings (1). SNP data can also be used to estimate genetic overlap between different diagnoses, known as genetic correlation, which is useful for studies of nosology, endophenotypes, and genetic architecture (2).

Over the past 15 years, GWASs have successfully identified hundreds of risk alleles that contribute to many different psychiatric disorders. Currently, more than 145 risk loci have been identified in schizophrenia (3), 178 in depression (4), 64 in bipolar disorder (5), 12 in attention deficit hyperactivity disorder (ADHD) (6), and several in anxiety disorders (7). Risk alleles appear to act together in a strictly additive

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fashion, but individuals at the highest end of the PRS distribution may have substantial risk for disease. For example, individuals whose schizophrenia PRS is near the top of the distribution have a 5- to 15-fold increase in risk of schizophrenia (8), comparable to the risk conferred by having an affected first-degree relative. Many risk loci are shared across more than one disorder, and substantial genetic correlations exist across diagnostic groups. For example, schizophrenia and bipolar disorder have a genetic correlation close to 80% (9), which means that at least 64% of risk loci are shared between the disorders. Genetic correlations have also been identified between psychiatric disorders and other traits, such as cognition, sleep patterns, brain anatomy, and substance use disorders (2, 10). These findings demonstrate that common genetic variation contributes substantially to risk for psychiatric disorders, that genetic risk factors overlap between diagnoses, and that genetic risk can be expressed as a variety of phenotypes, many of which are not considered illnesses.

GWAS methods have also been applied to treatment outcome phenotypes, such as response to antidepressants. Despite high expectations early on (11), such pharmacogenetic traits have proven to be very challenging genetic targets. Some GWASs have reported genome-wide significant single-marker or polygenic effects (12–14), but robust findings have not yet emerged. This may reflect the relatively small samples studied so far, the wide variety of psychopharmacologic agents used, and the complexity of treatment outcome phenotypes. Genetic variants that influence metabolism of many drugs processed by cytochrome P450 enzymes have long been known to affect blood levels and adverse events, and probably explain some poor treatment outcomes (15), but there is a lack of consistent evidence to support a major role of such variants in treatment response for most psychiatric patients.

## COPY NUMBER VARIANTS

Genome-wide studies have also found a large number of variants that affect the structure of chromosomes, leading to the deletion or duplication of many genes. These are known as copy number variants (CNVs). CNVs can be found through specialized analysis of SNP array data, through other assays such as chromosomal microarrays, and in sequencing data, but they are typically too small to be detectable by older methods of karyotype analysis. Most CNVs are unique to an individual, but many are recurrent, owing to repetitive DNA sequences that flank the CNVs and increase recombination errors. CNVs affect expression of genes within the variable region and elsewhere in the genome, so they can exert substantial effects on gene dosage.

Large CNVs spanning hundreds of thousands or millions of DNA base pairs and many genes confer substantial risk for certain psychiatric disorders, such as schizophrenia, neurodevelopmental disorders, and mood disorders, along with some nonpsychiatric disorders that affect, for example, the heart, the peripheral nervous system, and the body habitus. Each of these CNVs is quite rare in the population but 5–50 times more common in those with severe psychiatric disorders. At least 45 of these CNVs are pathogenic, and over 2% of people diagnosed with schizophrenia carry one or more of them (16). Some of these CNVs are passed on to offspring, so multiple family members may carry the same CNV, providing a rich source of data on the range of expression within a family, which can vary widely (17). Other CNVs, particularly those that confer severe neurodevelopmental phenotypes, are usually not passed on to offspring and are thought to arise de novo during early development.

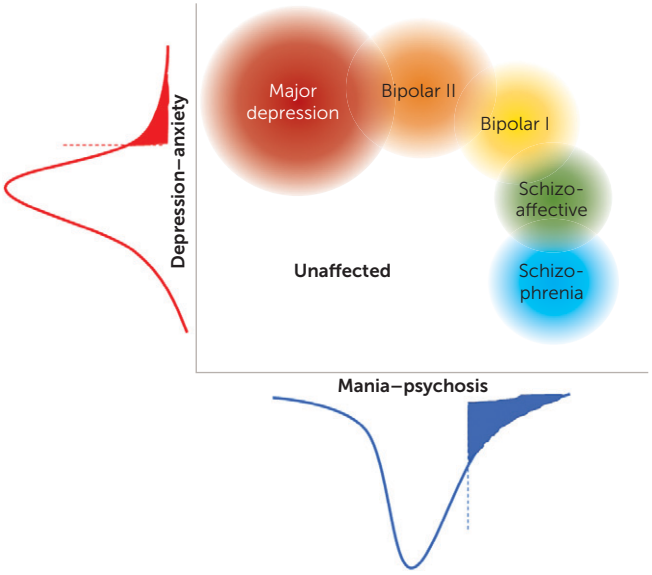
While some of these CNVs underlie known contiguous gene syndromes, such as velocardiofacial syndrome, which is caused by deletions on chromosome 22q, many present with a highly variable, largely psychiatric phenotype. Importantly, many of these CNVs predispose to a variety of psychiatric disorders, with little or no diagnostic specificity. Although CNVs do not explain many instances of psychiatric disorder, the way they influence disease risk suggests a common neurodevelopmental origin for many of the major psychiatric disorders, even those that typically present in adolescence or early adulthood. Consistent with this idea, genes overlapping neuropsychiatric CNVs tend to be expressed in the developing brain, with particular enrichment within neurons and synapses (18).

## GENOME SEQUENCING STUDIES

With the advent of large-scale sequencing technology in the past 5–10 years, it is now becoming routine to use genome sequencing to identify risk alleles for numerous diseases. Sequencing studies may focus on variants that arise during early development and are not shared with parents (de novo studies), or on coding variants that may affect the amino acid sequence or structure of translated proteins (exome studies). These study designs, when successful, identify specific genes with a high level of confidence. Whole-genome sequencing studies of all 3.2 billion base pairs of DNA are also possible, although our ability to interpret the impact of genetic variants outside the coding region of genes remains quite limited. Sequencing can be done in case-control samples like those used in GWASs, in trios with a case subject and two unaffected parents (for de novo analyses), in large families with multiple affected relatives (19), and in special samples drawn from genetically isolated populations or the extreme ends of a clinical spectrum of interest (20).

Most of the psychiatric findings to date are based on de novo or exome study designs. De novo studies of mutations that damage the protein product of a gene have implicated dozens of genes associated with autism spectrum disorder (ASD) (21), schizophrenia (22), and intellectual disability (23). Fewer findings have emerged so far from de novo studies of obsessive-compulsive disorder (OCD) (24) or bipolar disorder (25). This may reflect differences in the genetic architecture of these disorders but may also be due in part to the smaller samples studied to date. Exome studies have so far been most successful in schizophrenia, where it has been possible to assemble the very large samples needed to identify association with very rare alleles. These studies have

**FIGURE 1. A genetic model of major mental illnesses**[a]




[a] Genetic risk is normally distributed across two dimensions, labeled "mania-psychosis" on the x-axis and "depression-anxiety" on the y-axis. The filled end of each distribution represents individuals whose genetic risk exceeds a liability threshold (dotted line). Major categorical diagnoses will tend to fall within the colored balloons, but without distinct borders.

now identified 10 genes that carry a significantly increased burden of rare, damaging alleles in patients (26). Some of these genes had already been implicated by GWASs or de novo studies, but most are novel, and the mutations confer large risks comparable to those conferred by CNVs, providing important opportunities for unique biological insights.

## TRANSCRIPTOME STUDIES OF GENE EXPRESSION

Advances in sequencing technology over the past decade have enabled a renaissance in studies of gene expression driven by sequencing of RNA. Since RNA is transcribed from the DNA template, these studies are often referred to as transcriptome studies. Unlike older techniques that used probes on microarrays, RNA sequencing can quantify low levels of gene expression, differentiate among various isoforms or subtypes of a gene (mostly generated by alternative splicing of immature RNA), and capture types of RNA that are not translated into proteins but are thought to play a key role in coordinating expression among sets of genes. Since gene expression in the brain is most relevant for psychiatric disorders, I will focus here on studies of human postmortem tissue. Such studies rely on large banks of brain tissue donated from individuals who died with a psychiatric or nonpsychiatric disorder. Most studies have focused on dorsolateral prefrontal or anterior cingulate cortex from people diagnosed with schizophrenia, bipolar disorder, or ASD. Subcortical regions and other major psychiatric disorders have been little studied so far. Most studies have used bulk tissue, so they cannot distinguish expression changes attributable to changes in the underlying cellular composition of the tissue studied. Studies under way that use newer, single-cell RNA sequencing technology are generating results at cellular resolution. Brain tissue collected postmortem reflects a single endpoint in a lifetime of illnesses, stressful life experiences, and chemical exposures and necessarily undergoes variable levels of degradation before it can be studied. Thus, it is difficult to discriminate between gene expression changes that play a causal role in disease and those that are a consequence of that disease or its treatment. To clarify which of the findings from postmortem studies are most important in the etiology of psychiatric disorders, transcriptomic studies can also be performed in experimental model systems that employ developing animals (27), transgenic organisms, or neurons and glial cells derived from human induced pluripotent stem cells (28, 29).

Despite the limitations of transcriptome studies, several broad conclusions are now possible. Large studies published in the past 5 years have documented significant associations between major psychiatric disorders and widespread changes in the brain transcriptome (30–32). Observed expression changes are subtle and distributed over hundreds of genes and isoforms, consistent with the polygenic nature of psychiatric disorders already revealed by GWAS. Patterns of differential expression overlap substantially across psychiatric disorders, even though the magnitude of expression differences varies and some genes display contrasting expression differences between diagnostic groups (32). Differentially expressed genes are not random but tend to be enriched for functions related to synapses, brain development, and immunity. In some disorders, brain anatomical differences are correlated with the expression of risk genes (33). Many of the risk alleles identified by earlier GWASs affect expression or alternative splicing of nearby genes, although some alleles affect other genes located far away from the associated SNP (34). Bioinformatic integration of GWAS with transcriptome data has enabled the prioritization of genes whose expression or splicing is influenced by known risk alleles in a direction consistent with what is observed in postmortem brain. These genes are prime targets for laboratory studies aimed at the development of novel therapeutics.

## GENETIC MODELS OF PSYCHOPATHOLOGY

After this very abbreviated review of a large and growing literature, it should be apparent that we are in an era of rapid progress. Emerging findings are complex, but comprehensible, and there is a reassuring concordance of findings obtained through independent methods of investigation. While it is difficult to sketch a detailed clinical model of psychiatric disorders based on the genetic data obtained so far, some preliminary attempts are possible. Useful models must be able to account for the strong genetic overlap across clinically distinct disorders, unify the effects of common and rare risk alleles, and provide a framework for falsifiable hypotheses.

Figure 1 presents one such model. The model assumes that genetic risk varies across dimensions that are normally distributed in the population and that individuals at the high end

of the risk distribution may cross a liability threshold and be diagnosed with a disorder (35, 36). Earlier family and twin studies and recent GWASs suggest at least two major genetic risk dimensions that, while somewhat correlated, tend to vary independently across individuals: a depression-anxiety dimension strongly related to neuroticism, and a mania-psychosis dimension that captures the strong genetic overlap between bipolar disorder and schizophrenia (9, 37).

Under this model, each patient's clinical presentation is influenced by where they lie along the important dimensions of genetic risk. Patients with a high load of alleles predisposing to mania-psychosis but lower loads of depression-anxiety alleles will be overrepresented among those diagnosed with schizophrenia. In contrast, individuals with a high load of depression-anxiety alleles and a low load of mania-psychosis alleles may tend to be diagnosed with major depression or anxiety disorder. People with a diagnosis of bipolar disorder may tend to have moderate loads of both depression-anxiety and mania-psychosis alleles. Note that there are no strict cutoffs for allele loads under this model. Individuals with high loads of risk alleles across both dimensions may experience signs and symptoms leading to "mixed" diagnoses such as schizoaffective disorder or to "comorbid" conditions such as bipolar disorder with panic disorder (38) or psychotic depression. While conceptualized mainly around common low-risk alleles that are found by GWAS, this model can accommodate rare, high-risk alleles, such as CNVs, which tend to move carriers into the extreme tails of the genetic risk distributions. This model can also accommodate the important influence of nongenetic risk factors and adverse life events. These will tend to shift the liability threshold to the left within any given genetic risk distribution, so that individuals with a high burden of environmental risk may develop symptoms at a lower point in the genetic risk distribution.

While two dimensions are emphasized in the figure, other dimensions not shown here contribute further to clinical presentations, levels of impairment, and probability of being diagnosed with a mental illness. Some relevant dimensions include what has been called a "compulsivity" dimension, at whose extremes we find people with diagnoses of OCD or eating disorders, and a cognitive-developmental dimension that underlies impulsivity, externalizing behaviors, and educational attainment (37, 39, 40). Thus, each of us exists in a multidimensional space defined by various levels of genetic risk, even though any clinical outcomes are influenced by many nongenetic factors.

## CLINICAL HIGHLIGHTS

The rapid progress in the field of psychiatric genetics over the past decade has so far not been strongly felt in the clinic. Translation of research findings is never rapid, and the sheer volume and complexity of the findings to date belies simplistic notions of gene-based diagnoses, "druggable" genes, or primary prevention in high-risk individuals. Still, there are several recent psychiatric genetic findings that may carry particular clinical relevance.

### Genetic Risk Does Not Respect Diagnostic Boundaries

One of the big surprises of the GWAS era is the substantial genetic overlap among all psychiatric disorders. This is particularly true for bipolar disorder and schizophrenia, but substantial sharing of risk alleles is also observed across major depression, ASD, ADHD, OCD, eating disorders, and anxiety disorders (39). Diagnostic overlap is also seen across a range of rare, high-risk alleles, such as CNVs. For example, the duplication of a 600-kb region on chromosome 16p11.2 substantially increases risk for schizophrenia, ASD, bipolar disorder (41), and major depression (42) and will probably be found to be associated with other disorders as sample sizes increase.

This reality has several implications. First, as noted in a consensus report from the International Society of Psychiatric Genetics (43), genetic testing will probably not be informative for psychiatric differential diagnosis, since almost all known genetic risk factors are present in patients with a wide variety of diagnoses as well as people who have no obvious psychiatric disorder. Genetics will not supplant a good history, mental status examination, or family history. Second, convergent genetics implies convergent pathophysiology, so treatments developed on the basis of genetic discoveries are likely to be effective for a variety of psychiatric disorders, if they are effective at all. Conversely, there is at least one example of divergent genetics aligning with divergent treatment response: poorer response to lithium in bipolar disorder is associated with greater genetic burden of schizophrenia risk alleles (44).

### Most Psychiatric Disorders Have a Neurodevelopmental Component

The genes identified so far tend to act during the earliest stages of brain development, with expression data pointing to the first or second trimester. Some gene-first studies that longitudinally assess young people who carry high-risk alleles are seeing differences in emotional, cognitive, and social function in carriers, most of whom do not meet criteria for a psychiatric disorder (45). This implies that genetic risk for psychiatric disorders acts on the developing brain, sowing the seeds for psychiatric symptoms that, if they emerge at all, may not be evident for decades. Consider the analogy of coronary artery disease, where genetic risk influences lipids, body mass index, and glucose metabolism many decades before an occluded artery causes angina or myocardial infarction. This also implies that primary prevention, aimed at reducing the incidence of symptoms in high-risk individuals, would probably need to start in childhood. How to efficiently identify children at highest risk and how best to help them avoid poor psychiatric outcomes later in life should be a major target of future research.

### Genetic Signals Converge at the Synapse

While GWAS results were generally surprising, one result may have been predicted by what we already think we know about the actions of psychotropic agents: The genes implicated in the etiology of a variety of psychiatric disorders are strongly enriched for those that encode synaptic proteins. Among the most widely supported genes are those encoding shank proteins that anchor the postsynaptic density, genes encoding calcium channels (*CACNA1C*, *CACNB2*), glutamate receptors (*GRIN2A*, *GRM1*, *GRIA1*), and Erk signaling (*MAPK3*). Other biological enrichments, including immunity and neuronal development, are also of interest for future research, but the synapse continues to be the most promising target for development of novel therapeutics.

### "Rare" High-Risk Mutations Are More Numerous Than Previously Assumed

Early findings suggested that genetic variants that conferred substantial risk for psychiatric illness, including CNVs and de novo mutations, were very rare and likely to be present in only very few patients. As findings have accumulated, however, it has become clear that there are many of these high-risk variants in the human population, so that collectively they may account for a substantial fraction of disease risk (46). The largest samples so far represent children with neurodevelopmental disorders, where a combination of karyotyping, copy number detection, and exome sequencing identifies an apparently causal genetic event in over 25% of patients (47). If this is even half true in other patient populations, we may soon decide that a genetic workup should be part of a thorough psychiatric assessment for many of our patients.

### Pharmacogenetic Testing Has Been Oversold

Pharmacogenetics promised to deliver a world of "precision psychiatry" where it would be much easier to match patients with the safest and most efficacious medication. This promise remains unfulfilled. Genetic testing of variants associated with drug metabolism or severe adverse events is indicated in selected patients and special situations (48). However, widespread testing of genetic variants with no robust association with clinical outcomes and no demonstrated utility in treatment selection does not appear to be well supported by the current evidence.

## CONCLUDING REMARKS

So, is genetics ready to be put to work in the psychiatric clinic? The clinically relevant findings discussed above suggest that we have just begun a journey down a long road of translation. The limitations of categorical diagnoses that do not align well with genetic risk or underlying biology are clear, even though we are far from replacing DSM with genetically defined disease entities. Our approach to clinical care would doubtless benefit from a more neurodevelopmental perspective; we could begin by learning more about each patient's childhood development, learning differences, and early social experiences. New treatments may well arise from the genetically well-supported focus on the synapse, although knowing the target is not the same as knowing how to hit it effectively. If we should be testing more patients for rare variants, how do we best use the information provided by tests in managing patients' treatment? And while pharmacogenetics has not yet delivered, studies of larger samples may well reveal better ways to apply genetic information in treatment selection (49). As we look forward to a more genetically informed practice, psychiatrists should also ask ourselves whether we are ready to use genetic information skillfully in our clinical care (50).

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### Examination Questions for "Putting Genetics to Work in the Psychiatric Clinic"

1. **Genome-wide association studies typically aim to**
   A. Identify genes that cause disease
   B. Find common alleles that predispose to disease
   C. Test a priori hypotheses about candidate genes
   D. None of the above
2. **Which of the following best describe the current role of pharmacogenetic testing in psychiatry?**
   A. An essential first step in selecting an antidepressant drug
   B. Has no role in psychiatric treatment selection
   C. May be indicated in selected patients or special situations
   D. None of the above
3. **Which of the following represent current views of copy number variants (CNVs) in psychiatry?**
   A. CNVs are very useful in psychiatric differential diagnosis
   B. CNVs tend to have a larger impact than risk alleles found by GWAS
   C. CNVs usually affect only one or two genes
   D. All of the above