Genetic Testing for Psychiatric Disorders: Its Current Role in Clinical Psychiatric Practice

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Genetics seems to be a subject of particular interest for everyone. News stories often emerge in the mainstream press that report on the latest genetic research into different disorders, including psychiatric disorders. However, it is not always clear what the results of these studies really mean in terms of their implications for clinical practice.

A big picture perspective

Research data from family, twin, and adoption studies show that psychiatric disorders (such as depression, schizophrenia, anxiety, and bipolar disorder) are complex (or multifactorial) disorders that typically arise as a result of the combined effects of genetic and environmental factors. Psychiatric disorders are etiologically heterogeneous. Thus, even within a single discrete diagnostic category, each individual will have accumulated different combinations of contributing genetic and environmental influences that ultimately result in illness manifestation. Although very broad, this knowledge provides intuitive yet fundamental information that is of relevance to clinical practice—no genetic test can predict with certainty who will and who will not become mentally ill. Despite this, there remains considerable value in identifying the genetic variants that increase risk of psychiatric disorders—for example, the potential to refine nosology and diagnosis of psychiatric disorders, improve treatments, and identify those at risk. Thus, there has been considerable research in this area.

Contextualizing current research

Some of the first attempts to identify specific genetic variations that could predict the risk of a psychiatric disorder used linkage studies. This strategy aims to identify regions of chromosomes that are transmitted together with the phenotype in question (eg, psychiatric disorders) through generations of a family. Linkage studies are incredibly powerful when searching for genes that play a large role in a particular phenotype. For example, in the 1980s, linkage studies were responsible for locating the genes responsible for both cystic fibrosis and Huntington disease. However, when applied to the study of psychiatric disorders, linkage studies offered only equivocal results. Attempts to replicate initial findings produced only partial or conditional success. The disappointing data drove psychiatric geneticists to consider whether the genes that contribute to the development of psychiatric disorders were typically of an effect size that was not large enough to be detected by linkage studies.

The traditional association study, which is theoretically more powerful for detecting genes of smaller effect, was logically the next approach in an attempt to identify genetic variations that confer vulnerability to psychiatric disorders. Traditional association studies test individual genetic variants to determine whether they occur more frequently in persons with psychiatric disorders than in those who are not affected. However, again, extensive research using this approach generated largely equivocal results.

Genome-wide association studies

By the early 2000s, technological developments made genome-wide association studies (GWAS) possible. A GWAS typically involves testing half a million individual genetic variations (single nucleotide polymorphisms [SNPs]) for association with the phenotype in question at the same time. This study approach requires very large sample sizes and very stringent thresholds for statistical significance, but it is theoretically very powerful for detecting variations of small effect.
There was much anticipation that the genes that had generated the most support from traditional linkage and association techniques would be confirmed by the results of GWAS. The data from the first, relatively small studies, however, did not deliver this result: few genetic variants surpassed the stringent criteria for statistical significance, and fewer still were variants that had been previously suggested by traditional linkage and association approaches. Many attributed these outcomes to inadequate sample sizes. Consequently, international collaborations were established, and huge data-sets (involving more than 50,000 individuals) were accumulated for powerful genome-wide association investigations of psychiatric disorders. These studies identified genetic variations that met stringent criteria for genome-wide statistical significance and showed that in some cases the same variation seemed able to contribute toward vulnerability for more than one psychiatric disorder.

Individually, the variations that were identified did not seem to play a large role in vulnerability to psychiatric disorders. At most, an individual variation doubled an individual’s risk of developing a psychiatric disorder over the background population risk. When considered in terms of absolute risk, this simply means that if the population risk for schizophrenia is 1%, an individual with one of the variations identified from a GWAS might have, at most, a 2% risk for the same condition. Thus, testing for these variations (at least individually) provides little information of meaningful clinical utility; we still lack information about the effects of having different combinations of these variations. Some researchers felt that these data demonstrated that the idea that psychiatric disorders are caused by multiple common variants, each of small effect, was wrong, and they proposed that psychiatric disorders might instead arise as a result of a large array of individually rare variants, each of which contribute a large effect.

Copy number variations
It has been well known for some time that deletions or duplications—even those that are too small to be seen with a microscope—can cause rare genetic syndromes that present clinically with many different manifestations, which can include psychiatric disorders. The archetype is 22q11.2 deletion syndrome, which is associated with a risk of approximately 30% for psychosis. This was the impetus to look at the role of copy number variations (CNVs) in psychiatric disorders.

CNVs are sections of DNA larger than 1 kb but that are too small to be seen with a microscope and are gained or lost compared with a reference genome. Although CNVs occur less frequently in the human genome than SNPs, they are still relatively (and perhaps surprisingly) common. CNVs occur not only among populations of individuals in whom specific pathologies have been identified but also in the general population. Certain specific CNVs have been shown to occur more frequently among populations of individuals with psychiatric disorders than among the general population. In some cases, a single CNV seems to confer risk for more than 1 psychiatric diagnosis (for a review, see O’Donovan et al). CNVs can be inherited or can occur spontaneously in a de novo fashion. Although it can be tempting to assume that a de novo CNV in an affected individual who has no affected family members is pathogenic, this is not necessarily the case. Essentially, interpreting the clinical significance of most CNVs (beyond those with clearly defined phenotypes, such as 22q11.2 deletion syndrome) is extremely challenging.
Current thinking about the genetics of psychiatric disorders

A consensus is emerging that both common SNPs, each of small effect, and rarer CNVs, each of larger effect, are likely to contribute to the development of psychiatric disorders. Recent data show that there seems to be an increased frequency of de novo genetic variations (both SNPs and CNVs) among populations of persons with psychiatric disorders compared with the general population. However, the distributions of the frequencies of variation overlap between the two groups, which precludes using this information to distinguish between those with and those without a psychiatric disorder, or to predict risk of psychiatric illness.

What do we know (or don’t we know) about the genetics of psychiatric disorders?

- There seem to be many different genetic variations (and types of variation, eg, SNPs and CNVs) that can increase an individual’s vulnerability to psychiatric illness, few of which (if any) are necessary or sufficient to develop a psychiatric disorder.
- It is highly likely that all of the variations that can contribute to genetic vulnerability for psychiatric disorders have not yet been identified.
- A single genetic variation may confer vulnerability to different psychiatric diagnoses as opposed to each variant conferring vulnerability to a single discrete diagnosis.
- Even well-replicated data that demonstrate (with a compelling P value) that a genetic variation plays a role in the etiology of a disorder do not mean that the variation necessarily confers a large amount of vulnerability to psychiatric illness or that genetic testing for it in the clinical setting is warranted; this type of information speaks only about the confidence that the variation plays some kind of role.
- Although we have traditionally thought of gains or losses of sections of DNA as causative of certain phenotypes, CNVs do not seem to cause psychiatric disorders; rather, they simply increase vulnerability.
- Not all of the genetic variations that can contribute to vulnerability to psychiatric disorders are necessarily inherited—there is some evidence that de novo mutation rates (for both SNPs and CNVs) are higher among individuals with psychiatric disorders than among the general population.
- We still do not have a clear understanding of the effects of having multiple genetic variations (eg, an individual’s cumulative risk for a psychiatric disorder could be a function of simple additive effects of each variation, or the effects could be multiplicative).
- The mechanisms by which the genetic variations that have been identified increase vulnerability to psychiatric disorders remain unclear.

Genetic testing for psychiatric disorders

Genetic testing to diagnose psychiatric disorders. Given our present knowledge, in general there is essentially no meaningful role for genetic testing in establishing, confirming, or refining a psychiatric diagnosis in routine psychiatric practice.

Genetic testing to predict psychiatric disorders. Conditions such as 22q11.2 deletion syndrome that are known to be associated with a greater chance of psychiatric illness are relatively rare in the general population (the syndrome occurs at a rate of approximately 1 in 4000 births). But there will be rare situations in which it may make sense to test for a genetic syndrome in a young person who currently has no psychiatric problems—if he or she has a parent in whom the syndrome has been diagnosed. In this scenario, identifying the presence of the syndrome provides the information that there is an approximately 30% chance that psychotic symptoms will develop in the young person. It also indicates that regular psychiatric monitoring can allow early intervention strategies to be implemented if psychiatric issues do emerge.

Aside from these rare situations, the best strategy for predicting risk for psychiatric disorders is based on analysis of a detailed 3-generation psychiatric family history. While data provide empirical information about the chance for similar conditions to develop in relatives of individuals with psychiatric disorders, direct application of these figures to individuals in clinical practice can be misleading and inaccurate. However, a genetic counselor can provide accurate, individualized information about risk in the context of supportive counseling. So, for individuals with a personal or family history of psychiatric disorders who are interested in understanding the chances for other family members to be similarly affected, referral to a genetic counselor for documentation and interpretation of detailed psychiatric family history information is appropriate (see Part A: Additional Resources).

Direct-to-consumer genetic testing. Some companies are providing information about risk for psychiatric disorders, such as schizophrenia and bipolar disorder, directly to the consumer that is based on testing of a small selection of genetic variants that have been implicated in these conditions (eg, www.23andme.com). Physicians of all specialties will increasingly be confronted with
patients who need help in understanding the personal meaning and implications of these types of genetic test result. The discussion presented above (and in Part B: Additional Resources) may help physicians in this task; however, referral to genetic counseling services for patients who present with questions in this regard is also appropriate.

Disclosures:
Dr Austin is Associate Professor of Psychiatry and Medical Genetics on the Faculty of Medicine at the University of British Columbia, and is a research scientist at the BC Mental Health and Addictions Research Institute in Vancouver. She reports no conflicts of interest concerning the subject matter of this article.

References:


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