GUEST EDITORIAL

Genome-wide association studies in psychiatry research: Give it up or hold it out?

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What part does genetics play in the development of mental illnesses such as schizophrenia and bipolar disorder? In a person who appears to be healthy, is it possible to determine whether or not they may develop a mental illness using genetic testing? Although a vast amount of information has been gathered ever since the Human Genome Project was completed in 2003, these issues have not been satisfactorily resolved. This endeavor resulted in the generation of the first sequence of the human genome, and since then, hundreds of genome-wide association studies (GWASs) have been conducted in the context of various complicated diseases and disorders (1).

GWAS is a hypothesis-free method for testing associations between genetic variants with small effects called single nucleotide polymorphisms (SNPs) and characteristics in populations. Understanding the genetic underpinnings of prevalent complex disorders such as hypertension, diabetes, dementia, and schizophrenia is the primary objective of GWAS. This requires large number of samples to get appropriate statistical power and avoid producing false positive results. It is possible to achieve such huge sample sizes only by combining data from multiple cohorts at the same time. Since 2007, many different consortia have been established with the purpose of pooling datasets to achieve high sample sizes. The Psychiatric Genomics Consortium (PGC) is, as of the present time, the most comprehensive consortium in the field of psychiatric genetics (2,3). The PGC has several subgroups, including schizophrenia, major depressive disorder, bipolar disorder, attention deficiency and hyperactivity disorder, eating disorders, and cross-disorder.

In 2007, Nature released the first GWAS in the field of psychiatry; this study comprised 3000 healthy controls and 2000 patients suffering from various psychiatric conditions (4). Since then, more than three thousand studies on various psychiatric conditions and traits have been published (5). Researchers have identified several novel risk loci and pathways in a range of psychiatric disorders. The GWAS involves the examination of several hundred thousand different genomic variations. On the other hand, there are a few concerns raised about the conclusions of GWAS. First, GWAS can detect common genetic variants with small effects. However, rare genetic variants might be related to psychiatric disorders, and GWAS is not proper to study rare genetic variants. Second, GWAS may not explain familial genetic risk completely. Third, only a small amount of variance can be explained with GWAS, and its contribution to psychiatric genetics is limited. Finally, it is difficult to pinpoint the true causal relationship in GWAS.

Despite several limitations of the GWAS, it is still one of the most breathtaking research methods in genetics. Owing to GWAS, several new methodological concepts have been developed, such as Polygenic Risk Score, Mendelian Randomization, genetic correlation. Cumulative generic load of an individual can be calculated using Polygenic Risk Score by summing the risk alleles that an individual carries, weighted by their effect size in the discovery GWAS. The PRS is a single continuous variable that can be used in statistical analysis as any other.

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continuous variable. Several hypotheses can be tested using PRS. There are numerous questions that address the hypotheses related to PRS, such as “Can we predict the presence or occurrence of a psychiatric disorder with the PRS of the same disorder?” Several studies have been done to explore this question. In the PGC schizophrenia GWAS, researchers calculated PRS for schizophrenia. Across ancestries, those with a polygenic score in the top 1% of the distribution were at a sixfold increased risk of schizophrenia compared with all others, and those in the top PGS decile (i.e., the 10% of the population with the highest polygenic loading) had a 16-fold increased risk compared with those in the lowest decile (6,7). The PRS is still not a powerful tool to predict schizophrenia status in the general population. However, it might be used in people with high clinical or familial risk for the disorder to estimate diagnosis, prognosis, and treatment response.

In conclusion, GWAS has contributed a sizeable amount of knowledge to the field of psychiatric genetics. Furthermore, the novel statistical approaches developed as a direct result of GWAS have allowed us to expand our understanding of the nosology and etiology of psychiatric illnesses.

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