WHY STUDY THE GENETICS OF PSYCHIATRIC DISORDERS?

Our limited understanding of the biology underlying psychiatric disorders has stymied drug development for more than half a century. Brain development and environmental risk factors play a role in these disorders, but the high heritability of conditions such as schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD), and autism suggests that risk of developing these conditions is highly influenced by genetics. Advances in our understanding of the genome, combined with the development of new technologies and analytical methods, are giving researchers unprecedented access to brain biology and are pointing to some of the most promising drug targets seen in more than 60 years.

UNMET NEED

In aggregate, psychiatric disorders are the leading cause of disability worldwide with more than twice the impact on disease burden (as measured in disability-adjusted life years) of cancer or heart disease, which tend to affect people later in life. Because many psychiatric conditions strike early — often emerging in the teens and early 20s — the lifetime impact on individuals and society is high, both in terms of years lost to disability and financial cost. In 2010, the World Health Organization estimated the global cost of mental illness at nearly $2.5 trillion annually — a figure set to skyrocket to $6 trillion by 2030.

Despite the prevalence of psychiatric disorders and the toll they exact on the lives and families of those afflicted, their biological origins remain elusive. This is partly because the living brain poses research challenges. It is inaccessible, so researchers can’t study tissue samples as they would in diseases such as cancer or heart disease. Also, brain circuitry has proven to be far more intricate and advanced in humans than in even our closest mammalian relatives, making research in animals more challenging for the study of psychiatric disorders than for other diseases. The research community has concluded that, with few exceptions, valid disease models simply don’t exist for psychiatric disorders.

Consequently, drug development for psychiatric disorders has been at a virtual standstill for more than half a century. Existing drugs target the symptoms of the conditions rather than the root causes, and no drugs with fundamentally new mechanisms of action have been introduced in over 60 years. Lithium, for instance, the landmark treatment first used to treat manic behavior in 1949, is still the go-to treatment for bipolar disorder, and clozapine — first used in the mid-1960s — remains the prevailing antipsychotic drug. While existing classes of drugs have been made safer, with fewer side effects, no new drug types have been found.

This is not to downplay the importance of these drugs: they were a boon for patients, who had lacked pharmacological treatment options, and their discovery shifted the focus of psychiatric therapy from treating the psyche to treating the biological condition. However, few pharmacological advances have been made since those early discoveries. Despite great investment of time and resources, efforts to find new therapies have come up short. In the decade before the completion of the human genome in 2003, only 8 percent of psychiatric drug candidates tested in humans were approved. The rest failed either because of toxicity or because they were found to be no better than existing therapies.
Recognizing that few advances could be made until the biological mechanisms underlying these disorders were understood, pharmaceutical companies began to shy away from developing new treatments for psychiatric disorders, applying their resources elsewhere.

THE PROMISE OF GENOMICS

One of the most promising clues we have to the biology of psychiatric disorders is inheritance. Schizophrenia, bipolar disorder, and other devastating mental illnesses are highly heritable — meaning they run in families — suggesting that the secret to their underlying biology likely lies in the human genome. Twin studies suggest that as much as 80 percent of the risk for schizophrenia and autism, and 75 percent of the risk for bipolar disorder, can be traced to genetics.

Since the unveiling of the reference human genome a decade ago, it has become possible to systematically search for these genetic links and to begin to develop rational treatments for the disorders. Genome sequencing, which looks for rare variations and mutations in the genome, and genome-wide association studies (GWAS), which compare common variations across populations, have allowed researchers to conduct large-scale genome-wide searches both cheaply and accurately, and are yielding replicable and informative results.

These methods have not revealed a smoking gun – that is, a single gene responsible for each of these debilitating conditions. Instead, the genetic evidence has shown that schizophrenia, bipolar disorder, autism, and other heritable disorders are polygenic, with disease risk distributed across many genes. For example, more than 100 loci have been associated with schizophrenia. Moreover, the genetic variation linked to these disorders is not all inherited, and studies of de novo mutations (genetic variations that are new to an individual and are not inherited) have provided some of the most informative genetic leads to date in autism.

These molecular “parts lists” are informative in themselves, but their greatest utility may be as clues to the biology of disease. Genes can serve as tools for discovering pathways or molecular networks involved in the development of disease, and they can point to molecular mechanisms that may be viable targets for treatment. Indeed, various studies (sequencing studies, GWAS, and analyses of de novo mutations) are converging on many of the same mechanisms and pathways. A variety of schizophrenia studies, for instance, have implicated gene networks that govern synaptic function, including the voltage-gated calcium ion channel, and networks that play a role in synaptic plasticity.

These successes will enable us to understand the molecular underpinnings of psychiatric disorders. More importantly, they point to a future in which we can design drugs to rationally treat the biological causes of psychiatric illness rather than merely control the symptoms.

A BOLD APPROACH

Based at the Broad Institute, the Stanley Center for Psychiatric Research has been a leader in this genomic revolution in psychiatric research. Founded with the help of visionary philanthropists, the Broad Institute has remained deeply committed to a new paradigm for medical research that seeks to transform the understanding and treatment of disease by making its discoveries freely available, and by bringing together investigators across institutions and continents. This bold approach has enabled the global psychiatric
research community to break new ground by fostering collaboration, and by pushing the boundaries of genetic discovery for serious, heritable psychiatric disorders.

Perhaps nothing exemplifies this approach more than the Broad research community’s commitment to GWAS – a method which, despite success in other common diseases such as type 2 diabetes and Crohn’s disease, was believed to have failed for psychiatric disorders. Two years ago, the use of GWAS for psychiatric research was roundly criticized in major journals, and many researchers despaired of obtaining grants to analyze the DNA they had collected from thousands of research participants. However, scientists at the Stanley Center stubbornly held a different view: they believed that GWAS sample sizes had simply been too small to yield results, and they increased their commitment to the approach. An earlier philanthropic partnership with the Stanleys allowed them to assemble and start to analyze the largest collection of DNA samples to date for psychiatric disorders.

This extraordinary commitment is now bearing fruit. A collection of 175,000 human DNA samples from over 60 institutions and 25 countries have been amassed for psychiatric research and are helping to crack open the biology of neuropsychiatric disorders. Analysis of 80,000 of these samples so far by Broad researchers and collaborators has linked more than 100 genomic regions to schizophrenia and begun to identify specific gene mutations and the critical underlying biological processes, such as an impaired ability of neurons to communicate with each other. Significant efforts are ramping up in bipolar disorder, autism, and other conditions.

And GWAS is just one part of the picture. As the cost of DNA sequencing has plummeted, GWAS designed to identify the common genetic variants associated with these disorders are now being followed up by sequencing studies to complete the picture by identifying rare genetic variants as well.

Technology and methods developed by Broad researchers, including innovative DNA arrays and groundbreaking analytical tools, have made these breakthroughs possible and have helped lower the cost of genomic research worldwide.

In its first seven years, the Stanley Center has catalyzed a major shift in psychiatry. But the recent genetic findings are only the beginning. These early successes can be compared to findings in cancer, where the watershed discovery of cancer genes in the 1970s set off a flurry of breakthroughs that completely transformed our molecular knowledge of the disease and paved the way for fundamentally new treatments.

The Stanley Center foresees a near future in which innovative new treatments with new mechanisms of action, like those that have been developed for certain types of cancer, can be made to treat even the most complex of psychiatric disorders.

The material above references the following sources:

- Archives of General Psychiatry (schizophrenia twin study)
- American Journal of Medical Genetics (autism twin disorder; bipolar disorder twin study)
• Nature (Genome-wide association study of schizophrenia; de novo mutation study in autism; rare mutations in schizophrenia)
• Center for Statistical Genetics (exome chip DNA arrays)
• American Journal of Human Genetics (GWAS analysis tools)