BROAD INSTITUTE

**Office of Communications**
www.broadinstitute.org
T 617-714-8600
communications@broadinstitute.org
415 Main Street, Cambridge, MA 02142

# GENOMICS: REINVIGORATING THE FIELD OF PSYCHIATRIC RESEARCH

For decades, scientists have struggled to understand the biological causes of psychiatric disorders such as schizophrenia and bipolar disorder, and patients have faced both significant stigma and limited treatment options. No drugs with fundamentally new mechanisms of action have been developed since the 1950s, and pharmaceutical companies have largely given up on the pursuit. But in the last few years, advances in human genomics have given researchers unprecedented clues to brain biology and pointed to new potential drug targets. "We finally have specific genes and proteins implicated in a definitive way," said Steven McCarroll, director of genetics for the Stanley Center for Psychiatric Research at the Broad Institute. "These are important steps toward understanding the biology that underlies psychiatric illness."

The greatest contributions to the genetic dissection of psychiatric disorders have come from immense international efforts in which the Stanley Center has played a central role. Five years ago, researchers could not definitively name a single gene that contributes to schizophrenia; today, the largest international collaboration has identified 108 distinct genomic regions associated with the disorder. (The paper outlining these discoveries is in press at *Nature*.) Many of the genes in these regions are involved in critical neurobiological processes such as neuron signaling and the synaptic remodeling that underlies both brain development and learning and memory. Flaws in these processes may cause some of schizophrenia's most disabling symptoms. Now researchers are following up these leads, investigating how genetic variants contribute to schizophrenia and related illnesses such as bipolar disorder, and how their effects might ultimately be neutralized with drugs.

**Why is psychiatric disease so hard to study?**

Until now, researchers have failed to understand the biology of psychiatric disorders largely because they have not had the right tools. To study other diseases such as cancer or diabetes, scientists can take samples from relevant tissues in living patients – but they cannot easily or ethically biopsy the living brain in psychiatric patients. And while other diseases that affect the brain leave pathological evidence that can be studied after autopsy (for instance, Alzheimer's disease leaves behind a tangle of plaques in brain tissue), psychiatric conditions such as schizophrenia do not leave any such evidence.

Cell and animal models have their own limitations. It is difficult to grow neurons in the lab that biologically resemble the neurons of patients, and studying a cell in a dish, out of its natural context, can yield only so much information about a disease that affects not just single cells but whole neural networks. Current animal models also provide few reliable clues because brain circuitry is far more intricate in humans than in even our closest mammalian relatives – so comparisons between the species are indirect at best.

**To understand human disease, start with humans**

A more direct approach to studying human disease is to start with humans themselves. "If you really want to discover the molecular mechanisms of these disorders, you have to study the disorders as they actually exist in human patients," said McCarroll. "That's where the genome is key: The human genome is accessible and full of information. And thousands of patients willingly contribute their genomes to research." Scientists can compare the DNA of healthy people with that of people with a disorder in order to find genetic variants that are significantly more common in one group or the other. If the groups are similar

enough in all respects except disease status, these genetic variants can be assumed to play some role in the development of the disease in humans. Using cutting-edge tools such as induced-pluripotent stem cells and genome editing, scientists can then learn more about the variants' effects on proteins, tissues, organs, and systems by studying the variants in new cell and animal models created especially to mimic human genetic variation.

This approach is especially effective if genetic factors strongly contribute to the development of the diseases in question – and that is the case for some devastating mental illnesses, including schizophrenia and bipolar disorder. These disorders cluster in families, and studies of twins 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.

But attempts to use human genetics in the 1990s and early 2000s failed, again because of a lack of appropriate tools and approaches. One wave of studies (called "linkage analysis") looked at families with several affected individuals, hoping to find one or a few strong-acting genetic variants that appeared in patients but not healthy family members. The studies found few variants. "Complex" disorders such as schizophrenia are caused not by one or a few variants with strong effects but by hundreds or even thousands of genetic variants, many of which have relatively weak effects – and linkage studies were not capable of detecting these subtle influences.

A second wave of genetic studies in the 1990s and early 2000s looked only at genes for which there was some prior biological reason to suspect involvement. In schizophrenia, for example, more than 1,400 such studies were published, of which half focused on a set of just 18 genes. But researchers were choosing genes based on weak biological hypotheses. Ultimately, the studies' results were inconsistent, and none stood the test of time when others tried to replicate them.

By the mid-2000s, it was clear that a different approach was needed – one with direct relevance to humans, a rigorous experimental design well-suited for the study of complex disease, and the ability to search in an unbiased manner, independently of biological hypotheses. Human genomics provided that approach, allowing scientists to widen their scope to the entire genome and work not with cells or animals but directly with the human patients they ultimately hoped to help.

**Schizophrenia genes: The dam breaks**

Schizophrenia was one of the earliest subjects of genome-wide association studies (GWAS), which focused on common variants (*i.e.*, sequence variants found in more than five percent of the general population). At first, these studies too looked destined for failure. "At first there appeared to be no hits at all," said McCarroll, "Then there was one hit in 2009, at the major histocompatibility locus, which was challenging to explain. Then years went by, with few additional hits; much of the field looked at that and said, 'Well, that technique didn't work.'"

Researchers at the Stanley Center looked at the same data but came to a very different conclusion. They believed the technique was fine – the problem was that the earliest studies weren't big enough. Genome-wide association studies set a very high threshold for statistical significance to ensure that their results are not false-positive flukes. This is even more important for the study of disorders that are influenced by many subtle genetic factors, such as schizophrenia. "We thought if we analyzed enough genomes, we would turn

a corner and become successful, and we would change the conversation in the field," said McCarroll. "And that is exactly what happened."

With support from the Stanley family and other philanthropists, researchers at the Broad were able to collect samples from groups around the world and ultimately performed genotyping on one third of the 80,000 samples from schizophrenia patients and healthy control subjects used for the most recent study.

Scientists within the Stanley Center also played the lead roles in the meta-analysis of all of the genotypes that made it possible to identify the 108 independent schizophrenia-associated loci that are now known with certainty. All of these loci reach the high bar that has been set for genome-wide significance, and still more "hits" lie just below that bar and may yet turn out to be significant in larger, future studies. "Four years ago, the narrative was that psychiatric illness is so different from other diseases, that the genetic approaches that worked well in Crohn's disease and diabetes just wouldn't work in psychiatric research," said McCarroll. "But today, schizophrenia is among the diseases with the most genomic regions implicated."

The challenge now is to study these regions and others more intensely to determine how genetic variants within them contribute to disease.

**The new biology of schizophrenia**

Scientists already have a good start on this work – many of the implicated genomic regions include genes involved in a set of interlinked biological processes and pathways that are critical to brain function. Specifically, the studies point toward genes that are expressed in neurons (rather than in other brain cell types, such as glia). Some of the genomic "hits" cluster in expected genomic regions, such as around the gene *DRD2*, which encodes the dopamine receptor that is the target of all currently used antipsychotic drugs. But most of them point to new biology – and thus, potentially, to new drug targets.

Some of the first genomic regions to be implicated in schizophrenia contain genes that encode the instructions for pieces of voltage-gated calcium channels – structures that allow calcium ions to enter cells. These channels are key to many cellular activities throughout the body. In the brain, they help regulate the flow of neurotransmitters across synapses, a process that ultimately causes the synapses to change in response to information. This ability to change, or "plasticity," allows the brain to learn; abnormalities in the calcium channels can impair the brain's ability to form memories.

More recent schizophrenia studies have borne out the importance of both common and rare variants in genes that manufacture parts of voltage-gated calcium channels. One of the most heavily implicated genes, *CACNB2*, encodes a protein that controls the activity of the channels. Another, *CACNA1C*, helps make the "pore," the hole in the channel that allows calcium ions to travel in and out of cells. Two types of variants in or near this gene raise schizophrenia risk: rare ones that disrupt the gene's product (preventing it from making the right protein) and common ones that appear to regulate its activity (causing it to make the right protein at the wrong levels, at the wrong time, or in the wrong cells or tissues). Intriguingly, a different set of variants in the *CACNA1C* gene consists of highly deleterious mutations that cause the rare disease known as Timothy syndrome, which affects cellular calcium channels throughout the body (symptoms include lethal cardiac arrhythmia, cognitive deficits, and immune deficiency). But the common schizophrenia-associated *CACNA1C* variants do not cause cardiac or immune problems – in fact, they do not appear to be damaging at all unless they co-occur with other schizophrenia-associated risk variants.

Another emerging biological insight is the importance of the "post-synaptic density" (PSD), a neuronal structure that facilitates signaling by ensuring that neurotransmitter receptors are properly positioned to interact with their neurotransmitters. (Because the signaling process is key to synaptic plasticity, the PSD ultimately helps regulate that process, too.)

Yet another class of genes now implicated in schizophrenia is involved in glutamate signaling. (Glutamate is the most common neurotransmitter in the brain.) Both common and rare variants in schizophrenia patients affect glutamate receptor genes. This finding may be consistent with the longstanding observations that NMDA receptor blocking drugs, such as ketamine and phencyclidine, can mimic some symptoms of schizophrenia.

At this early stage it would be wrong to draw firm conclusions; nonetheless these three broad classes of genes – calcium channel components, post-synaptic density genes, and glutamate receptors – all play roles in the synapses' ability to respond to neurological signals by remodeling themselves. The new *Nature* paper confirms the importance of variants involved in glutamate signaling and more. There is still a long way to go, but this work has already provided new biological insights and potential clues to new therapeutics.

**Bipolar disorder, autism, and other conditions**

Scientists have also made strides in understanding other psychiatric disorders. They have identified scores of genomic regions that are involved in autism and homed in on specific variants that affect genes involved in key processes such as neuron growth, gene expression, and the formation of channels that allow sodium ions to cross cell membranes. They are also beginning to identify genomic regions involved in bipolar disorder. The sample sizes of these studies are much smaller than those of the schizophrenia studies – but the analysis of many additional samples is pending. Researchers are confident that they will link many more regions to bipolar disorder once they have analyzed enough samples. Moreover, in a new collaboration aimed at sequencing all of the protein coding genes for schizophrenia, bipolar disorder, autism, and several other psychiatric disorders, the Stanley Center has partnered with more than 60 institutions worldwide, and has already received more than 175,000 DNA samples.

In addition, the scientists' work has also prodded them to rethink the way they classify and approach schizophrenia, autism, and bipolar disorder – a timely shift given increasing dissatisfaction with the traditional mental illness categories as listed in the DSM-5. For instance, there appear to be numerous links between schizophrenia and autism – some patients with both disorders may be missing the same chromosomal chunks, or carrying other identical types of *de novo* (spontaneous) mutations. In both cases, there is evidence that problems with neuronal signaling and plasticity are to blame. Of particular interest for both schizophrenia and autism is the *FMR1* gene, which regulates the growth and function of synapses. Damaging mutations in *FMR1* have been known for more than 20 years to cause Fragile X syndrome, a rare, single-gene form of intellectual disability. Genomic studies are now revealing that biological pathways involving *FMR1* may also contribute to both autism and schizophrenia – scientists searching for mutations in genes that interact with *FMR1*'s protein have found disproportionate numbers of such mutations in patients with either disorder.

Scientists are also "rethinking bipolar disorder as a category," said McCarroll. In some but not all patients, bipolar highs and lows are accompanied by psychosis – and in these patients, the genetics of the disorder more closely resemble those of schizophrenia. For instance, the same common variants that appear to

regulate the activity of *CACNA1C* and *CACNB2* – the calcium channel genes implicated in schizophrenia – also raise risk of bipolar disorder with psychosis by about 15 percent. But they are not implicated in bipolar patients who do not suffer psychosis. "It's estimated that as much as two-thirds of the common-variant influences may be shared between bipolar disorder and schizophrenia," said McCarroll, "but not if you're looking at bipolar patients who don't have psychosis. It starts to raise questions: maybe we should think about [bipolar disorder] as two different illnesses depending on whether psychosis is a feature or not." Maybe, he adds, one version has more in common with schizophrenia, and the other has more in common with depression.

"Those are the kinds of questions it will be possible to ask with more genetic data," McCarroll said. "I think now we're comfortable saying, 'Look where we are in schizophrenia – let's go back to these other diseases and catch up.'"

**Further reading**


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