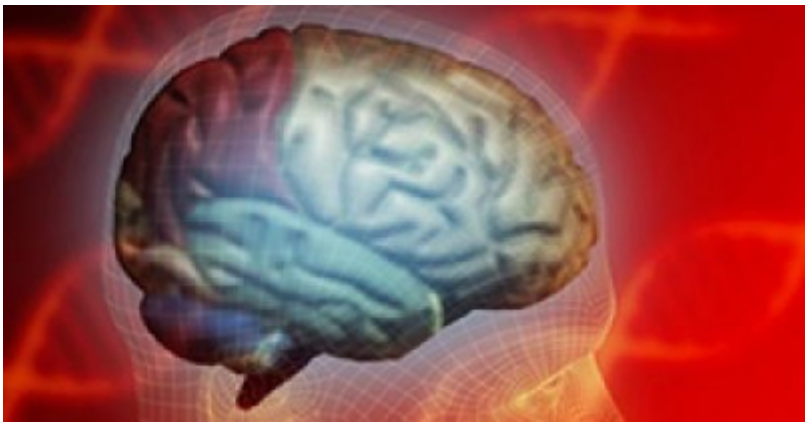
Collaborating to unravel clues about neuropsychiatric diseases [1]

Discovery [2]

After decades in the doldrums, drug discovery in neuropsychiatry could soon experience a renaissance. At long last, scientists have clues about the molecular underpinnings of genetically-complex diseases such as schizophrenia and autism. But they must convert the clues into actionable knowledge before devising new treatments.



“We’ve reached a milestone in the genetic analysis of complex neuropsychiatric diseases,” says Chris Wilson, Senior Investigator II in Neuroscience at the Novartis Institutes for BioMedical Research (NIBR). “We finally have a list of genes that might be involved, thanks to genome-wide association studies. The challenge now is to go the next step to understand individual targets from that list for drug discovery.”

To accomplish this daunting task, NIBR is collaborating with the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, which was instrumental in developing the list. The NIBR-Broad team will explore hits for autism, schizophrenia, and bipolar disorder, interrogating particular genes to determine their role in disease. They’ll expand the investigation to ADHD (attention deficit hyperactivity disorder) and major depression in a later phase of the project.

“At first glance, it looks like many of the genes coalesce into molecular pathways, which is very exciting,” says Steve Hyman, Director of the Broad Institute’s Stanley Center and Distinguished Service Professor of Stem Cell and Regenerative Biology at Harvard University. In addition, there’s considerable overlap between the diseases. “It’s not like we’re throwing darts at the genome,” he says.

The two groups bring complementary skills to this in-kind project. The Stanley Center employs experts in human genetics, the very scientists who generated the data that now requires

analysis. They have deep insights into the preliminary list of genes. And NIBR knows how to aggregate genetic information into pathways, with capabilities in high-throughput biology to do the job right.

“Together, we have the people, experience, and resources to map the molecular architecture of these diseases,” says Dan Curtis, a Director in Neuroscience at NIBR. “This project should provide a springboard for drug discovery in the new Neuroscience group.”

Catching the next wave

The last pharmaceutical revolution in psychiatry occurred in the 1950s, powered by a series of serendipitous discoveries. Researchers stumbled across substances that affected mental activity and behavior, leading to the development of psychotropic drugs, including chlorpromazine, imipramine, and iproniazid. As a result, treatment for schizophrenia, depression and bipolar disorder shifted from specialized hospitals to the community setting. But progress stalled when the lucky streak ended.

Leaders at NIBR and the Broad don’t want to leave the next wave of treatments to chance. The unmet medical need is too great.

Brain disorders take a significant toll on individuals, families, and communities. The 2010 Global Burden of Disease Study (published in The Lancet) revealed that they’re the leading cause of disability globally, both in the developed and developing world. Existing pharmacologic treatments, widely accepted to be inadequate, address the symptoms of neuropsychiatric diseases rather than the underlying causes.

“The treatments we have are nowhere near where they need to be,” says Ricardo Dolmetsch, Global Head of Neuroscience at NIBR. “For some conditions, like the core social disability of autism, there are no pharmacologic treatments at all.”

The current state of affairs is ironic, considering that the diseases in question are highly heritable, with genetic differences—rather than environmental factors—explaining much of the neurodevelopmental variation within the population. The heritability of autism, for example, approaches 90 percent, according to some twin studies. In theory, scientists should be able to use genetics to identify disease mechanisms and then develop treatments based on that information. Unfortunately, the solution is not so simple.

Common variants versus rare mutations

The two proposed genetic models of psychiatric disease seem to be at odds. The first assumes that common variants of genes drive disease, with many genes exerting subtle effects that add up to trouble. The second lays the blame on rare mutations, with just one or two aberrant genes wreaking havoc on the brain.

In reality, both models are probably correct, and they complement each other. Some cases of psychiatric disease are due to combinations of common variants while others are due to rare mutations, including de novo mutations that were not present in a patient's parents. But the rare variants may not cause disease unless they occur in the context of at least some of the "risky" common variants. It's important to uncover both.

Scientists use genome-wide association studies (GWAS) to identify common variants that may play a role and DNA sequencing—including trio sequencing—to pinpoint rare mutations. GWAS involves scanning the genomes of patients and controls for ancient genetic markers that arose and spread through the human population when it was still relatively small some 50,000 to 100,000 years ago. Trio studies require deep DNA sequencing of patients and their parents (i.e., trios) to identify disease-causing de novo mutations that are not inherited, but occur by chance. Down's syndrome, for example, occurs when a child gets an extra chromosome 21 and is an extreme version of a de novo change.

The NIBR-Broad team uses information from both types of studies to probe the molecular mechanisms of psychiatric disease. Knowledge of de novo mutations helps them sort through GWAS hits, providing hints about which common variants really matter.

Coping with complexity

Neuropsychiatric diseases, especially the milder forms of them, seldom stem from a single mutation or variant of a gene. Instead, recent studies suggest a complex model of pathogenesis, with many common variants of genes exerting subtle effects on the brain that add up to trouble.

"There's an ongoing debate about the role of common variants versus de novo mutations, which aren't present in the patient's parents," says Wilson. "Both are important, but the common variants are probably bigger players in terms of the total patient population." (See sidebar on common variants versus rare mutations.)

Genetic technologies have matured to the point that scientists can link common variants to disease, and, importantly, studies are finally powered properly. The latest analysis of schizophrenia, published in Nature Genetics in October 2013, includes data from tens of thousands of individuals and conclusively links numerous regions of the genome to the disease. The Broad Institute's Stanley Center is one of the leaders of this most recent study.

Due to the new collaboration, NIBR scientists were able to work with researchers at the Stanley Center to review hits from all of the recent published studies. They recently prioritized the candidates, selecting a number of genes for further analysis. Next, they split into teams and divvied up the shortlist.

The teams are now in the midst of developing assays to probe candidate genes and determine their roles. The complexity of neural circuits presents a major—yet surmountable—challenge. Each neuron is embedded in a network that ultimately contributes to higher brain function. In addition to studying how genes impact signaling within cells, the teams must monitor connections between cells.

Luckily, recent advances in genome editing, induced pluripotent stem cells, and

optogenetics—a technology that involves using light to manipulate individual neurons—make it possible to study neural circuits. They will aid assay development.

“We finally have this amazing genetic information, plus we have the tools and technologies to make sense of it,” says Dolmetsch.

When asked about quick wins, Hyman counsels patience. “This is going to take some time, but the unmet medical need is stunning,” he says. “This is the first time we’ve had molecular clues, and shame on us if we don’t exploit them.”

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