

Dana Guide to Brian Health: Schizophrenia

News: Dysfunctional Brain-Cell Protein Could Underlie Multiple Psychiatric Disorders — Researchers have proposed that abnormalities in a nervous-system protein known as DISC1 might be a cause of many cases of schizophrenia, bipolar disorder and depression. (July 2008)

Genetic Study Gives New Insight into Schizophrenia

By Kayt Sukel

July 2008

A recent study by researchers at the University of Washington and Cold Spring Harbor Laboratories suggests that random errors in the genome, many of them targeting glutamate pathways, may contribute to schizophrenia. The results have potential implications for how scientists should study the neurobiological effects behind the disorder as well as how they approach the design of new drug and other interventions.

The challenges of finding gene candidates in psychiatric disorders

Despite technological advances that allow researchers to more closely examine the human genome, what they have found has not, as yet, helped us understand much more about how psychiatric disorders develop. But despite those challenges, as genome-wide studies become more widespread, scientists expect that somewhere in the vastness of the human genome is a clue to understanding such illnesses as schizophrenia.

“One of the biggest challenges is that a disease like schizophrenia is very complex. It’s defined by a variety of objective clinical observations and subjective experiences,” says [Steven P. Hamilton](#), associate professor at the University of California, San Francisco, who studies the genetic causes of mood disorders. “The people who share the same diagnosis may have a very different clinical picture and differing prognostic outcome.” And these different outward signs and symptoms may have different genetic and other causes.

Similarly, though researchers believe that genes do influence the development of schizophrenia, it is becoming clearer that more than one gene may be playing a part.

“The genes may play, individually, very small roles in the development of the disease,” says Hamilton. “The combination of those genes, causing the disorder, may differ from individual to individual and definitely from population to population.”

Rare genomic events

Studying the DNA from 150 people with schizophrenia and 268 controls, Jon McClellan and colleagues at the University of Washington found that people with schizophrenia have more genetic errors in their DNA—deletions and duplications across multiple genes. But even though those errors occurred on different genes, many of them were involved in glutamate pathways, critical to the brain’s normal development. [Their research was reported in the March 27 edition of *Science*.](#)

“All the errors we found in patients were in different mutations in different spots involving different genes,” says McClellan. “And if that holds true, then most cases of people with schizophrenia have a different genetic cause for it.”

As such, the researchers believe that from a genetic standpoint, schizophrenia can develop in several different ways. The errors may occur in different places but many seem to be involved in pathways that can derail the organization of normal brain development. This finding has far-reaching implications for how the disorder is studied.

“Right now, most research is to look for similar markers in certain genes of interest,” says McClellan. “And if our findings are correct, then those current approaches just won’t work and find what we’re looking for.”

Looking for the right interventions

In 2005, the psychiatric community was stunned by the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that showed that second-generation anti-psychotic medications were not as effective as their predecessors.

[Jeffrey A. Lieberman](#), chairman of psychiatry at the Columbia University College of Physicians and Surgeons in New York, cites three reasons researchers were surprised.

"We had been convinced they [the new drugs] were superior," he says. "Partly due to the initial results, partly on our own hopes and expectations that better medications would come along and also, to a large degree, [due to] aggressive marketing by the pharmaceutical companies." None of the drugs was developed based on genetic research; instead they were modifications of existing anti-psychotic drug formulas.

Developing drugs based on new genetic approaches does hold promise, Lieberman says, but he encourages caution.

"We need to make sure that the susceptible genes are real and not scurrilous and that the studies are well-designed and large enough," Lieberman says. "But the most important thing is that we understand the underlying biology. And in most cases, that's a painstaking, arduous process."

He cites the genetic research in diseases with a simple genetic cause. "We've identified the genes in diseases like Huntington's and cystic fibrosis. They have one gene that causes the disease and full penetration where if you have the gene, you get the disease," he says. "But even though those genes were identified 10 years ago, we still don't understand exactly how they work. We still don't have a treatment."

McClellan agrees that a great deal of work lies ahead. "One of the challenges in psychiatry is understanding just how the normal brain works and develops," he says. "Any time you find a gene in a disorder, it may take a lifetime of study to figure out how it works normally."

More individuals, more genes to study

Hamilton says that pessimists may find the University of Washington multiple-gene finding disappointing because no single precursor genetic defect was discovered. But he finds reason to be optimistic.

"These studies inform our understanding of the biology by revealing genes, though they may play small roles," he says. "But even a gene that only plays a small role may still be important when targeted for treatment."

Other researchers also are optimistic. [William Byerley](#), a professor in residence at University of California, San Francisco, who also is examining the role of genes in schizophrenia, says that as genome-wide studies are able to tap into larger sample sizes, we'll have a better understanding of how the genes lead to the disorder.

"We need at least 25,000 DNA samples; some people even say that we need 50,000 to 100,000 genomes to get there," he says. "And that's going to take a while to get. But I think we do have it covered, ultimately."

Although sample size is important, McClellan is more focused on future technology.

"The technology has already gotten better," he says. "We can now look for even smaller errors, see where they land and what genes they break. With that we can continue to find mutations, continue to flesh out how neurobiological pathways work in the first place. And hopefully, as you sort those things out, you can understand how treatment can work better."

About Kayt Sukel

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