

Schizophrenia gene mutation found; target for new drugs

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In a major advance for schizophrenia research, an international team of scientists, led by Jonathan Sebat, PhD, assistant professor of psychiatry and cellular and molecular medicine at the University of California, San Diego School of Medicine, has identified a gene mutation strongly linked to the brain disorder – and a signaling pathway that may be treatable with existing compounds.

The work poses significant and immediate implications for neurobiology and the treatment of [schizophrenia](#) because the gene identified by the researchers is an especially attractive target for drug development.

"In some ways, this is the kind of gene that the pharmaceutical industry has been waiting for," said Sebat, who is also chief of the Beyster Center for Molecular Genomics of Neuropsychiatric Diseases and a member of the Institute for Genomic Medicine, both at UC San Diego. "Its activity can be modulated by synthetic peptides; and some have already been created."

The findings are published in the Feb. 3, 2011 online issue of the journal *Nature*.

Schizophrenia is a chronic, severe and disabling brain disorder, with symptoms that include hallucinations, delusions and thought disorders. It is believed to be caused by environmental and genetic factors, most notably the latter: the illness occurs in 1 percent of the general population, or 10 percent of people who have a first-degree relative with

the disorder, such as a parent or sibling.

In previous work, Sebat and collaborator Mary-Claire King, a professor of medical genetics at the University of Washington, discovered that rare mutations at many locations in the human genome resulted in significantly higher risk of schizophrenia. These mutations consisted of copy number variants or CNVs – a type of genetic variation in which the number of copies of a gene differs between individuals. The findings were the first conclusive evidence that rare mutations can cause schizophrenia, but they did not identify the specific [genes](#) involved.

The latest study goes much further. Researchers scanned for CNVs in the genomes of 8,290 individuals with diagnosed cases of schizophrenia and 7,431 healthy controls. "We found very strong links to multiple sites in the genome," said Sebat. "Some had been picked up before in earlier studies, but we uncovered a very important new finding: duplications at the tip of chromosome 7q were detected in individuals with schizophrenia at a rate 14 times higher than in healthy individuals. These CNVs impact a gene that is important for brain development – the neuropeptide receptor VIPR2."

Formally known as the Vasoactive Intestinal Peptide Receptor 2, VIPR2 is expressed in the nervous system, including in the brain, blood vessels and gastrointestinal tract. Previous studies have shown that VIPR2 helps to regulate the formation and activity of neurons in the brain. In mice, VIPR2 also has been found to play important roles in behavioral processes, including learning and timing of daily activity.

Sebat and colleagues measured expression of the VIPR2 gene in blood cells from the patients, and they found that individuals with mutations had greater expression of VIPR2 and greater activity of the receptor. "We concluded that the effect of the causal mutations is to raise the volume on the VIP signaling pathway," said Sebat.

"This discovery might be the best target yet to come out of genetic studies of mental illness." said Sebat. "This is what genomic medicine is all about, finding the relevant genes and using this genetic information to come up with a possible strategy for treatment."

Sebat said the next step will be to test whether compounds like these have beneficial effects in mice and in cultured human cells that carry the VIPR2 [gene mutation](#).

Provided by University of California - San Diego

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