

Schizophrenia Gene Mutation Found; Target for New Drugs

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Scott LaFee

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."

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.

Researchers involved are Vladimir Vacic, Stanley Center for Cognitive Genomics, Cold Spring Harbor Laboratory and the Department of Computer Science, Columbia University; Shane McCarthy, Stanley Center for Cognitive Genomics, Cold Spring Harbor Laboratory; Dheeraj Malhotra, Beyster Center for Genomics of Psychiatric Diseases, UCSD Department of Psychiatry and Stanley Center for Cognitive Genomics, Cold Spring Harbor Laboratory; Fiona Murray, UCSD departments of Medicine and Pharmacology; Hsun-Hua Chou, Beyster Center for Genomics of Psychiatric Diseases and UCSD Department of Psychiatry; Aine Peoples, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine and Department of Psychiatry, Trinity College Dublin, Ireland; Vladimir Makarov and Seungtae Yoon, Seaver Autism Center and Department of Psychiatry, Mount Sinai School of Medicine, New York; Abhishek Bhandari, Beyster Center for Genomics of Psychiatric Diseases, UCSD Department of Psychiatry, Stanley Center for Cognitive Genomics, Cold Spring Harbor Laboratory; Roser Corominas and Lilia M. Iakoucheva, UCSD Department of Psychiatry; Olga Krastoshevsky, Verena Krause and Deborah L. Levy, McLean Hospital, Belmont, MA; Verónica Larach-Walters, Universidad Andrés Bello, Santiago, Chile; David K. Welsh, UCSD Department of Psychiatry, UCSD Center for Chronobiology, Veterans Affairs San Diego Healthcare System; David Craig, Neurogenomics Division, Translational Genomics Research Institute; John R. Kelsoe, UCSD Department of Psychiatry, UCSD Institute for Genomic Medicine, Veterans Affairs San Diego Healthcare System; Elliot S. Gershon, Department of Psychiatry and Behavioral Neuroscience, The University of Chicago; Suzanne M. Leal, Department of Molecular and Human Genetics, Baylor College of Medicine; Marie Dell Aquila, UCSD Division of Medical Genetics, UCSD Department of Medicine; Derek W. Morris, Michael Gill and Aiden Corvin, Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine and Department of Psychiatry, Trinity College Dublin, Ireland; Paul A. Insel, UCSD Department of Pharmacology, Veterans Affairs San Diego Healthcare System; Jon McClellan, Department of Psychiatry, University of Washington; Mary-Claire King, departments of Genome Sciences and Medicine, University of Washington; Maria Karayiorgou, Department of Psychiatry, Columbia University; and Lynn E. DeLisi, Department of Psychiatry, Boston VA Healthcare System and Harvard Medical School.

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Media Contact: Scott LaFee, 619-543-6163, slafee@ucsd.edu

