Scientists discover schizophrenia gene roles in brain development

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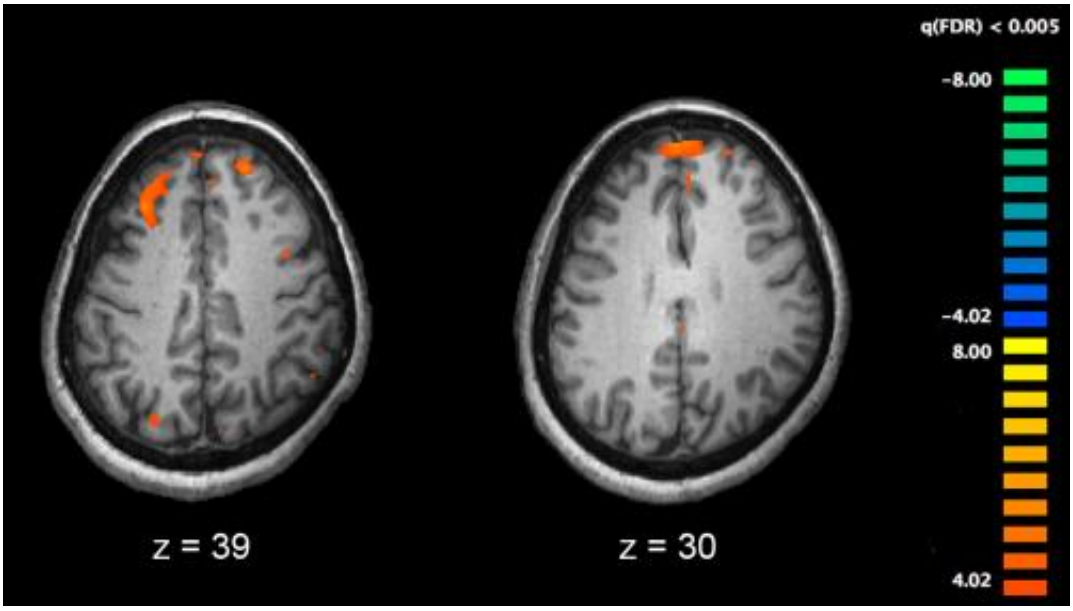

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

A USC research team identified 150 proteins affecting cell activity and brain development that contribute to mental disorders, including schizophrenia, bipolar condition and depression.

It's the first time these molecules, which are associated with the disrupted-in-schizophrenia 1 (DISC1) protein linked to mental disorders, have been identified. The scientists developed new tools involving stem cells to determine chemical reactions the proteins use to influence cell functions and nerve growth in people.

"This moves science closer to opportunities for treatment for serious mental illness," said Marcelo P. Coba, the study author and professor of psychiatry at the Zilkha Neurogenetic Institute at the Keck School of Medicine of USC.

The findings appear in *Biological Psychiatry*.

Schizophrenia affects less than 1 percent of the U.S. population, but has an outsized impact on disability, suicide and premature deaths.

The DISC1 gene was linked to schizophrenia nearly 20 years ago. It controls how nerve cells called neurons develop, as well as how the brain matures. DISC1 also directs a network of signals across cells that can contribute to the disease. Scientists say errors in these chemical reactions contribute to schizophrenia.

But the identity of proteins that DISC1 can regulate is poorly understood, prompting the USC researchers and colleagues from the State University of New York Downstate Medical Center to undertake the research. The challenge was to simulate conditions inside the human brain, Coba explained.

Using stem cells, they conducted assays resembling habitat where DISC1 does its work. Then, they used gene editing to insert a molecular tag on DISC1, allowing them to extract it from brain cells and identify the proteins with which it associates.

Identifying the proteins that interact with DISC1 in brain cells could lead to understanding how the risk factors for psychiatric diseases are connected to specific molecular functions, Coba explained. The discovery enables researchers to determine specific processes that differ in patients suffering from specific mental illnesses.

"This gives researchers specific trails to follow within cells from both healthy patients and those diagnosed with disorders," Coba said.

Schizophrenia is one of the top 15 leading causes of disability worldwide. People with schizophrenia live an average of nearly 29 years less than those without the disorder, according to the National Institutes of Mental Health (NIMH).

The illness is often accompanied by conditions such as heart disease and diabetes, which contribute to the high premature mortality rate among people with schizophrenia. About 5 percent of people with schizophrenia die by suicide, a rate far greater than the general population, with the highest risk in the early stages of illness, according to the NIMH.

More information: Brent Wilkinson et al, Endogenous Cell Type-Specific DISC1 Interactomes Reveal Protein Networks Associated to Neurodevelopmental Disorders, *Biological Psychiatry* (2018). DOI: 10.1016/j.biopsych.2018.05.009

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