Rare genetic mutations occur more often in schizophrenia patients, researchers find

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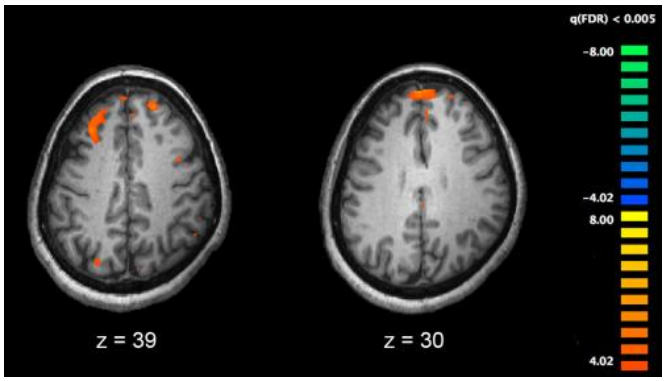

Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown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

A new study by UCLA scientists adds to the understanding of the genetic architecture of schizophrenia.

Past research has shown the impact of commonly occurring genetic variants on a person's risk of developing schizophrenia. This new study focused instead on rare coding mutations that affect protein function. It found that patients with schizophrenia have a higher-than-normal share of these mutations.

"While we cannot point to specific mutations that play a causal role in schizophrenia, we show that schizophrenia patients collectively have more of these mutations than unaffected individuals," said Loes Olde Loohuis, the study's first author and a postdoctoral fellow at UCLA's Center for Neurobehavioral Genetics. The center is part of the university's Jane and Terry Semel Institute for Neuroscience & Human Behavior.

The findings are reported in the July 15 edition of *Nature Communications*.

"Genes that are affected by these mutations play a key role in fetal brain development," said Roel Ophoff, the study's senior author and a principal investigator at the Center for Neurobehavioral Genetics. "Our finding further supports the hypothesis that schizophrenia is a disorder that may originate during the early stages of brain development."

A professor of psychiatry and human genetics, Dr. Ophoff has conducted research on the genetic basis of schizophrenia for the past decade. He is also one of the founding members of the Psychiatric Genomics Consortium's schizophrenia study group. The consortium is an international collaboration of researchers investigating the genetics of schizophrenia and related disorders.

Schizophrenia affects some 2 to 3 million people in the U.S.—about 1 percent of the population. It is characterized by hallucinations, delusions and disorganization, and can take a tremendous toll on patients and their families. Schizophrenia can cause a significant loss in quality of life, including unemployment and estrangement from loved ones. A better understanding of the causes of the disease may lead to better options for treating it.

Ophoff and his colleagues used an array-based technology to screen for 250,000 DNA coding variants in more than 1000 schizophrenia patients from the Netherlands and compared these samples to those from unaffected individuals. They found that the patients with schizophrenia had more of these variants than patients without schizophrenia. The researchers confirmed these findings in another cohort consisting of more than 13,000 schizophrenia patients and control subjects from the UK.

"Even though it's well-known that schizophrenia has a large genetic component, the specific biological mechanisms at work are not well understood," Ophoff said, "Our research shows that rare coding variants throughout the human genome also contribute to this complex genetic architecture."

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