Genetic analysis finds rare, damaging variants contribute to the risk of schizophrenia

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(Medical Xpress)—Via genetic analysis, a large international team of researchers has found rare, damaging gene variants that they believe contribute to the risk of a person developing schizophrenia. In their paper published in the journal *Nature Genetics*, the researchers describe their study, which involved analyzing data from a wide variety of sources, comparing what they found and describing their findings.

Schizophrenia is a brain disorder that impacts a person's ability to interpret reality. It is believed to have a genetic cause, though the parts of the genome that are involved have yet to be found. In this new effort, the researchers report on their data sources, what each contained, and the approach they took to organizing and analyzing all the information in an attempt to learn more about the disorder and its origins in the brain.

The study consisted of comparing data from other efforts that had produced statistics on exome sequences, copy number variant patterns, and de novo mutation profiles from thousands of schizophrenia patients and controls—the exome is the part of the genome that, quite naturally, includes all of the exons, which comprise parts of the gene that wind up in RNA. The group also compared the same data with similar statistics gathered for other neurological disorders such as autism.

All told, the researchers used exome sequence data from 4,133 schizophrenia patients and 9,300 controls from the general population—and de novo mutations that had been observed in 1,077 family trios. They further added single nucleotide variant profiles from 6,882 schizophrenia patients and another 11,225 people without any signs of neurological disorders.

After conducting the analysis, the researchers report that the schizophrenia patients in the study (and likely such patients in general) had variations in 3,488 genes, which prior research has shown to be intolerant to loss of function. They also report that such mutations may occur alone or alongside mutations that may account for intellectual disability. The team therefore believes they have found mutations in a part of the genome that may at least be partly behind the development of schizophrenia.

More information: Tarjinder Singh et al. The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability, *Nature Genetics* (2017). DOI: 10.1038/ng.3903

Abstract

By performing a meta-analysis of rare coding variants in whole-exome sequences from 4,133 schizophrenia cases and 9,274 controls, de novo mutations in 1,077 family trios, and copy number variants from 6,882 cases and 11,255 controls, we show that individuals with schizophrenia carry a

significant burden of rare, damaging variants in 3,488 genes previously identified as having a near-complete depletion of loss-of-function variants. In patients with schizophrenia who also have intellectual disability, this burden is concentrated in risk genes associated with neurodevelopmental disorders. After excluding known risk genes for neurodevelopmental disorders, a significant rare variant burden persists in other genes intolerant of loss-of-function variants; although this effect is notably stronger in patients with both schizophrenia and intellectual disability, it is also seen in patients with schizophrenia who do not have intellectual disability. Together, our results show that rare, damaging variants contribute to the risk of schizophrenia both with and without intellectual disability and support an overlap of genetic risk between schizophrenia and other neurodevelopmental disorders.

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