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Largest Study of its Kind Finds Rare Genetic Variations Linked to Schizophrenia

Genome-wide scan of more than 41,000 people reveals “copy number variants” that carry a significant risk for psychiatric illness

Many of the genetic variations that increase risk for schizophrenia are rare, making it difficult to study their role in the disease. To overcome this, the Psychiatric Genomics Consortium, an international team led by Jonathan Sebat, PhD, at University of California San Diego School of Medicine, analyzed the genomes of more than 41,000 people in the largest genome-wide study of its kind to date. Their study, published November 21 in *Nature Genetics*, reveals several regions of the genome where mutations increase schizophrenia risk between four- and 60-fold.

These mutations, known as copy number variants, are deletions or duplications of the DNA sequence. A copy number variant may affect dozens of genes, or it can disrupt or duplicate a single gene. This type of variation can cause significant alterations to the genome and lead to psychiatric disorders, said Sebat, who is a professor and chief of the Beyster Center for Genomics of Neuropsychiatric Diseases at UC San Diego School of Medicine. Sebat and other researchers previously discovered that relatively large copy number variants occur more frequently in schizophrenia than in the general population.

In this latest study, Sebat teamed up with more than 260 researchers from around the world, part of the Psychiatric Genomics Consortium, to analyze the genomes of 21,094 people with schizophrenia and 20,227 people without schizophrenia. They found eight locations in the genome with copy number variants associated with schizophrenia risk. Only a small fraction of cases (1.4 percent) carried these variants. The researchers also found that these copy number variants occurred more frequently in genes involved in the function of synapses, the connections between brain cells that transmit chemical messages.

With its large sample size, this study had the power to find copy number variants with large effects that occur in more than 0.1 percent of schizophrenia cases. However, the researchers said they are still missing many variants. More analyses will be needed to detect risk variants

with smaller effects, or ultra-rare variants.

“This study represents a milestone that demonstrates what large collaborations in psychiatric genetics can accomplish,” Sebat said. “We’re confident that applying this same approach to a lot of new data will help us discover additional genomic variations and identify specific genes that play a role in schizophrenia and other psychiatric conditions.”

Core funding for the Psychiatric Genomics Consortium was provided by the National Institutes of Health (grant U01MH094421). For the complete study, including full list of co-authors and institutions involved, please see: nature.com/ng/journal/vaop/ncurrent/full/ng.3725.html

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