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Genes found for schizophrenia are involved in brain signaling

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By analyzing the genomes of patients with schizophrenia, genetics researchers have discovered numerous copy number variations—deletions or duplications of DNA sequences—that increase the risk of developing schizophrenia. Significantly, many of these variations occur in genes that affect signaling among brain cells.

"When we compared the genomes of patients with schizophrenia to those of healthy subjects, we found variations in genes that regulate brain functions, several of which are already known to be perturbed in patients with this disorder," said study leader Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "Although much research remains to be done, detecting genes on specific pathways is a first step to identifying more specific targets for improved drug treatments."

The research appears in the Proceedings of the National Academy of Sciences, published online this week.

A devastating psychiatric disorder that affects an estimated 1.5 percent of the population, or millions of Americans, schizophrenia may include hallucinations, disorganized speech, abnormal thought processes and other symptoms. It typically becomes apparent in late adolescence or early adulthood. Patients often have a family history of schizophrenia, and scientists believe the disorder results from an interaction of genetic predisposition and environmental effects.

Hakonarson and colleagues compared DNA samples from a total of 1,735 adult patients with schizophrenia to DNA from 3,485 healthy adult subjects, using highly automated genotyping tools. They used a whole-genome approach, covering the full set of genetic material from each individual, following their first analysis with a replication study.

The study team found copy number variations (CNVs) in or near genes that play important roles in the brain. Among those genes were CACNA1B and DOC2A, both of which carry the codes for proteins that use calcium signals to help control how neurotransmitters are released in the brain. Two other genes, RET and RIT2, are members of another signaling gene family known to be involved in brain development.

The researchers found that the genes and signaling systems linked to schizophrenia had some overlap with those for autism and for attention-deficit hyperactivity disorder. In fact, the current study found deletions in the same region of chromosome 16 as that found in a CNV study of autism spectrum disorders that Hakonarson led in 2009. "Although different brain regions may be affected in these different neuropsychiatric disorders, these overlaps suggest that there may be common features in their underlying pathogenesis," said Hakonarson. "These genes affect synaptic function, so deletions or duplications in those genes may alter how brain circuits are formed."

Hakonarson said future studies will investigate how these CNVs and other CNVs yet to be discovered may alter brain function. Ultimately, he added, better understanding of signaling pathways in the brain may enable researchers to devise better drugs for schizophrenia, drugs that can selectively act on those biological pathways, with better efficacy and fewer side effects for patients.

More information: "Strong synaptic transmission impact by copy number variations in schizophrenia," Proceedings of the National

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