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Researchers develop new genetic method and identify novel genes for schizophrenia

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Scientists at the Zucker Hillside Hospital campus of the Feinstein Institute for Medical Research have identified nine genetic markers that can increase a person's risk for schizophrenia. In a study published this week in the *Proceedings of the National Academy of Sciences*, the research team uncovered original evidence that this disabling brain disease can be inherited in a recessive manner. A recessive trait is one that is inherited from both parents.

"If a person inherits identical copies of these markers from each parent, his or her risk for schizophrenia increases substantially," said Todd Lencz, PhD, associate director of research at Zucker Hillside and the lead author of the study. "If these results are confirmed, they could open up new avenues for research in schizophrenia and severe mental illness," said Anil Malhotra, MD, director of psychiatric research at Zucker Hillside and senior investigator of the study.

The scientists developed a complex mathematical approach called whole genome homozygosity association (WGHA) that provides a new way of analyzing genetic information. It enables scientists to simultaneously look at genetic information derived from the patient's mother and father, and identify pieces of chromosomes that are identical. They tested genetic material from 178 patients and 144 controls.

It has been the prevailing view in psychiatric genetics that there are probably dozens, if not hundreds, of genetic variations that could lead to schizophrenia, but each gene has a small effect. It is the wrong mix of

many genes, plus unknown environmental stressors, that trigger the onset of symptoms. One in every 100 people suffer from schizophrenia, a condition marked by episodes of hallucinations, delusions and disordered thinking.

The new findings suggest another scenario, at least for a subset of patients. Dr. Lencz and his colleagues identified nine regions along the chromosomes that might play a large role in triggering the disease when two identical variants are inherited. Four of these regions contain genes that have been previously associated with schizophrenia, providing validation for the technique. The remaining five regions provide an additional set of newly discovered genetic risk factors. Many genes located in these regions are involved with the structure and survival of neurons.

In genetic parlance, several of these markers demonstrated high penetrance, meaning that their effect on disease risk was large. In the study, 81 percent of the schizophrenia patients had at least one of these recessive markers, compared to only 45 percent of the normal control group. Nearly half of the patients had two or more compared to 11 percent of the controls. And while no one in the healthy group had identical chunks of chromosomes in four or more of these risk regions, subjects with more than three demonstrated a 24-fold increased risk of developing schizophrenia. “This type of analysis could greatly improve our ability to diagnose schizophrenia and clarify specific subtypes of patients,” Dr. Lencz said. “The critical next step is confirming these results in independent datasets.”

“What is most exciting is that the study implicates new genes in schizophrenia,” said David Goldman, MD, chief of laboratory of neurogenetics at the National Institute on Alcohol Abuse and Alcoholism. “Now, they have to trace down the genes that mediate this vulnerability.” Identifying these novel genes will eventually help improve

understanding of the disease and lead to the development of more effective treatments, the scientists said.

Source: North Shore-Long Island Jewish (LIJ) Health System

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