Schizophrenia Not One but Many Different Diseases

Schizophrenia is a group of heritable disorders caused by separate genotypic networks that are associated with several distinct clinical syndromes, and not just one single disease, new research suggests.

Dr. Igor Zwir

The finding may lead to better diagnosis and improved treatments personalized for each patient with the debilitating disorder, the authors hope.

"Basically what we are suggesting here is that there is not one schizophrenia, there are schizophrenias, and that there are several subtypes," Igor Zwir, PhD, from Washington University School of Medicine in St. Louis, Missouri, and one of the study authors, told *Medscape Medical News*.

"We identified at least 8 different classes of schizophrenia that have different symptoms and different severity that are caused essentially by separate clusters of genes that act together. I'm not saying it's just 8, there may be more," said Dr. Zwir, who is also an associate professor in the Department of Computer Science and Artificial Intelligence in the University of Granada, Spain.

Their work was published online September 15 in the *American Journal of Psychiatry*.

Important Implications

The finding that schizophrenia is not a single entity but a variety of schizophrenia subtypes has important implications for improved treatment of this illness, Dr. Zwir said.

"One of the problems right now is that patients with schizophrenia may receive the same diagnosis and yet share few symptoms in common. These symptoms can vary in terms of severity and response to treatment. Often, psychiatrists treating these patients say their treatment is more trial and error. For example, currently, in some instances there are patients who receive more than 7 different drugs. This is very costly and can also be extremely frustrating to patients," he said.

Dr. Zwir and his colleagues matched precise DNA variations in people with and without schizophrenia to symptoms in individual patients. In all, the researchers analyzed nearly 700,000 sites within the genome where a single unit of DNA is changed, often referred to as a single nucleotide polymorphism (SNP).

They looked at SNPs in 4200 people with schizophrenia and 3800 healthy control individuals, learning how individual genetic variations interacted with each other to produce the illness.

In some patients with hallucinations or delusions, the researchers matched distinct genetic features to patients' symptoms, demonstrating that specific genetic variations interacted to create a 95% certainty of schizophrenia.

In another group, they found that disorganized speech and behavior were specifically associated with a set of DNA variations that carried a 100% risk for schizophrenia.

In all, the researchers identified 42 clusters of genetic variations that increased the risk for schizophrenia.

They describe 3 patients with different schizophrenia profiles:

- One patient had severe process, positive schizophrenia that was associated with SNP set 81_13 and phenotypic sets 20_19 and 34_17.
- The second patient had moderate process, disorganized negative schizophrenia associated with SNP set 19_2 and phenotypic set 51_38.
- The third patient had severe process, positive and negative schizophrenia associated with SNP set 75_67 and phenotypic sets 15_13, 30_17, 61_18, and 65-64.

Informative Work Corroborates Other Findings

The finding of different genetic subsets in schizophrenia is not new, Jeffrey A. Lieberman, MD, chair of the Department of Psychiatry at Columbia University College of Physicians and Surgeons and Psychiatrist-in-Chief at New York Presbyterian Hospital–Columbia University Medical Center, New York City, told *Medscape Medical News*.

"It's a good study, and it's an informative study and adds to the body of evidence that has been accumulating over the past few years and that culminated in a paper that was published recently in *Nature*," Dr. Lieberman, who is also past president of the American Psychiatric Association, said.

That article, which was the work of the Psychiatrics Genetics Consortium, described 108 specific genetic associations with schizophrenia.

"It had the largest sample of patients, over 40,000, ever studied, and we learned that the mechanisms of heritability and transmission of illness are far more complex than we had originally expected," Dr. Lieberman, who was one of the study authors, said.

"Our study did not show any association between the different genes and different schizophrenia subtypes," Dr. Lieberman said.

"I'd be dancing in the streets if there were solid genetic underpinnings of specific, symptomatic dimensions, negative symptoms, cognitive deficits, but with a sample size of that number, it sounds very unlikely that the effect would be big enough to be detectable," he added.

"I think it is interesting to suggest that there may be symptomatic phenotypes that correlate with a specific pattern of genetic anomalies, but I would want to see some replication before I would be willing to accept the finding," he concluded. "The statement that certain genetic clusters are associated with clinical syndromes in schizophrenia is a reasonable hypothesis, but it certainly is not definitively proven by these data. It would be my most fervent wish that it were."

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