Scientists propose new direction in the search for genetic causes of schizophrenia

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A new study shows that schizophrenia is caused, at least in part, by large, rare structural changes in DNA referred to as copy number variants (CNVs) - not the tiny, single letter alterations (single nucleotide polymorphisms (SNPs) that scientists have pursued for years. The findings are published February 6 in the open-access journal *PLoS Genetics*.

Schizophrenia is one of the most common psychiatric disorders, but scientists have yet to determine significant genetic links. Over the past two decades, dozens of genes and SNPs have been identified as possible candidates, but the current study dismisses them.

"The literature is replete with dozens of genes and SNPs identified as associated with schizophrenia," says first author Anna Need, PhD, a postdoctoral associate in the Center for Human Genome Variation at the Duke Institute for Genome and Sciences Policy. "But we systematically retested all the leading candidates and concluded that most, if not all of them, are false positives." Need says she believes the previous studies were too small to properly assess the role of SNPs.

Need worked with senior author David Goldstein, of the Center for Human Genome variation, and a team of geneticists to scan the genome of schizophrenia patients and healthy controls for SNPs and copy number variants (CNVs). While none of the previously heralded SNPs appeared significant in schizophrenia, several CNVs emerged as potentially causative.

Copy number variants are common throughout the genome, usually appearing as deletions or duplications of significant stretches of DNA. They come in all sizes, but Goldstein says it is the largest deletions - those over two million bases long - that appear only in people with schizophrenia, and may be unique and causative in those individuals.

In schizophrenia patients, the researchers found eight such deletions, of which two were newly identified. While CNVs have been previously implicated in schizophrenia and other psychiatric conditions, the Duke researchers are the first to propose that the rarity of extremely large deletions suggest they are indeed pathogenic, at least in a small number of patients.

"What this means is that if we are going to make real headway in assessing genetic links to schizophrenia, we will have to sequence the entire genome of each schizophrenia patient," says Goldstein. "That is a tremendous amount of work, but it is the only way we will be able to find these extremely rare variations."

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