Mutations not inherited from parents cause more than half the cases of schizophrenia

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Columbia University Medical Center researchers have shown that new, or "de novo," protein-altering mutations—genetic errors that are present in patients but not in their parents—play a role in more than 50 percent of "sporadic" —i.e., not hereditary—cases of schizophrenia. The findings is published online in *Nature Genetics*.

A group led by Maria Karayiorgou, MD, and Joseph A. Gogos, MD, PhD, examined the genomes of patients with schizophrenia and their families, as well as healthy control groups. All were from the genetically isolated, European-descent Afrikaner population of South Africa.

These findings build on earlier studies by Karayiorgou, professor of psychiatry at Columbia University Medical Center. More than 15 years ago, Karayiorgou and her colleagues described a rare de novo mutation that accounts for 1-2 percent of sporadic cases of schizophrenia. With advances in technology, three years ago the Columbia team was able to search the entire genome for similar lesions that insert or remove small chunks of DNA. The mutations found accounted for about 10 percent of sporadic cases.

Encouraged by their progress, they wondered whether other, previously undetectable, de novo mutations accounted for an even greater percentage of sporadic cases. Using state-of-the-art "deep sequencing," they examined the nucleotide bases of almost all the genes in the human genome. This time they found 40 mutations, all from different genes and most of them protein-altering. The results point the way to finding more,

perhaps even hundreds, of mutations that contribute to the genetics of schizophrenia—a necessary step toward understanding how the disease develops.

"Identification of these damaging de novo mutations has fundamentally transformed our understanding of the genetic basis of schizophrenia," says Bin Xu, PhD, assistant professor of clinical neurobiology at Columbia University Medical Center and first author of the study.

"The fact that the mutations are all from different genes," says Karayiorgou, "is particularly fascinating. It suggests that many more mutations than we suspected may contribute to schizophrenia. This is probably because of the complexity of the neural circuits that are affected by the disease; many genes are needed for their development and function." Karayiorgou and her team will now search for recurring mutations, which may provide definitive evidence that any specific mutation contributes to schizophrenia.

The potentially large number of mutations makes a gene-therapy approach to treating schizophrenia unlikely. Researchers suspect, however, that all of the mutations affect the same neural circuitry mechanisms. "Using innovative neuroscience methods," says co-author Dr. Joseph Gogos, MD, PhD, and associate professor of physiology and neuroscience at Columbia University Medical Center, "we hope to identify those neural circuit dysfunctions, so we can target them for drug development."

The study's results also help to explain two puzzles: the persistence of schizophrenia, despite the fact that those with the disease do not tend to pass down their mutations through children; and the high global incidence of the disease, despite large environmental variations.