

Rare mutations may have big impact on schizophrenia pathology

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Schizophrenia is a neurodevelopmental disorder that disrupts brain activity producing hallucinations, delusions, and other cognitive disturbances. Researchers have long searched for genetic influences in the disease, but genetic mutations have been identified in only a small fraction—fewer than a quarter—of sequenced patients. A new study now shows that "somatic" gene mutations in brain cells could account for

some of the disease neuropathology.

The study, led by senior author Jeong Ho Lee, MD, Ph.D., at Korea Advanced Institute of Science and Technology and the team of Stanley Medical Research Institute, appears in *Biological Psychiatry*.

Traditional [genetic mutations](#), called [germline mutations](#), occur in sperm or egg cells and are passed on to offspring by their parents. Somatic mutations, in contrast, occur in an embryo after fertilization, and they can appear throughout the body or in isolated pockets of tissues, making them much harder to detect from blood or saliva samples, which are typically used for such sequencing studies.

Recently, more-advanced genetic sequencing techniques have allowed researchers to detect somatic mutations, and studies have shown that even mutations present at very low levels can have functional consequences. A previous study hinted that brain somatic mutations were associated with [schizophrenia](#) (SCZ), but it was not powerful enough to cement such an association.

In the current study, the researchers used deep whole-exome sequencing to determine the genetic code of all exomes, the parts of genes that encode proteins. The scientists sequenced postmortem samples from 27 people with schizophrenia and 31 control participants both from brain and from liver, heart or spleen tissue, allowing them to compare the sequences in the two tissues. Using a powerful analytic technique, the team identified an average of 4.9 somatic single-nucleotide variants (SNV), or mutations, in brain samples from people with SCZ and 5.6 somatic SNVs in brain samples from control subjects.

Although there was no significant quantitative difference in somatic SNVs between SCZ and control tissues, the researchers found that the mutations in SCZ patients were found in genes already associated with

SCZ. Of the germline mutations that had previously been associated with schizophrenia, the genes affected encoding proteins associated with synaptic neural communication, particularly in a brain region called the dorsolateral prefrontal cortex.

The researchers then determined which proteins might be affected by the newly identified somatic mutations. Remarkably, a protein called GRIN2B emerged as highly affected, and two patients with SCZ carried somatic mutations on the GRIN2B gene itself. GRIN2B is a protein component of NMDA-type glutamate receptors, which are critical for neural signaling. Faulty glutamate receptors have long been suspected to contribute to SCZ pathology; GRIN2B ranks among the most-studied genes in schizophrenia.

John Krystal, MD, editor of *Biological Psychiatry*, said of the work, "The genetics of schizophrenia has received intensive study for several decades. Now a new possibility emerges, that in some cases, mutations in the DNA of brain cells contributes to the biology of schizophrenia. Remarkably this new biology points to an old schizophrenia story: NMDA glutamate receptor dysfunction. Perhaps the path through which somatic mutations contribute to schizophrenia converges with other sources of abnormalities in glutamate signaling in this disorder."

Dr. Lee and the team next wanted to assess the functional consequences of the somatic mutations. Because of the location of the GRIN2B mutations found in SCZ patients, the researchers hypothesized that they might interfere with the receptors' localization on neurons. Experiments in cortical neurons from mice showed that the mutations indeed disrupted the receptors' usual localization to dendrites, the "listening" ends of neurons, which in turn prevented the formation of normal synapses in the neurons. The finding suggests that the somatic mutations could disrupt neural communication, contributing to SCZ pathology.

The somatic mutations identified in the study had a variant allele frequency of only about 1%, indicating that the mutations were rare among [brain cells](#) as a whole. Nevertheless, they have the potential to create widespread cortical dysfunction.

Dr. Lee said of the findings: "Besides the comprehensive genetic analysis of brain-only mutations in postmortem tissues from schizophrenia patients, this study experimentally showed the biological consequence of identified somatic [mutations](#), which led to neuronal abnormalities associated with SCZ. Thus, this study suggests that [brain somatic mutations](#) can be a hidden major contributor to SCZ and provides new insights into the molecular genetic architecture of SCZ."

More information: Myeong-Heui Kim et al. Low-level brain somatic mutations are implicated in schizophrenia, *Biological Psychiatry* (2021). [DOI: 10.1016/j.biopsych.2021.01.014](https://doi.org/10.1016/j.biopsych.2021.01.014)

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