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Evidence mounts for role of mutated genes in development of schizophrenia

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Johns Hopkins researchers have identified a rare gene mutation in a single family with a high rate of schizophrenia, adding to evidence that abnormal genes play a role in the development of the disease.

The researchers, in a report published in the journal Molecular Psychiatry, say that family members with the mutation in the gene Neuronal PAS domain protein 3 (NPAS3) appear at high risk of developing schizophrenia or another debilitating mental illnesses.

Normally functioning NPAS3 regulates the development of healthy neurons, especially in a region of the brain known as the hippocampus, which appears to be affected in schizophrenia. The Johns Hopkins researchers say they have evidence that the mutation found in the family may lead to abnormal activity of NPAS3, which has implications for brain development and function.

"Understanding the molecular and biological pathways of schizophrenia is a powerful way to advance the development of treatments that have fewer side effects and work better than the treatments now available," says study leader Frederick C. Nucifora Jr., Ph.D., D.O., M.H.S., an assistant professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. "We could definitely use better medicines."

Along with environmental factors, it is widely believed that many genes play some role in causing schizophrenia, a disease characterized by a

variable combination of hallucinations, delusions, impaired cognition and a loss of drive and initiative. The disorder strikes an estimated seven in every 1,000 adults in the United States. While the Johns Hopkins experiments to date show that the NPAS3 mutation is rare, Nucifora says learning as much as possible about the biological role of NPAS3 will likely lead to a better understanding of how other genes contribute to the development of schizophrenia, even in the absence of the NPAS3 mutation.

For the study, Nucifora and his team used blood samples to search the DNA of 34 people with schizophrenia or a related condition, schizoaffective disorder. All 34 were members of families in which more than one person had the disease. The investigators were specifically looking for NPAS3 mutations—previous research suggested it could be involved in schizophrenia—and found it in one of the families.

By analyzing blood samples from that single family—two parents and four adult children—they found that the mother, who has schizophrenia, her two children with schizophrenia, and her child with major depression all had the mutant version of NPAS3. The NPAS3 gene provides instructions for the production of a protein that contains 933 amino acids. The altered gene led to a single flaw: a valine was switched to an isoleucine. Nucifora says it is not yet known how this single mutation affects the function or structure of NPAS3. A possible hint comes from the finding of other investigators that a change from valine to isoleucine in a protein known as APP is linked to Alzheimer's disease.

Nucifora cautions that, by itself, finding a mutation in a single family with mental illness doesn't establish the altered gene as the cause of the illness. Nucifora and his colleagues therefore set out to determine whether the mutation plays any role in the function of NPAS3, which serves as a master switch in cells, controlling the fate of many other

genes involved in brain development and metabolism.

To do that, Nucifora and his colleagues grew neurons with either normal or mutated copies of NPAS3 in a dish, and found that the healthy neurons grew nice long extensions, a process that typically allows them to make good connections with other cells and is therefore critical for brain function. In neurons with the mutated gene, the extensions were abnormally short.

Other genes believed to be involved in mental illness also have been found to disrupt the growth of longer neuronal extensions.

"We showed that the mutation does change the function of NPAS3, with potentially harmful effects in neurons," he says. "The next step is to figure out exactly how the genetic disruption alters neuronal function, and how these abnormal neurons influence the broader function of the brain."

Nucifora and his team are now working to create a mouse with the NPAS3 mutation. "If this mutation in NPAS3 is indeed important for human disease, then we should detect abnormalities in the neurons of mice with mutant NPAS3, and the mice should have impairments in learning, memory and social behavior," he says.

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