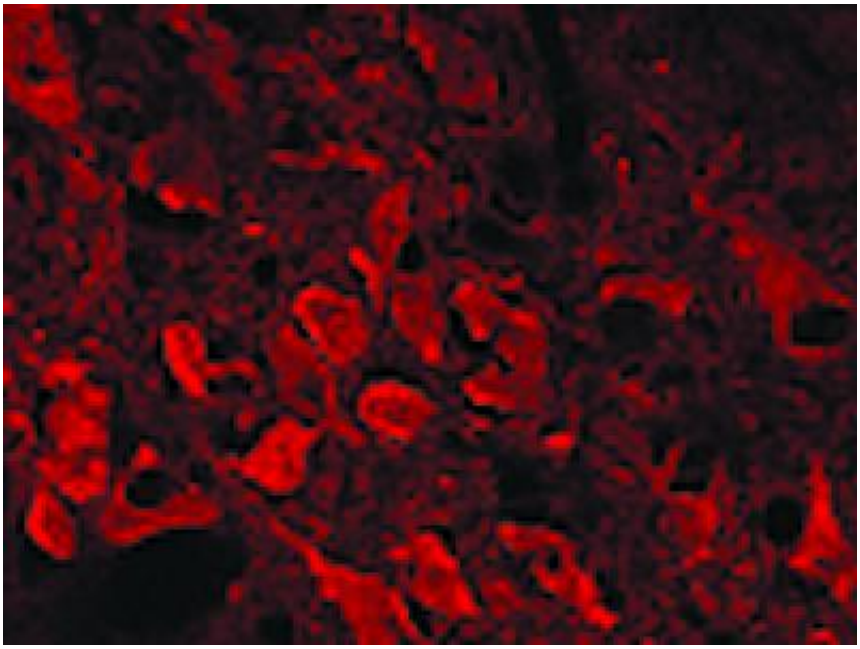
MedicalXpress

Some autism behaviors linked to altered gene

February 12 2013



A limited number of neurons (red) in the brain produce serotonin, a chemical messenger. A newly identified genetic mutation can disrupt the production of serotonin and may underlie common behaviors seen in some people with autism, such as difficulty communicating and resistance to change, according to new research at Washington University in St. Louis and Rockefeller University in New York. Credit: Washington University

Scientists at Washington University School of Medicine in St. Louis have identified a genetic mutation that may underlie common behaviors seen in some people with autism, such as difficulty communicating and resistance to change.

An error in the gene, CELF6, leads to disturbances in serotonin, a chemical that relays messages in the brain and has long been suspected to be involved in autism.

The researchers identified the error in a child with autism and then, working in mice, showed that the same genetic alteration results in autism-related behaviors and a sharp drop in the level of serotonin circulating in the brain.

While the newly discovered mutation appears to be rare, it provides some of the first clues to the biological basis of the disease, the scientists report Feb. 13 in the Journal of Neuroscience.

"Genetically, autism looks very complicated, with many different genetic routes that lead to the disease," says lead author Joseph D. Dougherty, PhD, an assistant professor of genetics at Washington University. "But it's not possible to design a different drug for every child. The real key is to find the common biological pathways that link these different genetic routes and target those pathways for treatment."

Autism is known to have a strong genetic component, but the handful of genes implicated in the condition so far explain only a small number of cases or make a small contribution to symptoms.

This led Dougherty and senior author Nathaniel Heintz, PhD, a Howard Hughes Medical Institute investigator at Rockefeller University, to speculate that some of the most common behavioral symptoms of autism may be caused by disruptions in a common biological pathway, like the one involved in serotonin signaling.

Some 30 percent of patients with autism have abnormal blood levels of serotonin. The chemical messenger plays an important role throughout the body, helping to regulate breathing, temperature and sleep as well as

mood and learning. But it is produced by only a limited number of neurons in the brain.

Using a new molecular technique, the researchers exclusively targeted serotonin-producing neurons in healthy mice to look for genes that are "turned on" in these cells. They found nearly 200 genes involved in this process.

Then, they searched for variations in these genes in some 400 autistic children, whose DNA was made available to the scientists through the Autism Genetic Resource Exchange.

The scientists found alterations in a gene, CELF6, which had never been linked to autism. CELF6 makes a protein that binds to DNA's chemical cousin, RNA, and appears to regulate levels of serotonin in the brain. When they looked more closely at CELF6, they found a copy of the gene was severely mutated in one patient, to the extent that it would no longer function in the neurons that produce serotonin or in other cells.

Because the mutation seemed rare, the researchers didn't know whether its occurrence was a coincidence or whether the defect could, in fact, cause autism. So, they looked for mutations in the same gene in another 860 children with autism, whose DNA was provided by Simons Foundation Autism Research Initiative. While none of them had the mutation in CELF6, neither did some 5,000 normal, healthy individuals whose DNA they examined.

Yet, having earlier found the genetic error in one child with autism suggested that it may be rare and, perhaps, have a link to the condition through the serotonin pathway. To understand its potential influence, the researchers again turned to the mice.

"If this gene has some influence on whether a person gets autism, then

mice with the same genetic mutation should have some behavioral features of autism," Dougherty says.

Indeed, when the researchers bred mice that didn't have the CELF6 gene, they had far less serotonin circulating in the brain, compared with healthy mice, and they exhibited some of the same behaviors seen in children with autism.

For example, when newborn mouse pups are separated from their mothers, they typically emit a high-pitched cry – a call to their mothers to bring them back to the nest. But mice without CELF6 experienced severe deficits in their vocalizations, an indicator of communication difficulties.

And other experiments showed how the autistic-like mice resisted changing their patterns of behavior. Mice are natural explorers and are drawn to odors. In one experiment, the researchers exposed mice to a variety of odors, including one novel scent for them – chocolate.

Later, the mice were allowed to eat the chocolate, typically a highly rewarding experience. And the next day, when the mice were exposed to various odors, including chocolate, the healthy mice dramatically increased their exploration – especially of the chocolate. But the mice without CELF6 continued to investigate each scent, showing no changes in their behavior.

"Our results suggest that we have found a mechanism by which a genetic mutation can disrupt serotonin signaling and lead to behavior that is characteristic of autism," Dougherty says. "Serotonin signaling is just one biological pathway that can be interrupted in patients with autism. We think similar investigations can find other pathways that may be important in this disease."