MedicalXpress

Deleting a single gene results in autism-like behavior; immunosuppressant drug prevents symptoms

July 2 2012

Deleting a single gene in the cerebellum of mice can cause key autistic-like symptoms, researchers have found. They also discovered that rapamycin, a commonly used immunosuppressant drug, prevented these symptoms.

The deleted gene is associated with Tuberous Sclerosis Complex (TSC), a rare genetic condition. Since nearly 50 percent of all people with TSC develop autism, the researchers believe their findings will help us better understand the condition's development.

"We are trying to find out if there are specific circuits in the brain that lead to autism-spectrum disorders in people with TSC," said Mustafa Sahin, Harvard Medical School associate professor of neurology at Boston Children's Hospital and senior author on the paper. "And knowing that deleting the genes associated with TSC in the cerebellum leads to autistic symptoms is a vital step in figuring out that circuitry."

This is the first time researchers have identified a molecular component for the cerebellum's role in autism. "What is so remarkable is that loss of this gene in a particular cell type in the cerebellum was sufficient to cause the autistic-like behaviors," said Peter Tsai, HMS instructor of neurology and the first author of this particular study.

These findings were published online July 1 in *Nature*.

TSC is a genetic disease caused by mutations in either one of two genes, TSC1 and TSC2. Patients develop benign tumors in various organs in the body, including the brain, kidneys and heart, and often suffer from seizures, delayed development and behavioral problems.

Researchers have known that there was a link between TSC genes and autism, and have even identified the cerebellum as the key area where autism and related conditions develop.

Previous studies have shown that certain cells essential for cerebellar function called Purkinje cells, which are among the largest neurons in the human brain, are fewer in number in patients with autism. To better understand the relationship between Purkinje cells and autism, Sahin and his team deleted copies of the TSC1 gene in the Purkinje cells of mice. Some mice had only one copy of the gene deleted, while others had both of their copies deleted.

In both cases, deleting this gene caused the three main signs of autistic-like behaviors:

- Abnormal social interactions. The mice spent less time with each other and more with inanimate objects, compared to controls.
- Repetitive behaviors. The mice spent extended amounts of time pursuing one activity or with one particular object far more than normal.
- Abnormal communication. Ultrasonic vocalizations, the communication method used among rodents, were highly distressed.

The researchers also tested learning. "These mice were able to learn new

things normally," said Tsai, "but they had trouble with 'reversal learning,' or re-learning what they had learned when their environment changed."

Tsai and colleagues tested this by training the mice to swim a particular path in which a platform where they could rest was set up on one side of the pool. When the researchers moved the platform to the other side of the pool, the mice had greater difficulty than the control mice re-learning to swim to the other side.

"These changes in behavior indicate that the TSC1 gene in Purkinje cells, and by extension, the cerebellum, are a part of the circuitry for autism disorders," emphasized Sahin.

The researchers also found that the drug rapamycin averted the effects of the deleted gene. Administering the drug to the mice during development prevented the formation of autistic-like behaviors.

Currently, Sahin is the sponsor-principal investigator for an ongoing Phase II clinical trial to test the efficacy of everolimus, a compound in the same family as rapamycin, in improving neurocognition in children with TSC. The trial will be open for enrollment until December 2013.

"Our next step will be to see how the abnormalities in Purkinje cells affect autism-like development. We don't know how generalizable our current findings are, but understanding mechanisms beyond TSC genes might be useful to autism," said Tsai.

Provided by Harvard Medical School