NEWS

Mouse study links gene to some autism symptoms

BY **RACHEL NUWER**

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Mice missing a gene called PTCHD1 in a sensory structure deep inside the brain are hyperactive and show attention deficits — features seen in some children with autism. Using a drug to substitute for the gene's effects tempers these symptoms[1].

The findings, published 23 March in *Nature*, suggest that the gene works to filter sensory input to the brain's outer layer, called the cerebral cortex. They also hint at a new treatment target for autism, attention deficit hyperactivity disorder and other conditions.

"We found very strong evidence that missing this gene causes symptoms of some developmental disorders," says **Guoping Feng**, Poitras Professor of Neuroscience at the Massachusetts Institute of Technology in Cambridge.

Up to 1 percent of people with autism and intellectual disability **carry a mutation in PTCHD1**, a gene that resides on the X chromosome[2]. But little was known about the gene's function. The new study shows it plays an important role in a part of the thalamus that regulates sleep and attention, and integrates sensory information.

"These findings provide a clear and straightforward pathway from gene to behavior," says **Joshua Gordon**, associate professor of psychiatry at Columbia University, who was not involved in the research.

Feng and his colleagues engineered mice with a PTCHD1 mutation that halts production of the corresponding protein. The mice are unusually aggressive, biting and fighting their cagemates. They also exhibit signs of hyperactivity, attention deficits and motor problems — features seen in some people with PTCHD1 mutations. "Basically, they mimicked human defects," Feng says.

Information leak:

To determine the origins of these problems, the researchers perturbed the gene in a particular part of the brain, a section of the thalamus called the thalamic reticular nucleus (TRN). This region serves as a sensory filter and is likely to play a role in attention and sleep.

Mice lacking PTCHD1 only in this region are hyperactive, inattentive and easily awakened — but not aggressive or uncoordinated. These symptoms suggest that PTCHD1 is critical for the normal function of neurons, which block unnecessary sensory information, such as distracting noises, from reaching the cortex.

“We call this a leaky thalamus,” Feng says. “Excessive information leaks out to the cortex, causing the mice to be easily distracted.”

Recording from brain slices, the researchers found that lack of PTCHD1 protein lessens the flow of potassium through a potassium ion channel in TRN neurons. As a result, the neurons are less likely to fire. Treating the mice with a compound that boosts potassium channel activity alleviates their attention problems and hyperactivity. The compound’s effects are too short-lived to assess its effects on sleep, however.

The drug is not suitable for use in people, as it may have toxic effects if used for extended periods. But the finding could lead to new drugs that have the same effect, Feng says.

Some scientists caution, however, that restoring the ion channel’s activity might not ease symptoms such as aggression and learning difficulties, which occur in people with the mutation.

“Even a disease caused by a single gene mutation can have complex downstream effects, potentially requiring therapies aimed at multiple different targets,” Gordon says.

Feng agrees. “It would be very difficult to find one target to treat everything,” he says.

REFERENCES:

1. Wells M.F. *et al. Nature* **532**, 58-63 (2016) **PubMed**
2. Chaudhry A. *et al. Clin. Genet*. **88**, 224-233 (2015) **PubMed**