NEWS

Mice missing key autism gene hint at new treatment target

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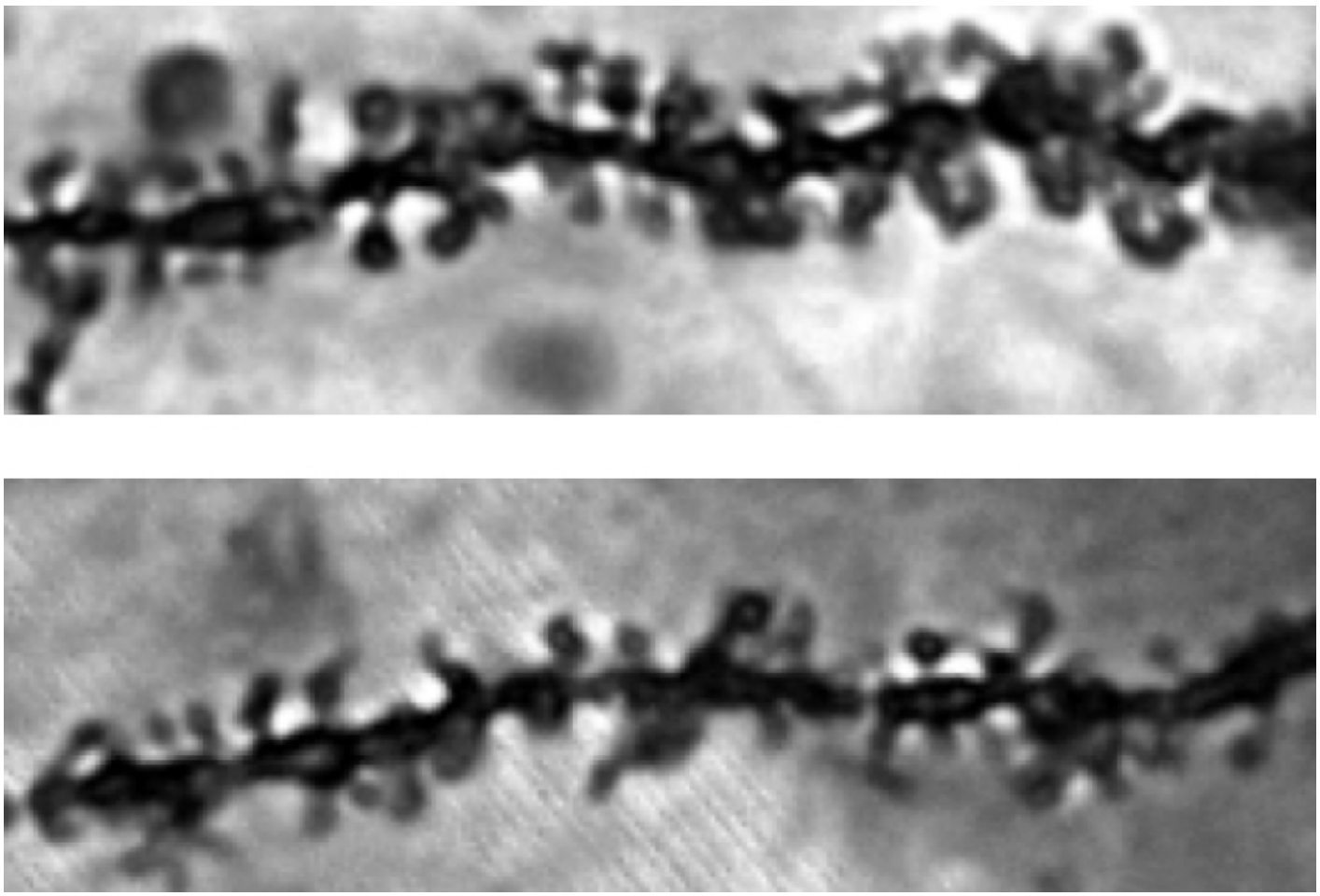
16 JUNE 2016



A newly created strain of mice lacking **SHANK3** closely mimics the effects of the protein's loss in some people with autism, according to a new study[1]. Drugs that target a pathway disrupted in the mice improve the animals' ability to learn and ease some of their repetitive behaviors, hinting at a

treatment strategy.

Nearly 1 percent of people with autism **have mutations in the SHANK3 gene**, and most of these glitches result in a loss of SHANK3 protein, which comes in several forms.

Scientists created the first SHANK3 mouse model in 2010, and have since made 10 others. Each of these strains carries a deletion or a variant in part of the SHANK3 gene. But because all of the mice have only a partial loss of the protein, none perfectly mirror the most common situation in people.

The new mouse model does not produce any known SHANK3 forms, and its behaviors resemble those in people. “It mimics the human condition better,” says study leader **Yong-Hui Jiang**, associate professor of pediatrics at Duke University in Durham, North Carolina. The work appeared in May in *Nature Communications*.

These mice show many of the same features as previous strains, such as weakened signaling among neurons, repetitive behaviors, social difficulties, anxiety, and motor and memory problems.

But they display a new problem: They do not learn to press a lever to receive a food reward. Difficulties with reward processing appear in **some people with autism**.

“We’re not aware of any other mouse model that is this profoundly impaired,” says **Alexandra Bey**, a graduate student in Jiang’s lab. “There’s increased interest in the field in looking at reward learning in terms of autistic behaviors, and we think this might be a nice way to start to bridge that gap.”

Rodent rejects:

Jiang and his colleagues created mice with a large deletion in both copies of SHANK3. This effectively removes all parts of the gene that code for SHANK3 protein. The mutant mice develop normally and do not have seizures.

Like previous strains, the new strain of mice shows a range of repetitive behaviors and restricted interests: The mice groom themselves so much that they develop sores. In a cage with holes in the floor, they repeatedly poke their noses into the same hole. They also show anxiety and problems with learning and memory in standard tests.

The rodents have unusual social features: They are interested in interacting with other mice, but they are unpopular; other mice tend to actively ignore them.

“This reminds us of some of the behaviors seen in some people with autism, where they have high levels of social interests, but the content of their interactions might be abnormal to another

observer," Bey says. So far, the researchers have been unable to figure out what exactly is off-putting about the mice to their peers.

Electrodes implanted in the brains of the mice reveal unusually high resting-state activity in a circuit involved in social behavior, but the activity doesn't rise as it should in the presence of an unfamiliar mouse. This unusual pattern may underlie some of the animals' behavioral oddities, says **Xiaoming Wang**, senior research associate in Jiang's lab.

Tricky treatment:

Neurons in brain slices from the mutant mice have too few extensions that end in **synapses**, the communication hubs between neurons. They also signal sluggishly.

The SHANK3 protein acts as a scaffold for other proteins at these hubs, so its loss may underlie these problems. SHANK3's loss seems to have ripple effects on other proteins as well: A protein called HOMER that interacts with SHANK3 is unusually scarce at synapses in the mutants, whereas a protein called mGluR5 is unusually abundant.

The rise in mGluR5 is puzzling, says **Guoping Feng**, professor of brain and cognitive sciences at the Massachusetts Institute of Technology, who was not involved in the new work. In January, Feng's team reported that one of their SHANK3 mutants has low levels of both HOMER and mGluR5 at synapses.

mGluR5 is known to interact with HOMER, so Jiang's team tried activating mGluR5 with a drug, reasoning that it might be underactive when HOMER levels are low. That treatment improved the animals' ability to learn, but worsened their grooming behavior.

When the researchers tried a drug that instead blocks the excess mGluR5, the animals' grooming normalized.

The two drugs both improve behavior, albeit in different ways, because the effects of SHANK3 on mGluR5 vary from cell to cell, Jiang says. The findings hint at the complexity of developing treatments for people with SHANK3 mutations.

REFERENCES:

1. Wang X. *et al. Nat. Commun.* **7**, 11459 (2016) **PubMed**