NEWS

Gene in autism risk region plays key role in brain development

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Mice missing TAOK2, a gene in a segment of chromosome 16 linked to autism, have big brains, immature neuronal junctions and asocial behavior, a new study shows[1].

The findings suggest that TAOK2 is a key contributor to autism from among the genes in this region. People missing a copy of some or all of this region, known as **16p11.2**, tend to have enlarged heads and cognitive impairments; about one in four has autism.

The researchers also found mutations in the gene in people with autism, and showed that some of these mutations alter the structure of neurons grown in culture.

“We now have data showing that TAOK2 is important in some patients, and the animal model of TAOK2 is reflecting some characteristics of these patients,” says co-lead investigator **Froylan Calderon de Anda**, head of the neuronal development research group at the University Medical Center Hamburg-Eppendorf in Germany.

The findings directly link TAOK2 to autism, says **Smita Yadav**, assistant professor of pharmacology at the University of Washington in Seattle, who was not involved in the work. “It’s a very comprehensive study.”

TAOK2 is unlikely to explain all of the features found in people with a deletion of or in 16p11.2, however. Other genes in the region may also be important in autism.

“It is becoming clear that there are multiple genes in the region that are contributing to related neurodevelopmental phenotypes,” says **Santhosh Girirajan**, assistant professor of biochemistry and molecular biology at Pennsylvania State University, who was not involved in the study.

Big difference:

In a 2012 study, Calderon de Anda and his colleagues **temporarily suppressed TAOK2** in mouse neurons. The neurons have fewer **dendrites** — neuronal branches that receive signals — than controls do.

In the new study, the team made mice missing one or both copies of the gene, to more closely mimic the situation in people.

The mutant mice have enlarged brains at age 8 to 10 weeks; this trend is more pronounced in mice missing both copies of the gene than in those lacking one copy.

However, some brain areas in the mice are unusually small, including the somatosensory cortex, a sensory processing area; and the **corpus callosum**, the nerve bundle that connects the brain's two hemispheres. The results appeared 21 February in *Molecular Psychiatry*.

These results jibe with studies showing that mice missing a copy of 16p11.2 have a **small corpus callosum**. By contrast, however, some people missing 16p11.2 have **thicker bundles than usual**.

That discrepancy "is frustrating and confusing," says **Nicola Grissom**, assistant professor of psychology at the University of Minnesota, who was not involved in the work. "But mice aren't humans."

Skeleton key:

The mutant mice have fewer and shorter dendrites than controls do. They also have immature spines — protrusions on dendrites — and transmit fewer excitatory signals. These defects crop up in the prefrontal cortex — a brain region involved in cognition and social interactions — but not in the **hippocampus**, a learning and memory center.

Supplying mice missing one copy of the gene with a second copy improves the shape and function of their neurons.

TAOK2 may regulate neuron structure and function by altering the cell skeleton. The protein interacts with an enzyme called RhoA, which rearranges the cell skeleton to enable dendritic spine formation, the researchers found.

Loss of TAOK2 lowers RhoA activity in the cerebral cortex, and decreases spine formation in the neurons there. Activating RhoA with a drug restores spine formation. By contrast, TAOK2 loss has no effect on RhoA in the hippocampus.

TAOK2 is the second gene in the 16p11.2 region found to influence the RhoA signaling pathway. A

study last year showed that **KCTD13** also **regulates RhoA**. These two genes appear to have opposite effects: TAOK2 activates RhoA, and KCTD13 inactivates it.

Acting out:

The mutant mice also show some behaviors reminiscent of autism. They spend less time sniffing unfamiliar mice than controls do, hinting at a social deficit. Unlike controls, they also show no preference for a relocated familiar object over a static one — a possible mouse version of 'insistence on sameness.'

But the mutants are hyperactive, which might account for some of this behavior, Grissom says. Other traits are inconsistent with autism: For instance, the mice are less anxious than controls.

The researchers also looked for TAOK2 mutations in more than 2,600 people with autism. They used information from a **project called MSSNG**, which aims to collect whole-genome sequences from 10,000 people.

They turned up 24 mutations in TAOK2, 3 of which appear to have arisen spontaneously. Only one of these spontaneous mutations lowers the levels of TAOK2 protein and inactivates RhoA.

To understand how TAOK2 regulates the RhoA pathway, the researchers are identifying proteins that TAOK2 tags with a phosphate group. They are also restoring TAOK2 levels in the mice missing 16p11.2 and assessing the effects on the mice's features.

REFERENCES:

1. Richter M. *et al. Mol. Psychiatry* Epub ahead of print (2018) **PubMed**