NEWS

Molecular mechanisms: Autism gene regulates neuron shape

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Altered development: Neurons lacking the autism-linked gene TAOK2 (above) have fewer projections that connect neurons than do controls (top).

TAOK2, a gene in the autism-associated **16p11.2 chromosomal region**, is part of a signaling pathway that builds neuronal connections during development, according to a study published 10 June in *Nature Neuroscience*[1].

The TAOK2 gene codes for a protein that adds phosphate groups to the MAPK/ERK family of enzymes, which help control cell growth. These enzymes are regulated by the RAS signaling pathway, which has been **implicated in autism** by genetic, biochemical and mouse studies.

TAOK2 is one of 25 genes in the 16p11.2 chromosomal region. About 30 percent of people with a deletion of this region have symptoms of autism. Overall, the deletion accounts for **about one percent** of individuals with autism. Duplication of the same region has also been **linked to schizophrenia**.

A study published this month shows that individuals with autism who express less TAOK2 in blood cells **tend to have larger heads** than those with more of the protein. Levels of the TAOK2 protein are **regulated by FMRP**, the protein lacking in fragile X syndrome, according to a study published last summer[2], further linking the protein to autism.

Better understanding of the effects of abnormal TAOK2 levels could clarify its role in the wide-ranging symptoms linked to 16p11.2 deletion and duplication, as well as autism more broadly.

In the new study, researchers found that cells with lower-than-typical levels of TAOK2 have fewer axons, the long neuronal projections that ferry signals to other cells, than do controls. They also have fewer dendrites, neural branches that receive signals from other neurons. Cells that make excess TAOK2 show the opposite pattern, the study found.

To better understand the role TAOK2 plays in neuron development, the researchers also shut down TAOK2 expression in a subset of neurons in prenatal mice at day 15 after conception — the equivalent of the end of the second trimester in people — and looked at the brains of these mice at 7 days old. Unlike control neurons, those lacking TAOK2 do not cross the midline of the brain through the corpus callosum, the study found.

Previous research has shown that deficits in **long-range signaling between brain regions** and **defects in the corpus callosum**, which connects the two hemispheres of the brain, are linked to autism.

TAOK2 interacts with three signaling proteins, NRP1, SEMA3A and JNK, the study found. Low levels of TAOK2 dampen the activity of an enzyme called JNK, a member of the MAPK signaling pathway. Conversely, turning up expression of the JNK protein in neurons lacking TAOK2 brings the number of dendrites back to normal.

These results suggest that impaired signaling through these three proteins could account for neurological deficits associated with 16p11.2 deletion, the researchers say, and further implicates the RAS pathway in autism.

References:

1: Calderon de Anda F. *et al. Nat. Neurosci.* **10**, 1022-1031 (2012) **PubMed**

2: Darnell J.C. *et al. Cell* **146**, 247-261 (2011) **PubMed**