NEWS

Autism gene needed for growth of neurons during gestation

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Mutations in one of the strongest autism candidate genes may block the proliferation of neurons during development, according to unpublished results presented yesterday at the **2014 Society for Neuroscience annual meeting** in Washington, D.C.

The gene, called **CHD8**, is the closest thing so far to an 'autism gene.' People with a severe mutation in the gene nearly always have autism and **share a set of distinct symptoms**, including gut problems and difficulty sleeping.

But how CHD8 mutations might lead to autism is an open question, and not an easy one: CHD8 **affects the expression of thousands** of other genes.

Omer Durak, a graduate student in **Le-Huei Tsai**'s lab at the Massachusetts Institute of Technology, looked at CHD8's expression during development. In mice and in humans, it peaks **during mid-gestation**, suggesting that it has an important role as the brain begins to form.

Durak introduced short pieces of RNA into [cortical] neural progenitor cells in fetal mouse brains to block production of the CHD8 protein. [Cortical] neural progenitor cells are stem cells that are en route to becoming neurons [in the cerebral cortex, the brain's outer section.] Durak targeted a time in development when the progenitors turn into pyramidal neurons, [a type of cortical neuron] that has been **linked to autism**.

Mice with the RNA have fewer actively dividing neural progenitor cells than controls do, and those cells that exist develop into neurons prematurely. [As adults,] these mice have immature pyramidal neurons with fewer branches than is typical.

Once the mice reach adulthood, they have symptoms reminiscent of autism: They [do not show a preference for] another mouse in the cage [compared with an object], and they avoid high [and]

open spaces — a sign of anxiety.

[Blocking CHD8 production reduces the expression of regulatory genes and genes involved in cell growth. But it boosts the expression of certain genes involved in neuron development. In line with previous findings, the study shows that low levels of CHD8 affect the expression of many other autism-linked genes.]

That having less CHD8 decreases the number of neural progenitors is completely unexpected, says Durak. CHD8 is thought to dampen the WNT signaling pathway, which stimulates cell growth, so mutations that disable the CHD8 protein would be expected to boost the numbers of progenitors. “[It does] completely the opposite of what is published,” says Durak.

What’s more, neural progenitors with lower-than-normal levels of CHD8 have lower WNT signaling, not more, than controls do. This is true in cultured neural progenitor cells from both mice and humans and in embryonic mouse brains. Cultured kidney cells have the expected response, however. The results suggest that CHD8 has a different role in the brain than it does in the rest of the body.

[In the brain, WNT signaling stabilizes the beta-catenin protein and prompts it to enter the nucleus, where it induces the expression of other genes.] Adding extra beta-catenin [at the same time as knocking down CHD8] restores the growth of neural progenitors in the mice. [As adults, these mice show typical social behavior and no signs of anxiety, the researchers found. This suggests that alterations in WNT and beta-catenin signaling underlie the behavioral effects of CHD8 mutations.]

CHD8’s effect on beta-catenin is only part of the story, says Durak, but it is an important step in understanding the gene’s role in the brain. “This is just one gene affected by CHD8, but CHD8 will affect thousands,” he says. “We don’t know what else is involved yet.”

[It is also unclear how CHD8 mutations influence head size. People who carry a mutation in one copy of the gene have an enlarged head, or **macrocephaly** — an observation at odds with the findings in mice.

It’s possible that CHD8 mutations lead to macrocephaly by affecting brain cells other than neurons, says Tsai, professor of neuroscience at the Massachusetts Institute of Technology. “We have to be more open-minded and wait for more evidence that will become available to really tell us why those patients have macrocephaly,” she says.

The new work is part of a growing effort to characterize the effects of CHD8 mutations in mice. A study published last month showed that mice lacking one copy of the CHD8 gene in all of their cells are anxious and **show abnormal social behaviors**. But these mice, unlike Durak’s, show a slight activation in the WNT pathway during mid-gestation.

This discrepancy could stem from the fact that the new study focused on CHD8's effect in neurons, whereas the other study looked at all cells in the brain, says **Ben Cheyette**, associate professor of psychiatry at the University of California, San Francisco. The new mice also only have a temporary disruption in CHD8 expression in certain neurons, whereas the other mice are missing one copy of the gene permanently in all their cells.

"Because of all these complications, it may take a while before the community as a whole can figure out which of these differences in which of these mouse models is really the relevant one for autism in humans," Cheyette says.]

REFERENCES:

1. Durak O. *et al. Nat. Neurosci.* Epub ahead of print (2016) **PubMed**