NEWS

Mouse with key autism mutation defies expectations

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14 MAY 2016

Mice with a mutation in CHD8, the top autism risk gene, made their debut today at the **2016 International Meeting for Autism Research** in Baltimore — and they show no signs of any of the condition's core traits.

But the features they do show make them a good model for studying how CHD8 mutations affect the brain, researchers say.

Since CHD8 rose to prominence as a top autism gene a few years ago, multiple teams have been scrambling to make mice with a CHD8 mutation. The mice described yesterday are the first of these models and carry a mutation in one of the two copies of the gene.

On the face of it, their behavior is disappointing. The mice seem just as social as control mice do. And they don't groom compulsively or frantically bury marbles in their cages — behaviors that researchers use as proxies for the restricted interests and repetitive behaviors seen in autism.

However, they do show the enlarged brains and problems with learning and memory that **people who carry a CHD8 mutation** also have. The mouse neurons also show differences in the expression of genes that CHD8 is **known to regulate**, including several autism candidates.

"We were surprisingly happy with the data that we found," says **Jill Silverman**, assistant professor of psychiatry and behavioral sciences at the University of California, Davis, who characterized the mouse model's behavior. Silverman plans to keep evaluating the mice for other behaviors, such as play, and by looking at juveniles as well as adults.

Brain change:

One of the characteristic features of people who carry mutations in CHD8 is an enlarged head, or

macrocephaly. The mutant mice also show an increase in volume in several brain regions compared with controls.

The researchers analyzed brains from the mice they had tested for behavior, allowing them to link the two aspects. Mice with the largest brains were the ones that showed the most problems with learning and memory. This association was especially true for the volumes of the amygdala, the cortex and the hippocampus, three brain regions that are linked to autism.

To track the effects of the mutation during development, the researchers collected brains from mice at three time points *in utero*, at birth and in adulthood. At day 14.5 of gestation, the mice show signs of abnormalities in the precursor cells of neurons, the researchers found.

This finding may account for the mice's enlarged brains later on, but additional experiments are needed to be sure, says **Alex Nord**, assistant professor of neuroscience at the University of California, Davis, who presented the findings.

Nord and his team also tracked changes in gene expression, comparing an average of all brain cells in the mutants and controls. They found that expression of 20 of the strongest autism-candidate genes, including **ANK2** and **CTTNBP2**, is altered in the mutant mice compared with controls.

Last year, two studies carefully cataloged **the hundreds of genes that CHD8 regulates**. "We can take that data and layer it on our data and it looks beautiful," says Nord.

The fact that the mice recapitulate the cognitive deficits seen in people with the mutation, and that those features track with changes to the mouse brains, more than makes up for the lack of classic autism traits, says **Jeremy Veestra-VanderWeele**, associate professor of psychiatry at Columbia University in New York, who was not involved in the study.

"This is going to get [the research team] faster to understanding what is actually happening in the brain than simply having a behavioral change that may be appealing," he says.

*For more reports from the 2016 International Meeting for Autism Research, please **click here**.*