NEWS

Women with severe autism point to new gene candidates

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Looking in families with a history of severe autism among women, researchers have unearthed 18 new candidate genes for the disorder. One of these genes, delta-catenin, or CTNND2, plays a critical role in brain development, researchers reported Wednesday in *Nature*[1].

The study's female focus stems from mounting evidence that it takes a **bigger genetic hit** to cause autism in girls than in boys. This may explain why autism affects **four boys for every girl**.

Homing in on the effects of these 'severe' mutations could point to biological processes at the root of autism, says lead researcher **Aravinda Chakravarti**, professor of medicine at Johns Hopkins University in Baltimore. "When females are affected, they must really have to overcome some major biological threshold," he says. "Finding the genes that are mutant in females could give us the rate-limiting steps" leading to the disorder.

Chakravarti and his team started their search in 13 girls and women with severe autism who have another female family member with the disorder. This targeted approach contrasts with the broader efforts of two massive sequencing studies published last year, in which scientists scoured DNA from more than 6,000 people with autism to **reveal 50 strong autism candidate genes**.

"The study illustrates how powerful a well-informed genetic study design can be," says **Lauren Weiss**, assistant professor of psychiatry at the University of California, San Francisco, who was not involved with the work. "Sometimes we forget that a much smaller-scale study can also be effective if it's really well conceived."

Sequencing the protein-coding regions of the genome, called **exomes**, the researchers uncovered 18 genes that are mutated in at least 2 of the 13 women with autism but none of 71 female controls. They then focused on one of these genes, CTNND2, which shows two different mutations

in affected individuals. (Using existing databases, the researchers also found 10 chromosomal deletions and 2 duplications that include this gene in people with autism.)

The researchers then found the same two CTNND2 mutations in genetic sequences from another 362 girls and women with autism. They also identified five new mutations in the gene in this larger group.

Females first:

One of the mutations, called R713C, is not included among sequences from more than 16,000 female controls. Another mutation, called G34S, is absent from a database of 3,889 European controls but present at a low frequency among 1,869 people of African descent. This mutation is also present in a girl with autism as well as her unaffected mother, signaling that its potency may be limited.

“Even some of the most severe mutations may not be sufficient by themselves,” says **Christian Schaaf**, assistant professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas, who was not involved with the study. “They are part of the story, but they are not the whole story.”

Schaaf checked a **database of 63,000 people** who have no known psychiatric diagnoses and found 3 people with the R713C mutation and 9 with the G34S mutation. The presence of these mutations in unaffected individuals supports the notion that other genes or environmental factors often act in concert with autism-linked mutations to trigger the disorder, he says.

To probe CTNND2’s function, the researchers looked at zebrafish embryos that lack the gene. The embryos are unusually short and show other signs of abnormal development that are consistent with defects in a signaling pathway that helps direct development, called WNT.

Similarly, cultured neurons from rats missing CTNND2 have smaller signal-receiving branches, called dendrites. They also make fewer neuronal connections, or **synapses** — particularly those that convey excitatory signals, suggesting an imbalance in brain activity.

Introducing normal CTNND2 into these mutant zebrafish and rat neurons reverses these defects. But providing CTNND2 with the R713C mutation has no effect, suggesting that the mutation abolishes the gene’s function. By contrast, giving back CTNND2 with the G34S mutation eases the defects somewhat, but not completely.

To further understand the effect of mutations in CTNND2, the researchers measured the gene’s expression in adult and fetal postmortem brain tissue. They found that CTNND2 is primarily expressed during fetal development, suggesting that it plays a role in brain development.

CTNND2 becomes active in the brain at the same time as other proteins that regulate gene expression. This and other evidence suggest that the gene modifies chromatin — the coiled complex of DNA and protein that helps to regulate gene expression.

“It’s likely that mutations in CTNND2 are so much more impactful than other mutations because of this chromatin connection,” Chakravarti says. Other autism-linked mutations are known to affect the structure of chromatin, making CTNND2’s effects consistent with an emerging story about the importance of chromatin in autism.

The effect of CTNND2 mutations in boys is not clear. Although the study focused on females, the researchers did report finding one CTNND2 mutation in a boy with autism.

Still, probing the function of CTNND2 and other ‘female’ autism mutations may help researchers to better understand how autism manifests in women, says **Evan Eichler**, professor of genome sciences at the University of Washington in Seattle, who was not involved with the study. “This paper tells us we should be considering different types of mutations and genes when thinking about females with autism,” he says.

References:

1: Turner T.N. *et al. Nature* Epub ahead of print (2015) **Abstract**