NEWS

SHANK3 mutations turn up in high proportion of autism cases

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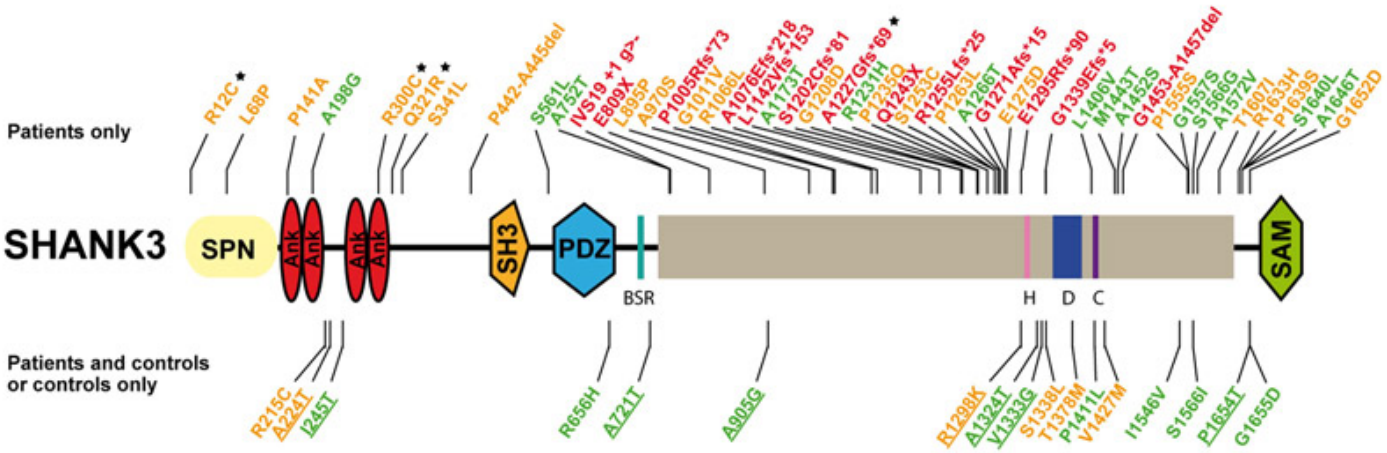

About 2 percent of people who have both autism and intellectual disability carry harmful mutations in **SHANK3**, a protein that helps organize the connections between neurons, according to a study published 4 September in *PLoS Genetics*[1].

A team of researchers led by **Thomas Bourgeron** first found mutations in SHANK3 in 2007 in just over 200 people with autism[2]. Since then, **several studies**, and **hordes of rodent models**, have cemented SHANK3's role as a risk factor for autism.

Deletion of SHANK3 also leads to **Phelan-McDermid syndrome**, a disorder characterized by low muscle tone, intellectual disability and symptoms of autism.

The new study found a harmful mutation in or deletion of SHANK3 in about 0.7 percent of all people who have autism. This nearly doubles the previously estimated rate, making SHANK3 a top autism gene candidate. For comparison, a deletion of chromosomal region **16p11.2**, one of the

strongest risk factors for autism, is found in about 1 percent of people with autism.

“There are not too many genes with quite as many mutations,” says Bourgeron, professor of genetics at the Institut Pasteur in Paris, France, who led the new study.

The findings suggest that clinicians should routinely sequence SHANK3 when looking for genetic causes of autism.

“We have to do a better job of screening for SHANK3 mutations in people with intellectual disability and autism,” says **Thomas Frazier**, director of the Center for Autism at Cleveland Clinic Children’s, who was not involved with the study. “There’s definitely clinical impact here that’s important.”

Slippery sequence:

Studies have found deletions of the 22q13.3 chromosomal region — which includes SHANK3 — **in people with autism**, as well as smaller deletions affecting only SHANK3. Researchers had much less success finding single-nucleotide changes in the gene, however.

For example, a 2012 study of **965 people with autism** found only one spontaneous mutation in SHANK3 and no ‘truncating mutations’ — those that prevent production of the full protein.

This may be because the gene is extremely difficult to sequence, says Bourgeron. SHANK3 contains a preponderance of guanines and cytosines, which form stronger hydrogen bonds than do adenines or thymines. As a result, the two strands of DNA may not peel apart easily, a necessary step for sequencing.

Bourgeron says his team was able to overcome this problem by designing a new set of primers, which are fragments of DNA that bind to the gene and initiate the sequence. They also corrected errors in the reference sequence, against which researchers compare all gene sequences.

Using this method, they found eight truncating mutations in SHANK3 in 429 people with autism and one more by carefully sequencing a portion of the gene in 138 people with autism.

They also collated known SHANK3 mutations in people with autism from other datasets. Overall, 11 of 2,147 people with autism have a truncating mutation in SHANK3 and 10 of 5,657 have a deletion. They found no reports of truncating mutations in 1,031 controls and only 2 deletions in 19,163 controls.

“I’m hoping that the fact that this paper corrected some of the sequencing problems will spur

people to include SHANK3 in their autism panel," says **Katy Phelan**, director of the cytogenetics laboratory at Tulane University School of Medicine in New Orleans, who was not involved in the study. She identified the first case of Phelan-McDermid syndrome in 1992.

Bourgeron's team also looked for mutations in **SHANK1** and **SHANK2**. These genes, which belong to the same family as SHANK3, have **also been implicated in autism**.

Overall, 0.04 percent of people with autism have a harmful mutation in or deletion of SHANK1 and 0.17 percent have one in SHANK2. Of the three types of mutation, people with a SHANK1 mutation are the least affected and show no signs of intellectual disability, whereas those with a SHANK3 mutation have the most severe symptoms.

"SHANK1, SHANK2 and SHANK3 are very similar proteins, but they are expressed in different parts of the brain," says Bourgeron. "So it's interesting to see that you have a gradient of cognitive impairments."

Although less than 1 percent of people with autism have truncating mutations in or deletions of SHANK3, factors that affect the gene's expression may combine with other mild mutations to trigger autism. "We're just scratching the surface of this stuff and it could account for an even larger percentage of autism," says Frazier.

Still, clinics may not rush to begin sequencing SHANK3 routinely, says **Edwin Cook**, professor of psychiatry at the University of Illinois at Chicago, who was not involved in the study.

"Geneticists, not surprisingly, are usually interested in genetic testing," he says. "They don't take into account whether parents would rather spend money on testing if they don't have insurance for it than on babysitting or therapy."

References:

1: Leblond C.S. *et al. PLoS Genet.* **10**, e1004580 (2014) **PubMed**

2: Durand C.M. et al. Nat. Genet. **39**, 25-27 (2007) **PubMed**