NEWS

Nature of risk mutations varies with families' history of autism

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Large autism-linked mutations tend to be inherited in families with a history of the condition. By contrast, they often arise spontaneously in families with a single affected person, suggests a new study[1].

The findings validate something researchers have long assumed: Studying multiplex families — those in which two or more siblings have autism — yields clues about autism's heritability, whereas simplex families point to spontaneous, or *de novo*, mutations.

"The kinds of families you pick will influence what kinds of genetic variation you find," says lead investigator **Daniel Geschwind**, distinguished professor of neurology, psychiatry and human genetics at the University of California, Los Angeles.

In the new study, his team found that large deletions or duplications of DNA tend not to occur spontaneously in multiplex families. These large mutations are called **copy number variants** (CNVs). They are known to be enriched in people with autism from simplex families, but their role in multiplex families was unclear.

The study, described 1 September in the *American Journal of Human Genetics*, also reveals a twist: Even though CNVs in multiplex families tend to be inherited, not all the siblings with autism in those families carry the same CNV. The finding suggests that other factors besides the CNV contribute to their condition.

"The take-home message is, if you just focus on one particular flavor of genetic variation, you don't get the whole story," says **Jonathan Sebat**, chief of the Beyster Center for Genomics of Neuropsychiatric Diseases at the University of California, San Diego. Sebat was not involved in the study.

Sibling rivalry:

Geschwind's team looked for rare CNVs found in less than 1 percent of the population. Of the 1,532 families with autism they looked at, 78 percent have more than one child with the condition; the rest are simplex families. The DNA samples came from the **Autism Genetic Resource Exchange**.

The researchers then compared CNVs in the individuals who have autism with CNVs in the unaffected siblings. They found a total of 524 rare CNVs; these CNVs are present in 147 of the children with autism but only 36 of their unaffected siblings.

Most of these mutations were inherited from the parents: Only 27 of the children with autism (about 2 percent) and 1 unaffected sibling carry a spontaneous CNV. By contrast, a 2015 study of 2,591 simplex families found **spontaneous CNVs in nearly 4 percent** of children with autism.

The lower rate in the new study suggests that people in multiplex families, which make up the bulk of the study group, tend not to have *de novo* CNVs.

Random differences:

Two of the CNVs in the children with autism lie in a region of chromosome 2 called 2q24.1, which has not previously been linked to autism. After searching two other public datasets, the researchers found five more individuals who have autism-like features and CNVs in the same region.

The researchers then restricted their analysis to the 49 CNVs they found in regions previously linked to autism. They found that 24 of these CNVs were inherited and 19 arose spontaneously. (They were unable to determine the inheritance of the remaining six CNVs).

Altogether, these autism-linked CNVs occur 3.3 times more often in children with autism than in their unaffected siblings, the study found.

Unexpectedly, the researchers found that siblings with autism rarely share the same autism-linked CNV. In 21 multiplex families, the mutation the researchers found is not present in all children with autism in the family.

"You would expect these individuals to share the predisposing factors," says study investigator **Rita Cantor**, professor of human genetics at the University of California, Los Angeles Medical School.

The findings add to mounting evidence that siblings with autism can **carry different genetic risk factors** for the condition. In these cases, the CNV might contribute to autism but not be the primary cause. "It's just one of the many potential causes," Cantor says.

REFERENCES:

1. Leppa V.M. *et al. Am. J. Hum. Genet.* **99**, 540-554 (2016) **PubMed**