NEWS

Sibling study bolsters role of common variants in autism

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Children with autism, as a group, are genetically more similar to one another than to a group of their unaffected siblings, a new study suggests[1]. The findings support the notion that people with the condition share common inherited variants that boost autism risk.

Studies comparing people who have autism with unrelated controls suggest common variants can contribute as much as **49 percent** to autism risk. But ethnic differences between the two groups in previous studies may have skewed this estimate too high, says **Michael Wigler**, professor at Cold Spring Harbor Laboratory in New York.

In the new study, Wigler and his team compared people with autism with their unaffected siblings, who have similar genetic backgrounds. They found strong evidence that variants of small effect that are passed down for generations contribute to autism risk, Wigler says. “It was significant at a very substantial level,” he says.

The study does not provide an estimate of how much common variants contribute to autism risk. But it adds to mounting evidence that these variants play an important role, says **David Goldstein**, director of the Institute for Genomic Medicine at Columbia University in New York, who was not involved in the study.

“In science, it’s nice to have completely independent ways of showing things,” Goldstein says. “This is a neat, clever, independent way of implicating inherited variation.”

Sibling differences:

Much of the work on autism genetics so far has focused on rare, harmful variants that arise in the egg or sperm before or shortly after conception. Researchers have made substantial inroads in **identifying these de novo variants**

by focusing on simplex families, which have a single child with autism.

Wigler's team looked at single letter variants in sequences from the **Simons Simplex Collection** (SSC), a repository of genetic and medical information from simplex families. (The SSC is funded by the Simons Foundation, *Spectrum*'s parent organization.)

The researchers measured the frequency of common variants in 2,591 children with autism and 2,113 unaffected siblings. Overall, children with autism share more of these variants with one another than with their siblings, the researchers found.

Unaffected siblings do not share more variants with one another than they do with children who have autism. And the children's parents are just as genetically similar to the children with autism as they are to the unaffected siblings. These results suggest that the shared variants in the autism group contribute to the condition.

The findings held up when the researchers restricted their analysis to white or male-only sibling pairs to control for the influence of ethnicity or gender.

Family effect:

The researchers repeated their analysis using genetic data from a separate group of 1,374 children with autism. These data came from the Autism Genome Resource Exchange (AGRE), a repository of families that have multiple children with autism. The AGRE children with autism share more common variants with children who have autism in the SSC than with the unaffected siblings group in the SSC.

Because the AGRE families have multiple affected children, these children would be expected to carry more inherited variants tied to autism than children from simplex families. Using statistical tests, the researchers found support for this prediction, suggesting that their approach is valid.

Fathers of children in the AGRE group, but not those in the SSC group, share more common variants with the SSC children who have autism than with their unaffected siblings. Mothers from neither group show this relationship.

This result suggests that fathers are more likely than mothers to pass down variants that increase autism risk. The finding needs to be replicated, Wigler says, but it is surprising because it runs counter to the theory that women must **carry more risk variants** before they show autism features — and so would be more likely than men to transmit risk factors to their children.

"This is a very ripe area for further comprehension and observation and thinking," Wigler says.

The new approach is unlikely to provide an estimate of the contribution of common variants to autism risk, Wigler says. But he plans to use it to estimate how many common variants increase the risk, and how recently in evolution they arose.

REFERENCES:

1. Ye K. *et al. Proc. Natl. Acad. Sci. USA* **114**, 7073-7076 (2017) **PubMed**