NEWS

Common variants, rare mutations combine to shape autism risk

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Children with autism inherit a greater burden of common genetic variants associated with autism than would be expected by chance[1]. These variants combine with rare, spontaneous autism mutations to boost autism risk. The unpublished results were presented today at the **2017 International Meeting for Autism Research** in San Francisco, California.

Researchers have identified several rare, *de novo* mutations that may cause autism. But these mutations account for less than 10 percent of autism cases and do not account for why the

condition runs in families. Common variants, although harder to find, are thought to contribute to a much larger proportion of autism cases.

The new study, which was **posted on the preprint server bioRxiv** in November, shows that these two types of variants work together to shape autism risk.

“The additivity hypothesis has been around for a long time,” says lead researcher **Elise Robinson**, assistant professor of epidemiology at Harvard University. “But this is the first time we can clearly see evidence of it.” **Daniel Weiner**, an analyst in Robinson’s lab, presented the results.

Ordinarily, a child’s propensity for a complex trait, such as height, is the average of that of each of his parents. The study relies on a new statistical method to calculate whether children inherit a certain measure of this propensity — called a polygenic risk score — that is greater than this average.

The findings revealed that children with autism have a higher polygenic risk score for the condition than would be expected from their parents’ scores. By contrast, they inherit the average of their parents’ scores for body mass index, a measure of body fat.

These children also carry an atypically high burden of common genetic variants that are normally associated with greater educational achievement. This measure of ‘educational attainment’ is taken as a proxy of intelligence.

This finding is surprising given that many *de novo* mutations tied to autism are associated with intellectual disability.

“This paper shows that that those two types of variants work in opposite ways,” says **Jonathan Flint**, professor of psychiatry and biobehavioral sciences at the University of California, Los Angeles, who was not involved with the study.

Tipping the balance:

The researchers used their new test, called the polygenic transmission disequilibrium test, to analyze data from 6,454 children with autism and their first-degree relatives. The test controls for variables that can influence a particular trait, such as socioeconomic status.

Among children with autism, the pattern of polygenic risk inheritance is similar for boys and girls with the condition and for children with and without intellectual disability.

Children with autism have unexpectedly high risk scores for schizophrenia, which is also typically associated with low intelligence quotients (IQ). However, the study does not identify specific common variants tied to any of these conditions.

Of the 6,454 children with autism included in the analysis, 221 are known to carry a rare, *de novo* mutation. This class of mutations is thought to confer a 20-fold increase in autism risk. Many children with autism who carry *de novo* mutations also have intellectual disability, motor delays or seizures.

The findings fit with the **'second-hit' hypothesis** of autism, in which common variants contribute to the differences seen among individuals with similar *de novo* mutations.

"It is important to realize that *de novo* mutations are really important in autism, but by definition they are not the inherited part of autism," says **Thomas Bourgeron**, professor of genetics at the Institut Pasteur in Paris, who was not involved with the study.

Common variants that influence autism risk are "neurologically gentle" compared with *de novo* mutations, Robinson says. Whereas *de novo* variants are associated with global developmental delay and **epilepsy**, she says, "the common polygenic influences don't show these patterns and, in many cases, are associated with positive outcomes, like higher IQ."

The researchers plan to use their test to determine whether children with autism also inherit a disproportionate number of variants associated with autoimmune conditions or parental age.

*For more reports from the 2017 International Meeting for Autism Research, please **click here**.*

REFERENCES:

1. Weiner D.J. *et al. Nat. Genet.* Epub ahead of print (2017) **Abstract**