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Gene-Disrupting Ultra-Rare Variants More Common in Children With Autism Spectrum Disorder

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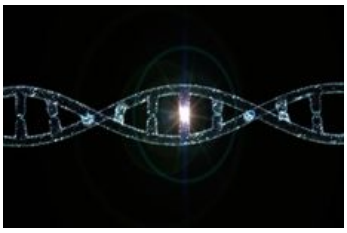

NEW YORK — Ultra-rare genetic variants that likely disrupt genes are more common among children with autism spectrum disorder, a new study has found.

Autism spectrum disorder affects about 1 in 59 children in the US, and while *de novo* mutations are known to account for part of autism risk, the role of ultra-rare variants in disease risk has been less studied.

Researchers led by the University of Washington's Evan Eichler used whole-genome sequencing data from nearly 3,500 families with either multiplex or simplex autism spectrum disorder to examine the transmission of ultra-rare variants among affected individuals.

"We focused on this other class of variants because only a relatively small fraction (estimates of about 20 to 25 percent) are thought to be explained by *de novo* disruptive mutations or large copy number variants," Eichler said in an email. "We were searching for another class of impactful gene disruptive events that might explain more of the genetic cause of autism."

As they reported in *Nature Genetics* on Monday, he and his colleagues found that children with autism were more likely to have ultra-rare genetic variants that likely disrupt genes than their unaffected siblings and that these variants tend to converge on biological pathways like the E3 ubiquitin-protein ligase complex signaling pathway. The findings further support a multi-hit model for autism, the researchers said.

The researchers sequenced more than 2,500 samples from nearly 400 families with multiplex autism and about 250 families with simplex autism and combined that data with previously published data to generate a combined dataset of 4,363 individuals with autism, 2,235 unaffected siblings, and parent-child SNV data from 774 multiplex and 2,700 simplex families. Overall, there were 26.6 million unique private mutations among both affected children and their unaffected siblings.

By comparing the siblings, the researchers found ultra-rare variants were more common among the siblings with autism and that this signal became stronger as genes become less tolerant to mutations. At the same time, though, that signal was still present among genes that are more tolerant to mutations. This, Eichler noted, contrasts with the pattern found among *de novo* mutations associated with autism.

The researchers further homed in on a set of 163 candidate genes and noted that several of them were involved in pathways previously tied to autism spectrum disorder risk. For instance, there was an enrichment of genes in the E3 ubiquitin ligase pathway, which is involved in proteasome degradation and has a known role in autism.

The burden of private ultra-rare likely gene-disrupting variants was higher among children from multiplex families, though still present among children from simplex families.

According to the researchers, their findings support a multi-hit model for the development of autism. "Our estimates suggest the [multi-hit model] is a big contributor especially among cases where autism runs in the family," Eichler said, adding that it could be "as important as *de novo* mutations — so it doesn't explain all cases but is part of the missing genetics of the disorder."

He and his colleagues estimated that ultra-rare transmitted likely gene-disruptive variants account for about 4.5 percent of ASD risk — *de novo* SNVs and indel contribute, by comparison, between 6 percent and 9 percent of autism risk — and suggested that these are an understudied class of variants.

Next, Eichler said he and his lab will be studying the individual genes that contribute to this signal, an analysis he noted will require very large sample sizes.

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