

Variants in non-coding DNA contribute to inherited autism risk

19 April 2018



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In recent years, researchers have firmly established that gene mutations appearing for the first time, called *de novo* mutations, contribute to approximately one-third of cases of autism spectrum disorder (ASD). In a new study, an international team led by scientists at University of California San Diego School of Medicine have identified a culprit that may explain some of the remaining risk: rare inherited variants in regions of non-coding DNA.

The findings are published online in the April 20, 2018 issue of *Science*.

The newly discovered risk factors differ from known [genetic causes](#) of autism in two important ways. First, these variants do not alter the genes directly but instead disrupt the neighboring DNA control elements that turn genes on and off, called cis-regulatory elements or CREs. Second, these variants do not occur as new mutations in children with autism, but instead are inherited from their parents.

"For ten years we've known that the genetic causes of autism consist partly of *de novo* mutations in the protein sequences of genes" said Jonathan Sebat, a professor of psychiatry, cellular

and molecular medicine and pediatrics at UC San Diego School of Medicine and chief of the Beyster Center for Genomics of Psychiatric Genomics. "However, gene sequences represent only 2 percent of the genome."

To investigate the other 98 percent of the genome in ASD, Sebat and his colleagues analyzed the complete genomes of 9,274 subjects from 2,600 families. One thousand were sequenced in San Diego at Human Longevity Inc. (HLI) and at Illumina Inc., and DNA sequences were analyzed at the San Diego Supercomputer Center at UC San Diego. These data were then combined with other large studies from the Simons Simplex Collection and the Autism Speaks MSSNG Whole Genome Sequencing Project.

The researchers then analyzed structural variants, deleted or duplicated segments of DNA that disrupt regulatory elements of [genes](#), dubbed CRE-SVs. From the complete genomes of families, the researchers found that CRE-SVs that are inherited from parents also contributed to ASD.

"We also found that CRE-SVs were inherited predominantly from fathers, which was a surprise," said co-first author William M. Brandler, PhD, a postdoctoral scholar in Sebat's lab at UC San Diego and bioinformatics scientist at HLI.

"Previous studies have found evidence that some protein-coding variants are inherited predominantly from mothers, a phenomenon known as a maternal origin effect. The paternal origin effect we see for non-coding variants suggests that the inherited genetic contribution from mothers and fathers may be qualitatively different."

Sebat said current research does not explain with certainty what mechanism determines these parent-of-origin effects, but he has proposed a plausible model.

"There is a wide spectrum of genetic variation in the human population, with coding variants having strong effects and noncoding variants having weaker effects", he said. "If men and women differ in their capacity to tolerate such variants, this could give rise to the parent-of-origin effects that we see."

More information: Paternally inherited cis-regulatory structural variants are associated with autism, *Science* (2018). DOI: [10.1126/science.aan2261](https://doi.org/10.1126/science.aan2261)

Provided by University of California - San Diego

APA citation: Variants in non-coding DNA contribute to inherited autism risk (2018, April 19) retrieved 25 October 2021 from <https://medicalxpress.com/news/2018-04-variants-non-coding-dna-contribute-inherited.html>

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