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Genetic changes that cause autism are more diverse than previously thought

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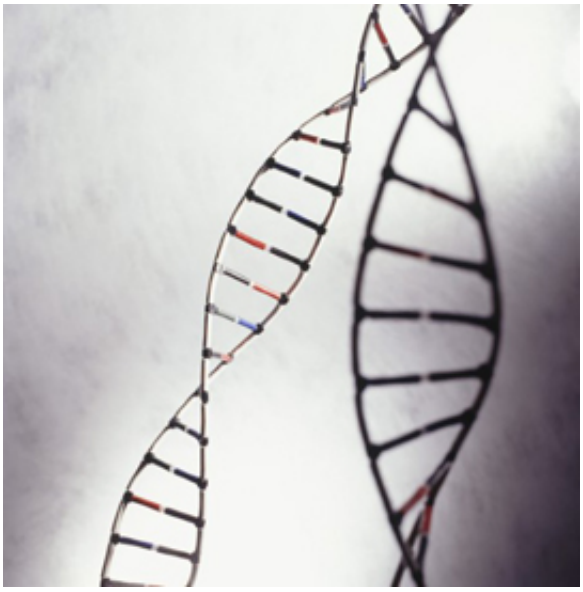

Credit: NIH

The types of gene mutations that contribute to autism are more diverse than previously thought, report researchers at University of California, San Diego School of Medicine in the March 24 online issue of *The American Journal of Human Genetics*. The findings, they say, represent a significant advance in efforts to unravel the genetic basis of autism spectrum disorder (ASD).

To conduct their study, researchers enrolled hundreds of volunteers from families with one child affected by ASD and sequenced the complete

genomes of every family member, including the parents and typically developing siblings. The researchers then looked for *de novo* mutations, gene alterations that appear spontaneously in one's offspring and are due to a mutation in a father's sperm or a mother's egg. Based on the authors' previous discoveries, it is known that *de novo* mutations contribute to risk, particularly in sporadic cases where there is no family history of autism.

The most common type of *de novo* mutations are spelling mistakes that change a single letter of the DNA code. However, in their new study, the researchers discovered many other mutations that introduce changes that are more complex. Called structural variants, these alterations involve the insertion or deletion of entire words or sentences of the DNA code.

The research team found a surprising variety of spontaneous mutations, from simple deletions or insertions to "jumping genes" - elements of DNA that copy and paste themselves into other parts of the genome. They also found that structural mutations sometimes occur in tight clusters where a combination of different mutations occur all at once.

"These mutations can insert, delete or in some cases scramble the DNA sequence," said senior author Jonathan Sebat, PhD, associate professor of psychiatry and cellular and molecular medicine and director of the Beyster Center for Genomics of Psychiatric Disease at UC San Diego School of Medicine.

Sebat and colleagues discovered that spontaneous structural mutations occurred at a surprisingly high rate in individuals - 20 percent—and mutations in autism tended to disrupt genes. "Children with autism do not have more mutations overall," said Sebat, "but their mutations are more likely to disrupt genes involved in brain development."

The study, Sebat noted, highlights several genes that could play a key

role in brain development. For example, the scientists identified a deletion in one gene called "stargazin" that is required for regulating the transmission of signals between neurons in the brain.

"Mutations in stargazin are very rare," said first author, William Brandler, PhD, a postdoctoral scholar in Sebat's lab, "but they point us to a biochemical pathway that may be important for social development. In the future, discoveries like this could lead to more effective personalized treatments for autism."

More information: *The American Journal of Human Genetics*, dx.doi.org/10.1016/j.ajhg.2016.02.018

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