Noncoding mutations contribute to autism risk

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A whole-genome sequencing study of nearly 2,000 families has implicated mutations in 'promoter regions' of the genome—regions that precede the start of a gene—in autism. The study, which appears in the December 14 issue of *Science*, is the first genome-wide analysis to uncover a role for mutations in the noncoding portion of the genome in any human condition.

Most sequencing studies of autism and other conditions have focused on the coding portion of the genome—that is, the genes, which encode the recipe for each protein a cell can build. But more than 98 percent of the human genome consists of material other than genes. "We wouldn't have that DNA if it didn't do something," says Stephan Sanders of the University of California, San Francisco, one of the scientists who led the new study.

Mapping the role of these noncoding regions in conditions such as autism is vastly more difficult than mapping the role of genes, both because of the volume of data and because the functions of these noncoding regions are poorly understood. But the new study shows that 2,000 families' worth of data is enough to start extracting a signal from the noise.

Sanders' team looked at 1,902 'quartets'—families that include one child with autism, unaffected parents and an unaffected sibling—in the Simons Simplex Collection, a repository of data from families with autism. In promoter regions of the genome, the study found, children with autism have more de novo mutations (spontaneous mutations that aren't inherited from a parent) than their siblings do.

"Being able to show that de novo mutations in noncoding regions contribute to autism is phenomenally exciting," Sanders says. "It's our first chance to really come to grips with rare mutations in the other 98 percent of the genome."

Some of the mutations, the team found, are in promoters for genes involved in neuronal differentiation or developmental delay, as well as genes that interact with CHD8, one of the most common autism risk genes.

"All of that collectively fits," says Alan Packer, a senior scientist at the Simons Foundation Autism Research Initiative. "It's a reassuring sign that they're on the right track."

The signal appears strongest in promoter regions that are conserved across many different animal species, rather than parts of the genome that are uniquely human. "Although autism is a very human trait, the mechanisms involved are potentially ones that have been with us for millions of years," Sanders says. The finding suggests, encouragingly, that animal models of autism may indeed help illuminate the condition, despite the differences among species.

Promoter regions play a key role in determining which types of cells express a particular gene, and

during which stages of development. So the new finding may shed light on autism traits that cannot be understood by looking at genes alone. "The eventual long-term payoff of the study may be in pointing to particular places and times in brain development that you want to focus on, from among the many possibilities," Packer says.

The study was made possible by the unique design of the Simons Simplex Collection, which not only makes available whole-blood samples that allow for sequencing studies, but also focuses on 'simplex' families, which have one affected child and unaffected parents and siblings—precisely the families in which de novo mutations are most likely to be found. The structure of the collection, which was launched in 2006, "has been hugely influential," Packer says, not just for autism research but also for completely different conditions, such as congenital heart disease. Researchers of such conditions have followed the collection's lead in looking for de novo mutations in simplex families.

Researchers can soon take the new study's approach to an entirely different level, via whole-genome sequencing of families in the SPARK cohort study. SPARK includes behavioral data and DNA from about 21,000 families. The New York Genome Center has begun whole-genome sequencing on 400 SPARK families, with another 400 families in the pipeline and many more planned for 2019. "SPARK is the largest study of autism in the United States," says lead investigator Wendy Chung of Columbia University. "With a goal of studying over 50,000 individuals with autism, we will be confident of the genetic factors we identify."

More information: J.-Y. An el al., "Genome-wide de novo risk score implicates promoter variation in autism spectrum disorder," *Science* (2018). science.sciencemag.org/cgi/doi … 1126/science.aat6576

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