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Variants in Non-Coding DNA Contribute to Inherited Autism Risk

These regulatory elements heighten risk—and are inherited predominantly from the father

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.”

Co-authors include joint co-first authors Danny Antaki and Madhusudan Gujral, Morgan L. Kleiber, Michelle S. Maile, Oanh Hong, Timothy R. Chapman, Shirley Tan, Prateek Tandon, Keith K. Vaux, Karen S. Messer, Caroline M. Nievergelt, Eric Courchesne, Karen Pierce, Alysson R. Muotri and Lilia M. Iakoucheva, UC San Diego; Joe Whitney, Gaganjot Kaur, Zhuozhi Wang and Bhooma Thiruvahindrapuram, The Hospital for Sick Children, Toronto; Timothy Pang, Shih C. Tang and Christina Corsello, UC San Diego and Rady Children’s Hospital; Yan Yang, Eoghan Harrington, Sissel Juul and Daniel J. Turner, Oxford Nanopore Technologies, NY and UK; Stephen F. Kingsmore, Rady Children’s Hospital; Joseph G. Gleeson, UC San Diego, Rady Children’s Hospital and Howard Hughes Medical Institute; Denis Bisson, Boyko Kakaradov and Amalio Telenti, Human Longevity Inc., San Diego; J Craig Venter, Human Longevity Inc. and J Craig Venter Institute; Roser Corominas, Universitat Pompeu Fabra and CIBERER, Spain; Claudio Toma, Universitat de Barcelona, Spain and Neuroscience Research Australia; Bru Cormand, CIBERER, Universitat de Barcelona and Institut de Recerca Sant Joan de Deu, Spain; Isabel Rueda, Hospital Sant Joan de Deu; Silvina Guijarro and Amaia Hervas, Hospital

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Disclosures: Jonathan Sebat has declared that a patent has been issued to the Cold Spring Harbor Laboratory (U.S. Patent 8554488) on genetic methods for the diagnosis of autism.

Alysson Muotri is a co-founder and has equity interest in TISMOO, a company dedicated to genetic analysis focusing on therapeutic applications customized for autism spectrum disorder and other neurological disorders with genetic origins. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies.

Full study: http://science.sciencemag.org/content/360/6386/327.full

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