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Autism linked to increased genetic change in regions of genome instability

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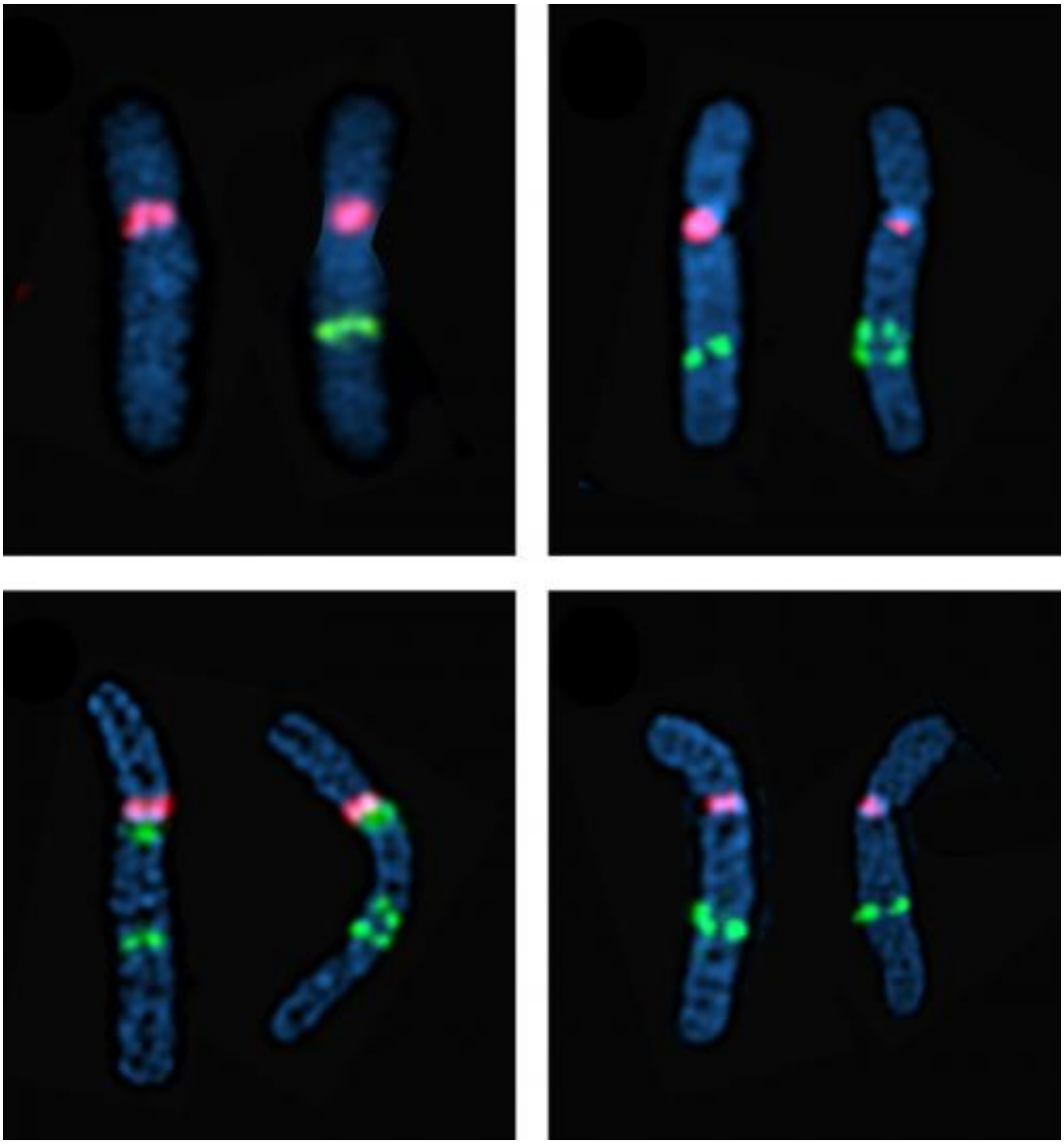

These microscopic images were taken as part of research to explore rearrangements of DNA in one of the "hotspots" of the human genome, where

deletions and duplications occur at higher rates. Credit: Betsy Hirsch/University of Minnesota and Scott Selleck/Penn State University

(Medical Xpress)—Children with autism have increased levels of genetic change in regions of the genome prone to DNA rearrangements, so called "hotspots," according to a research discovery to be published in the print edition of the journal *Human Molecular Genetics*. The research indicates that these genetic changes come in the form of an excess of duplicated DNA segments in hotspot regions and may affect the chances that a child will develop autism—a behavioral disorder that affects about 1 of every 88 children in the United States, according to the Centers for Disease Control.

Earlier work had identified, in children with autism, a greater frequency of rare DNA deletions or duplications, known as DNA copy number changes. These rare and harmful events are found in approximately 5 to 10 percent of cases, raising the question as to what other genetic changes might contribute to the disorders known as autism spectrum disorders.

The new research shows that children with autism have—in addition to these rare events—an excess of duplicated DNA including more common variants not exclusively found in children with autism, but are found at elevated levels compared to typically developing children. The research collaboration includes groups led at Penn State by Scott Selleck; at the University of California Davis/MIND Institute by Isaac Pessah, Irva Hertz-Picciotto, Flora Tassone, and Robin Hansen; and at the University of Washington by Evan Eichler.

The investigators also found that the balance of DNA duplications and deletions in children with autism was different from that found in more severe developmental disorders, such as intellectual disability or multiple

congenital anomalies, where the levels of both deletions and duplications are increased compared to controls, and are even higher than in children with autism.

They also found that children who had more difficulty with daily living skills also had the greatest level of copy number change throughout their genome. "These measures of adaptive behavior provide an indication of the severity of the impairment in the children with autism. These behaviors were significantly correlated with the amount of DNA copy number change," Selleck said, emphasizing that the research revealed "clear and graded effects of the genetic change."

"These results beg the question as to the origin of this genetic change," Selleck said. "The increased levels of both rare and common variants suggests the possibility that these individuals are predisposed to genetic alteration."

A vigorous debate is ongoing in the research community about the degree of genetic versus environmental contributions to autism. Selleck said the finding of an overall increase in genetic change in children with autism heightens the need to search for the basis of this variation. "We know that environmental factors can affect the stability of the genome, but we don't know if the DNA copy number change we detect in these children is a result of environmental exposures, nutrition, medical factors, lifestyle, genetic susceptibility, or combinations of many elements together," Selleck said. "The elevated levels of common variants is telling us something. It suggests that pure selection of randomly generated variants may not be the whole story."

The Penn State team includes Department of Biochemistry and Molecular Biology Associate Professor Marylyn Ritchie and Assistant Professor Santhosh Girirajan. "The relationship between the level of copy number change and the degree of neurodevelopmental disability is

something we have noted previously for large, rare variants" says Girirajan, "but this work extends those observations to common copy number variants, suggesting the level of copy number change in children with autism is larger than we had appreciated." Girirajan, the first author of the study, coordinated the effort between the Penn State and University of Washington researchers.

The research collaboration began with studies supported by the Minnesota Medical Foundation and the Martin Lenz Harrison Endowed Chair in Pediatrics when Selleck was Director of the Autism Initiative at the University of Minnesota. When Selleck arrived at Penn State in 2009, he began a new phase of the analysis with replication studies of early findings conducted with the help and expertise of Evan Eichler and colleagues at the University of Washington using the clinical data and DNA collected by Isaac Pessah, Irva Hertz-Picciotto, Flora Tassone, and Robin Hansen at the University of California Davis/MIND Institute group, which directs a large population-based case-control study of autism called CHARGE (Childhood Autism Risks from Genetics and Environment). In this multiyear study, clinical history, environmental, nutritional, family, and medical data are collected from the families of children with autism and other developmental disorders, as well as from randomly selected control children from the general population. The research took advantage of the CHARGE study, supported by the National Institute of Environmental Health Sciences and the Environmental Protection Agency.

"The CHARGE study is a true population-based case-control cohort for the study of autism, the only one of its kind that I am aware of" says Selleck, and allows for comparisons between the children with autism and controls matched for geographical location and time of birth. The research team plans to continue its collaboration to further characterize the more common genetic variants found to be associated with autism and to explore the relationship between genome variation and

environmental exposures.

More information: Open access paper: hmg.oxfordjournals.org/content … /hmg.ddt136.abstract

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