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25 new autism-related gene variants discovered

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Genetics researchers have identified 25 additional copy number variations (CNVs)—missing or duplicated stretches of DNA—that occur in some patients with autism. These CNVs, say the researchers, are "high impact": although individually rare, each has a strong effect in raising an individual's risk for autism.

"Many of these gene variants may serve as valuable predictive markers," said the study's corresponding author, Hakon Hakonarson, M.D., Ph.D., director of the Center for Applied Genomics at The Children's Hospital of Philadelphia. "If so, they may become part of a clinical test that will help evaluate whether a child has an autism spectrum disorder."

Hakonarson collaborated with scientists from the University of Utah and the biotechnology company Lineagen, Inc., in the study, published today in the journal PLOS ONE.

The current study builds on and extends previous gene research by Hakonarson and other scientists on autism spectrum disorders (ASDs), a group of childhood neurodevelopmental disorders that cause impairments in verbal communication, social interaction and behavior. Estimated by the CDC to affect as many as one in 88 U.S. children, ASDs are known from family studies to be strongly influenced by genetics.

In the current study, the researchers first analyzed DNA from 55 individuals from Utah families with multiple members diagnosed with

ASDs. Study co-author Mark Leppert, Ph.D., of the University of Utah, had collected the data from these high-risk families. The team identified 153 CNVs as potentially specific to autism.

To investigate these CNVs in a broader ASD population, the study team custom-designed a DNA array with probes for those 153 CNVs, as well as for another 185 CNVs previously reported to be associated with autism. They then analyzed the actual prevalence of all the CNVs in a larger sample set of 3,000 ASD cases and 6,000 control subjects previously gathered in studies by The Children's Hospital of Philadelphia.

The researchers found that 15 of the CNVs found in the family studies, in addition to nine other CNVs found by their custom array, all had odds ratios greater than 2.0, meaning that subjects with those variants had at least two-fold increased risk of having an ASD, compared to controls. Another 31 CNVs previously reported to be associated with autism also had odds ratios above 2.0.

These findings, said Hakonarson, could be incorporated into clinical tests for evaluating children for ASDs. "These high-impact variants could be most useful in advising parents who already have one child with an ASD," said Hakonarson. "If a second child has delays in reaching developmental milestones, testing for these CNVs could help predict whether that child is also likely to develop an ASD." He added that the newly identified variants would need to be added to the existing commercially available diagnostic array in current use.

The CNVs detected in the current study, Hakonarson said, occur in genes involved in neuronal development and signaling pathways—reinforcing similar findings by Hakonarson and colleagues in their ASD-related genomic research published in 2009.

"Many of these gene pathways active in ASDs overlap with those in other nervous system disorders, such as schizophrenia and epilepsy," he added. "At the same time, our results are consistent with other studies suggesting that many different biological pathways, when disrupted, can lead to ASDs." Hakonarson concluded that further research may help establish whether the CNVs reported in the current study may be categorized by how they contribute to specific clinical subtypes of ASDs.

More information: Matsunami N, Hadley D, Hensel CH, Christensen GB, Kim C, et al. (2013) "Identification of Rare Recurrent Copy Number Variants in High-Risk Autism Families and Their Prevalence in a Large ASD Population," *PLOS ONE* 8(1): e52239. doi:10.1371/journal.pone.0052239

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