Gene variants in autism linked to brain development

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New research on the genomics of autism confirms that the genetic roots of the disorder are highly complicated, but that common biological themes underlie this complexity. In the current study, researchers have implicated several new candidate genes and genomic variants as contributors to autism, and conclude that many more remain to be discovered. While the gene alterations are individually very rare, they mostly appear to disrupt genes that play important functional roles in brain development and nerve signaling.

While an association between genomic variants in certain nervous system processes and autism has been hypothesized in the past, the current research definitively links these biological functions to autism.

"This large study is the first to demonstrate a statistically significant connection between genomic variants in autism and both synaptic function and neurotransmission," said senior author Peter S. White, Ph.D., a molecular geneticist and director of the Center for Biomedical Informatics at The Children's Hospital of Philadelphia. Synapses are the contact points at which nerve cells communicate with other nerve cells, while neurotransmitters are the chemical messengers carrying those signals.

"Prior genomic studies of autism have successfully identified several genes that appear to confer risk for autism, but each gene appears to contribute to only a small percentage of cases," said the lead author, Xiaowu Gai, Ph.D. "Our approach considered whether groups of genes

with common biological functions collectively accounted for a greater percentage of autism risk."

The study appears online today in the journal Molecular Psychiatry.

White and colleagues compared the DNA of more than 1,000 children with autism to control sets of healthy subjects, searching for gene variants called copy number variations (CNVs) appearing in the genomes of autistic individuals and their families, but not in healthy controls. The study team reinforced their findings using information from mouse models, showing that mice with abnormal motor and learning behaviors similar to human autistic behaviors were more likely to have CNVs in genes analogous to human autism genes.

"Because the gene alterations that we found influence brain development , our hope is that they may eventually provide clues to developing diagnostic tests as well as treatments for children with autism," said co-author and lead clinician Josephine Elia, M.D., a child psychiatrist at Children's Hospital.

Unlike changes to single bases in DNA, called single-nucleotide polymorphisms (SNPs or "snips"), CNVs are larger alterations in DNA structure—missing or repeated stretches of dozens or hundreds of bases in sequence. CNVs have been implicated in other neuropsychiatric disorders, such as schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder (ADHD)—the latter in a previous study by White and Elia.

In the current research, White and colleagues searched for CNVs in a discovery cohort of 631 children with autism, 1,162 parents of these children, and a healthy control set of 1,775 children. They found nearly 400 inherited CNVs in autism subjects that did not occur in controls. They also analyzed a second cohort of 593 additional autism subjects,

1,109 corresponding parents, and 2,026 healthy controls. This second study found another set of nearly 400 inherited CNVs exclusive to children with autism. Surprisingly, no single gene was frequently disrupted in either set, and only a few genes harbored CNVs in both sets.

Although there was relatively little overlap between sets of CNVs found in the two cohorts, the CNVs tended to occur in genes that affected biological processes relevant to autism. "While individually, CNVs are rare, each of them often appearing only in one family in our study, we found in this study that CNVs tend to occur in genes with similar functional roles—most especially in affecting synapse function, neurotransmission and brain development," said White. "This suggested to us that there may be many different—possibly even hundreds—of genetic paths to autism, with only a few gene alterations relevant to each individual patient. But if those hundreds of genes have similar roles in the nervous system, the end result may lead to the same diagnosis: an autism spectrum disorder."

With many genes possibly involved in autism, adds White, researchers face a stronger challenge in devising gene-based diagnostic tests and eventually developing drug treatments than would be the case if fewer genes were involved.

However, the fact that the current study consistently pointed to the same functional pathways and gene sets associated with neurological processes strongly suggests these pathways could be fruitful targets for further investigation.

More information: "Rare Structural Variation of Synapse and Neurotransmission Genes in Autism," *Molecular Psychiatry*, published online March 1, 2011.

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