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Researchers Identify Copy Number Variation Linked to Autism by Subtracting 'Normal' Variation

By Andrea Anderson [March 19, 2008]
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NEW YORK (GenomeWeb News) – A new copy number variation study is revealing a link between deletions or duplications of a gene on chromosome three and a subset of autism cases.

Researchers from the State University of New York at Stony Brook and elsewhere compared copy number variations in individuals with autism spectrum disorder with those in unaffected controls. Using this approach, which is the same as that touted by the Melville, New York-based company Population Diagnostics, the team identified three autistic subjects with copy number variations that affected a gene coding for the cell adhesion protein called contactin 4. Their results appeared online yesterday in the *Journal of Medical Genetics*.

"The degree of human genomic variation in the normal population is much greater than previously estimated," senior author Eli Hatchwell, director of SUNY Stony Brook's Genomics Core Facility and chief scientific officer and co-founder of Population Diagnostics, said in an e-mail message to *GenomeWeb Daily News*. "Without the normal variation data, it is next to impossible to interpret findings in patients."

Autism and autism spectrum disorders affect roughly one in every 150 children. Though there is widespread variation in symptoms and severity, the conditions in general are characterized by behavioral symptoms that include impaired social interactions and communication as well as altered interests and activities compared with other children.

For this study, the researchers recruited 92 subjects diagnosed with ASD from 81 different families, as well as each child's biological parents. They analyzed blood samples using karyotyping and tested for related conditions called Fragile X and Rett syndrome. Participants with Rett or Fragile X syndromes were excluded from the study.

The researchers looked for copy number variations in the remaining participants by hybridizing their genomic DNA onto tiling path bacterial artificial chromosome arrays. Copy number variants were verified using fluorescent *in situ* hybridization. They also did fine-scale analyses of chromosome three using a custom 385,000 oligonucleotide NimbleGen fine tiling array.

Of the 92 subjects, the researchers identified three subjects from two families who had copy number variations in the same region of their paternally inherited copy of chromosome three.

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These copy number variations interrupted CNTN4, a gene coding for contactin 4, a cell adhesion molecule associated with axons in various parts of the brain.

In general, cell adhesion molecules play roles in neurogenesis and neural network function. In particular, those associated with axons seem to participate in processes such as axonal elongation and the formation of synaptic connections.

Previous research has linked CNTN4 disruption with developmental delays and so-called chromosome 3p deletion syndrome, which is characterized by dysmorphic facial features, smaller head size, and slowed growth and mental development. While none of the subjects in this study who had duplication or deletions in CNTN4 displayed typical chromosome 3p deletion syndrome symptoms, they were all diagnosed with ASD.

“Our work implicates CNTN4 as a candidate gene in ASD,” the authors wrote. “Ongoing efforts are underway to sequence the gene in large numbers of subjects with ASD and normal controls to identify subtle mutations that might be involved in pathogenesis.”

In addition, the authors noted that mutations in a gene coding for a contactin-associated protein have been linked to ASD or ASD-like syndromes.

The researchers hope that this work will ultimately reveal the biology behind a subset of autism cases and perhaps lead to the development of DNA-based diagnostic test that identifies some ASD children earlier — before they display typical behavioral symptoms. This could be beneficial, Hatchwell said, since many believe early educational and behavioral interventions improve the long-term outcomes for those with ASD. Down the road, understanding the CNTN4 connection to some autism cases may also reveal new drug targets.

“[T]he contactin 4 only explains a small percentage of ASD, but that small subset of individuals will likely benefit from research aimed at ameliorating the specific defect they have,” Hatchwell said.

Population Diagnostics, which today announced that its “mutation discovery technology” had a key role in the research, has emphasized the need for understanding normal human variation in order to identify fast, cost-effective, causative biomarkers.

“The approach that Population Diagnostics is taking mirrors that used in this study,” Hatchwell explained. “Namely, it is to use knowledge of genomic variation in large cohorts of normal individuals to interpret findings in the genomes of those with a given disease/disorder.”

He added that the company plans to try to determine this normal variation by creating reference datasets for ethnically defined cohorts of 10,000 individuals each.