Autism, Developmental Delay Gene Candidates Compiled From De Novo Variant, CNV Data

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NEW YORK (GenomeWeb) – *De novo* mutations and copy number variants seem to repeatedly arise in similar genes in individuals with neurodevelopmental diseases (NDD) such as autism spectrum disorder (ASD), intellectual disability (ID), or developmental delay (DD), new research suggests.

Researchers from the University of Washington and elsewhere used exome sequences for a meta-analysis, searching for *de novo* single nucleotide variants and small insertions and deletions in more than 10,900 individuals with ASD or ID/DD. In the process, they uncovered 253 genes that were recurrently altered by such *de novo* mutations, including at least 124 genes with exome-wide significant ties to one or both disorders.

As the team reported online today in *Nature Genetics*, the *de novo* mutations often overlapped with parts of the genome impacted by copy number changes in individuals with NDDs. For example, the findings revealed *de novo* mutations at sites that overlapped with deletion or duplication syndromes as well as sites with other recurrent CNVs.

"Overall, the genes we highlight demonstrate strong conservation, refine pathogenic CNVs, define distinct functional pathways, and support the role of striatal networks in the pathogenicity of both ASD and ID/DD," senior author Evan Eichler, a researcher in the Department of Genome Sciences at the University of Washington School of Medicine, and his co-authors wrote, adding that "the majority of the genes identified in this study present with [*de novo* mutations] in both ASD and ID/DD."

Several prior studies have implicated *de novo* alterations, including CNVs, in NDDs and epilepsy, the authors explained, and high-throughput sequencing methods have pinned down still more *de novo* changes involving single base changes. Even so, they argued that "few attempts have been made to integrate the wealth of CNV data with recent exome sequencing results despite a common mutational model of dosage imbalance."

With that in mind, the researchers brought together information for *de novo* variants found in 10,927 exomes. The participants included 5,624 individuals who had a primary diagnosis of ASD and 5,303 whose main diagnoses was ID/DD.

The team's analyses unearthed 12,172 *de novo* mutations in 253 genes — 9,815 missense mutations affecting 123 genes and 2,357 likely gene-disrupting mutations affecting 145 genes. This candidate gene set was classified into functional clusters and analyzed in relation to CNVs previously found in individuals with ASD, ID, or DD.

For example, the researchers found that at least some of the *de novo* mutations occurred in genes and other parts of the genome that are involved in KIF1A deletion syndrome, 2q37 deletion syndrome, a chromosome 16p11.2 duplication syndrome, and duplications falling on chromosomes 10 and 12.

And while the proportion of ID/DD cases involving *de novo* mutations appeared to be slightly higher than the proportion of individuals with ASD that did, the team noted that *de novo* mutations in 173 of the genes turned up in both ASD and ID/DD.

"While we expect a degree of diagnostic overlap, our results support a common genetic etiology among broad neurodevelopmental phenotypes," Eichler and colleagues concluded. They called the altered genes "candidates for a genotype-first paradigm, in which downstream follow-up of patients with the same *de novo*-disrupted gene is likely to provide additional insights into unique phenotypic features associated with these different genetic subtypes, and additional support for their role in NDD."

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