

## Analyses Narrow in on ASD, Neurodevelopment-Related De Novo Mutations

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NEW YORK (GenomeWeb) – A pair of new studies have described strategies for identifying *de novo* mutations that do — or do not — contribute to autism spectrum disorder, intellectual disability, or other neurodevelopmental conditions.

In one of the two papers, published in *Nature Genetics* today, University of Washington genome sciences researcher Evan Eichler and his colleagues [reported on](#) results from a targeted sequencing study of more than 11,700 individuals with neurodevelopmental disorder, including 6,342 individuals with ASD, and more than 2,800 unaffected controls.

As part of an international Autism Spectrum/Intellectual Disability consortium effort, the team used single-molecule inversion probes to capture protein-coding and splice site portions of 208 genes in cases and controls from 15 prior studies, uncovering 91 genes in which *de novo* mutations were overrepresented in individuals with neurodevelopmental disease.

The set included more than three dozen genes not implicated in such conditions in the past, the team noted. And when they took a closer look at this gene set using phenotypic assessments and functional assays in fruit flies, the researchers started to tease out genes prone to *de novo* mutations in a particular neurodevelopmental disease type, including genes that were most often mutated *de novo* in individuals with ASD.

"Although most genes are clearly risk factors for [neurodevelopmental disorder] in a broad sense, secondary analyses of both the genetic burden and subsequent patient follow-up for 25 genes in 303 cases did highlight genes with a statistical bias toward ASD versus [intellectual disability/developmental delay] diagnosis," Eichler and his co-authors wrote.

In a second [study](#), investigators at the Massachusetts General Hospital, the Broad Institute, Harvard University, and elsewhere presented evidence in favor of restraint — and the use of allele-frequency data for appropriate population controls — when attributing neurodevelopmental risk to *de novo* variants.

That team tapped exome sequences for more than 60,700 individuals from the Exome Aggregation Consortium (ExAC) to interpret *de novo* variant patterns in individuals from almost 9,300 families affected by ASD, intellectual disability, and/or developmental delay.

Nearly one-third of the more than 10,000 *de novo* variants identified in the families appeared to represent standing variation in ExAC, turning up in one or more individuals from ExAC. While *de novo* variants present in ExAC were not associated with ASD, intellectual disability, and/or developmental delay, the remaining *de novo* variants were more common in individuals with those conditions, even after removing psychiatric cases.

By searching for genes that were particularly intolerant to loss-of-function mutations not found in ExAc, the researchers were able to get a better idea of candidate genes with apparent ties to neurodevelopmental conditions — an approach they took forward to a case-control analysis of ASD.

"Our results reinforce that not all *de novo* variants are rare and contribute to risk, while highlighting the tremendous value of large population sequence resources, even for the interpretation of *de novo* variation and complex disease," the researchers wrote. "This aspect is especially important in the case of clinical sequencing, in which the paradigm has unfortunately become that if a protein-altering *de novo* variant is present in the gene of interest, then it is often considered the causal variant. Clearly, not all *de novo* variants are equal, and not all *de novo* variants in a gene contribute to risk in the same manner."

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