NEWS

Analysis winnows list of mutations tied to autism

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As many as one in three rare mutations seen in people with autism have nothing to do with the condition, a new study suggests[1].

Researchers looked at more than 10,000 spontaneous, or *de novo,* mutations identified in people with autism, intellectual disability or developmental delay. *De novo* mutations are non-inherited mutations that are present in a child but not in her parents.

The researchers found about 3,000 of these mutations in a database of sequences from people in the general population. Finding the same mutation at similar rates in people with and without autism casts doubt on the notion that the mutation plays a role in the condition, says lead researcher **Mark Daly**, associate professor of medicine at Massachusetts General Hospital.

The remaining mutations — those seen only in people with neurodevelopmental conditions —tend to affect a select type of genes: those that appear to be especially sensitive to mutation.

The findings, which appeared 13 February in *Nature Genetics*, narrow the search for *de novo* mutations that boost autism risk, Daly says.

“Studies like this offer some very useful criteria by which to evaluate whether a gene is a genuine risk factor worthy of following up,” says **Joseph Gogos**, a neuroscientist at the Zuckerman Mind Brain Behavior Institute at Columbia University, who was not involved in the study.

Rigorous approach:

Daly and his team focused on 10,093 *de novo* mutations in the protein-coding regions of the genome, called the **exome**. They looked at mutations seen in people with autism, their unaffected siblings or in people with intellectual disability or developmental delay. They looked for the same mutations in the **Exome Aggregation Consortium (ExAC),** a database of genetic sequences from nearly 61,000 individuals who do not have any severe developmental conditions.

The team found that 1,854 *de novo* mutations seen in people with autism and 841 variants in unaffected siblings also turn up in ExAC. Similarly, 410 *de novo* mutations seen in individuals with intellectual disability or developmental delay also exist in the ExAC population.

Within this combined group of 3,105 mutations, the researchers looked for mutations most likely to compromise the function of a protein. They found that these so-called ‘loss-of-function’ mutations are no more common in people with neurodevelopmental conditions than they are in unaffected siblings.

Among the remaining 6,988 mutations not seen in the general population, the researchers found significantly more loss-of-function mutations in people with neurodevelopmental conditions than in unaffected siblings. These variants are highly likely to contribute to the conditions, Daly says.

The findings prompt caution in interpreting previous studies that implicate *de novo* mutations in autism.

“There's an assumption in the literature that *de novo* variation must be causative,” says **Dan Arking**, associate professor of genetic medicine at Johns Hopkins University School of Medicine in Baltimore, who was not involved in the study. “The data here is quite compelling in suggesting that we need a much more rigorous approach.”

Zeroing in:

Daly’s team investigated whether *de novo* mutations seen only in people with neurodevelopmental conditions affect genes that appear to be **intolerant to mutation**. The genes do turn out to show a mutation rate in the general population that is lower than would be expected by chance — hinting that evolution selects against mutations in these genes.

The team found three times as many loss-of-function mutations in intolerant genes in people with autism as in their unaffected siblings.

“We've been able to zero in on a much smaller set of *de novo* variants that have a much bigger impact on risk,” Daly says.

The new findings overlap with those from another analysis last year, led by **Ivan Iossifov** at Cold Spring Harbor Laboratory in New York. Iossifov and his colleagues also found that genes with strong ties to autism have **fewer mutations** than would be expected by chance.

The new study “makes a convincing argument that focusing on variants that are missing in population samples and [that] fall in intolerant genes is a powerful strategy for analyzing genetic data,” Iossifov says.

Daly and his team validated their findings in a new population. They found that loss-of-function mutations in intolerant genes are significantly more common among 404 people with autism than in 3,654 controls from Sweden.

The researchers say their analysis doesn’t result in a definitive list of genes underlying autism. Rather, it puts the genes on a spectrum, with some having a hefty influence on the condition and others far less.

REFERENCES:

1. Kosmicki J.A. *et al. Nat. Genet.* **49**, 504-510 (2017) **PubMed**