Rare recessive mutations pry open new windows on autism

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Over the past decade, autism spectrum disorder has been linked to mutations in a variety of genes, explaining up to 30 percent of all cases to date. Most of these variants are de novo mutations, which are not inherited, affect just one copy of a gene, and are relatively easy to find. The lab of Timothy Yu, MD, Ph.D., at Boston Children's Hospital chose a road less travelled, tracking rare recessive mutations in which a child inherits two "bad" copies of a gene.

The study, involving one of the largest cohorts to date, suggests that recessive mutations are more common in autism than previously thought. The findings, published June 17 in *Nature Genetics*, provide a likely explanation for up to 5 percent of all autism cases and offer new clues to autism's biological causes.

"This is the deepest dive yet into recessive mutations in autism—but we're not done," says Yu, who led the study with first author Ryan Doan, Ph.D., in Boston Children's Division of Genetics and Genomics. "This study offers a glimpse of an interesting part of the puzzle we've yet to assemble."

Doubling down on double hits

Recessive mutations have been linked to autism in the past, mostly in small study populations in areas where marriages between relatives are common. When parents are fairly closely related genetically, their offspring are more likely to get "double hits" of genetic variants—mostly harmless, but some of which may be disease-causing.

The new study represented a much broader population: 8,195 individuals

in the international Autism Sequencing Consortium, founded by study co-author Joseph Buxbaum, Ph.D., of the Icahn School of Medicine at Mount Sinai. The study included 2,343 individuals affected with autism from the U.S., the U.K., Central America, Germany, Sweden, the Middle East, and Finland. It examined whole-exome data, comparing DNA sequences for all protein-coding genes in these individuals with autism, versus 5,852 unaffected controls.

The researchers first looked for "loss of function" or "knockout" mutations that completely disabled the gene, such that the proteins they normally encode are truncated and non-functional. "The concept is simple, though the execution took a lot of careful work," says Doan, who was the study's first author.

The team identified loss-of-function mutations that were both rare (affecting less than 1 percent of the cohort) and biallelic (affecting both copies of the gene) in 266 people with autism. Overall, people with autism were 62 percent more likely than the control group to have disabling mutations in both copies of a gene.

The team also looked for biallelic missense mutations, which involve a change in a single amino acid (a "spelling error"). Missense mutations are more common than loss-of-function mutations, and some of them cause just as much damage. Biallelic missense mutations, too, were significantly more common in the autism group.

Biological clues

After excluding genetic variants that were also found in the control group and in a separate large cohort of more than 60,000 individuals without autism, Doan, Yu and colleagues were left with 41 genes that were knocked out only in individuals with autism. Overall, the researchers estimate that these genes explain another 3 to 5 percent of all

cases of autism (2 percent from loss-of-function mutations, and 1 to 3 percent from missense mutations).

Eight of these had already been flagged in previous studies. The remaining 33 had never been linked to autism before, and several have intriguing attributes that call out for more investigation.

One gene, SLC1A1, for example, helps modulate activity of the brain neurotransmitter glutamate, and has been linked to a metabolic disorder associated with intellectual disability and obsessive-compulsive disorder. Another gene lost in two brothers, FEV, is critical for making the brain neurotransmitter serotonin, providing further support for the idea that dysfunction of serotonin signaling is central to autism.

Many of the double knockouts were found in just one individual and would need to be confirmed in other patients, Yu notes.

Male susceptibility to autism confirmed

Rates of autism are known to be higher among males than females, in a roughly 4:1 ratio. Yet previous studies, mostly looking at de novo mutations have found that boys tend to have milder mutations and girls tend to have more severe mutations, a seeming contradiction.

"One hypothesis is that the female brain is somehow more robust—that it has more reserve and are more resistant to autism, so it takes a bigger hit to knock them down," says Yu. "We asked, does the same pattern hold true for recessive mutations? And we found that it does—females had a higher rate of complete gene knockout than males."

In fact, a surprising 1 in 10 girls had a biallelic gene knockout caused by either loss-of-function mutations or severe missense mutations. And interestingly, one boy with autism lost a gene involved in estrogen

signaling, suggesting that something in the estrogen pathway could be a risk factor for autism.

More information: Recessive gene disruptions in autism spectrum disorder, *Nature Genetics* (2019). DOI: 10.1038/s41588-019-0433-8

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