Mutations in life's 'essential genes' tied to autism

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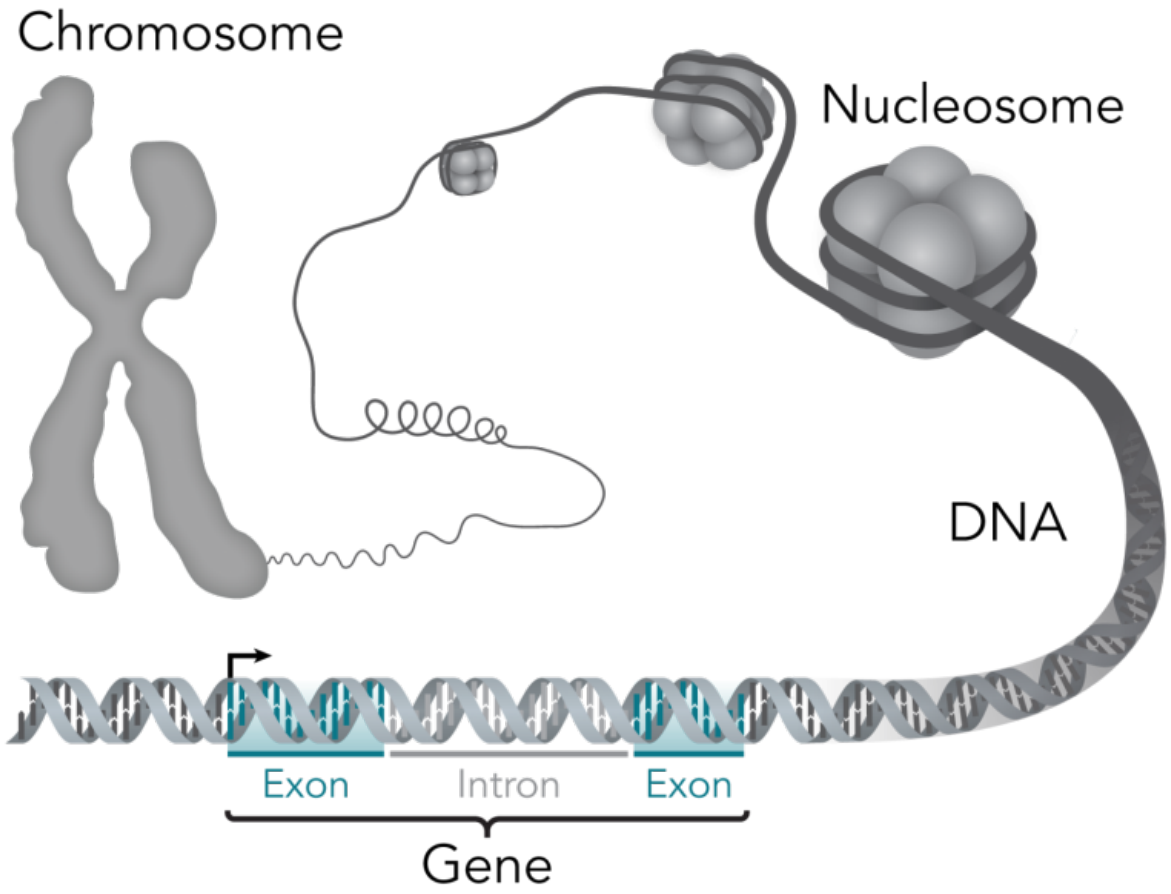

This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

Genes known to be essential to life—the ones humans need to survive and thrive in the womb—also play a critical role in the development of autism spectrum disorder (ASD), suggests a new study from Penn Medicine geneticists published online today in the *Proceedings of the National Academy of Sciences*. An analysis of genetic samples of over 1,700 families from a repository revealed that elevated levels of mutations in the "essential genes" was significantly associated with an increased risk for ASD and decreased social skills.

Because brain function may be particularly sensitive to mutation accumulation, identifying specific sets of genes in which mutations have a behavioral effect will assist in understanding how such an accumulation within a person can result in diseases, such as ASD, the authors said.

The work validates previous large-scale mouse model studies from the authors revealing that one third of genes are essential to life and likely related to human disease. The new study shows that siblings with ASD had much higher levels of damaging mutations in essential genes compared to their non-affected siblings. Essential genes also constituted a significant fraction of known ASD risk genes.

"This makes our jobs harder, with respect to treatment, but these findings are absolutely critical for our understanding of the disease," said senior author Maja Bucan, PhD, a professor of Genetics in the Perelman School of Medicine at the University of Pennsylvania. "We know it's not one gene that's causing autism spectrum disorders; it's a background of mutations, which we know is important. Here, we show what this background is."

The findings suggest that ASD stems from an aggregate effect of many damaged essential genes that "work" together during the early stages of development in the womb, as soon as eight weeks after conception. ASD is what's known as a polygenic disease, the authors said, where many small gene effects contribute to a disorder.

Hundreds of mutated genes have been previously implicated as the cause of this highly heritable, complex disease, but their importance, relationship with each other, and function have not been entirely clear. Today, nearly 1 in 68 children between the ages of three and 17, mostly boys, are diagnosed with autism, reports the Centers for Disease Control and Prevention. It is considered one of the fastest-growing developmental disorders in the U.S

Researchers analyzed almost 4,000 essential genes and 5,000 non-essential genes in 2,013 males with ASD and 317 females with ASD, as well as their siblings who did not have ASD, for known exonic de novo (began in the child) and inherited mutations. The team pulled data from the Simons Simplex Collection, a repository of genetic samples from 2,500 families with ASD under the Simons Foundation Autism Research Initiative.

They found that those with ASD had statistically significant elevated levels of mutatiions in essential genes compared to their siblings. The essential gene mutations were associated with a higher risk of ASD and disruption in normal social behavior, the authors report. On average, those with ASD had 44 percent more early-in-childhood mutations and 1.3 percent more inherited mutations in essential genes than their non-affected siblings.

Using RNA-sequencing data from 16 regions in the developing brain (from the BrainSpan database), the team also showed that three co-expressed gene "modules" enriched for essential genes are also

implicated in ASD.

The researchers, including first author Xiao Ji, a doctoral student in Bucan's lab, called out a list of 29 "high-priority" essential genes that are co-expressed in the developing human brain with previously identified ASD-associated genes. Such genes could serve as targets for future functional and behavioral studies that could not only add to the growing body of knowledge on the disease but also potentially impactful treatments.

"We provided another way to prioritize autism genes," Ji said. "We now see that essential genes are much more likely to be associated with autism than non-essential genes. Focusing in on this group of genes will help shed more light on the complex genetic architecture of this disorder."

"The next step is to dig deeper to better understand the specific combinations of mutations within the gene groups we have identified here," Bucan said. "Moreover, our study will help scientists working on model organisms - mice, fish, flies - to interpret their findings and relate them to complex neurodevelopmental disorders."

More information: Increased burden of deleterious variants in essential genes in autism spectrum disorder, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1613195113

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