NEWS

Sequencing studies sharpen focus on key autism genes

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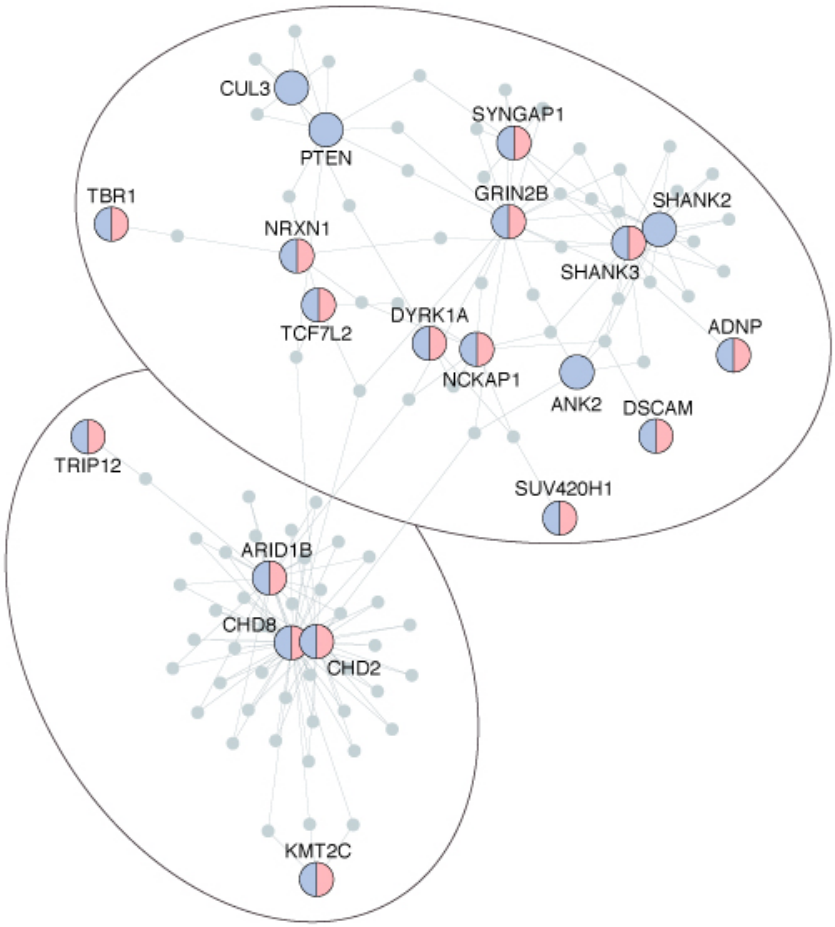

Painstakingly analyzing reams of data from multiple sequencing studies, a large team of researchers has expanded the number of genes they can say with near certainty are involved in autism from 16 to 28[1]. A second independent team halved a list of genes with moderate ties to

autism from roughly 500 to 239 by scouring the sequences of people from the general population[2].

The studies, published last week, are reassuring: They confirm that researchers' efforts to find the highest-risk autism genes have been on the right track.

They also clarify how different types of mutations might work together to heighten autism risk. For example, they find that small deletions of DNA are more likely than large ones to carry a strong autism candidate gene. And they add to mounting evidence that women act as carriers of autism mutations and are **shielded from the disorder** themselves.

Ultimately, the studies do the unglamorous but crucial work of carefully prioritizing autism risk genes for further research.

"We're approaching the stage when discovery is less important than understanding what the genes do," says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco, and lead investigator on the first study. "If you're going to go and get a grant and spend three years working on a gene, you want to be pretty sure that this is an autism gene."

Balancing act:

For their work, Sanders and his colleagues looked for duplications and deletions of DNA — collectively known as **copy number variations** (CNVs) — in 10,220 people from 2,591 families. They published their findings 23 September in *Neuron*.

A 2011 analysis of data **from 1,000 of these families** linked two chromosomal regions, 7q11.23 and **16p11.2**, to autism with 90 percent certainty. The new study found CNVs in four more regions with at least the same likelihood of being true autism candidates. All four have long been known to have some connection to the disorder.

"It's an important paper because it allows for more confidence in genes," says **Ivan Iossifov**, assistant professor at Cold Spring Harbor Laboratory in New York, who was not involved in the study.

Overall, the researchers found that only small CNVs — spanning between 3 and 10 genes — are likely to contain a high-risk autism gene, meaning a gene that is known to carry severe spontaneous, or *de novo*, mutations in people with autism.

By contrast, large CNVs seem to contain genes with more modest ties to the disorder that are likely to act in combination with one another. This may explain why numerous studies have struggled to find a single culprit gene in large CNVs linked to autism, says Sanders.

If a large CNV were to contain a high-risk autism gene, Sanders says, deletion of that region would

probably lead to something more severe than autism. “It’s this beautiful genomic balancing act of how a single point mutation and a large CNV can contribute to the same degree of risk,” he says.

Bigger is better:

Last year, two separate studies **released an analysis of exomes**, the protein-coding regions of the genome, from more than 20,000 people in total.

Both studies focused on mutations that disrupt a protein by changing a single letter in the DNA code. Together, they generated a list of 48 candidate genes that have at least a 90 percent chance of being true autism genes, and 16 genes with more than a 99 percent chance.

In the new study, Sanders and his colleagues integrated these data, their CNV analyses and information on CNVs from 2,096 additional families. They analyzed all of this information together using a single statistical algorithm called TADA.

This tool, which **combines data on multiple types of mutations** to prioritize autism genes, increased the number of high-risk genes from 48 to 65. It also increased the number of genes that have a 99 percent chance of being true autism genes — the highest possible level of statistical certainty — from 16 to 28.

Combining multiple datasets also gave the researchers enough statistical power to find a signal even among subgroups of people with autism. For example, they found that men with intelligence quotients (IQs) between 111 and 130 are more likely to carry *de novo* harmful mutations in strong autism genes or CNVs than are their unaffected siblings.

Previous studies had not been able to link *de novo* mutations to autism in men with IQs of 100 or above. This suggested that **autism risk in this group is different** than in people with a low IQ.

However, those studies may have had too few participants with high IQ, says **Elise Robinson**, instructor in medicine at Harvard University, who led one of the studies.

“It’s interesting to finally see an association between *de novo* variation and autism in individuals with high IQ,” says Robinson, who is included in the long list of the new study’s authors for advising the researchers on clinical features. “In our study, we couldn’t separate whether there really wasn’t anything there or if we were underpowered to see it.”

The researchers were also able to look at differences in autism risk between men and women. Of the 65 high-risk genes they identified, 20 are mutated in both men and women, suggesting that the same mutations lead to autism in both sexes. It also indicates that some other factor must be at play to make these mutations manifest differently in women than in men, Sanders says.

Ranking risk:

The second new study, published 23 September in the *Proceedings of the National Academy of Sciences*, sought to refine researchers' understanding of autism risk genes by looking for mutations in the general population. Any gene can be mutated by chance, but the researchers reasoned that mutations that lead to autism would be rare in the general population — and they found this to be so.

"We confirmed our prediction that autism genes are very clean in the population," says Iossifov, lead researcher on this study. "This is a nice tool to prioritize targets and sort them."

The researchers looked at nearly 5,000 parents of children with autism and 6,000 controls from a separate database. They started with a subset of roughly 500 candidate genes in which researchers have seen severe *de novo* mutations in people with autism.

Overall, these genes carry fewer harmful mutations in the general population than would be expected by chance, the study found.

For a given autism gene, harmless mutations should be more common than harmful ones in the general population or in unaffected siblings of people with autism. Using this logic to rank the 500 candidates, the researchers pulled out 239 priority genes.

The study is "extremely innovative," particularly in placing the genes in the context of evolutionary biology, says **John Constantino**, professor of psychiatry and pediatrics at Washington University in St. Louis, who was not involved in the study.

The researchers also found that severe mutations they found only once in the general population tend to have been passed down from a parent, often the mother — supporting the theory that women are somehow protected from autism.

Correction: A previous version incorrectly stated that the researchers looked at copy number variations in sequences. Those analyses are based on data from microarrays.

REFERENCES:

1. Sanders S.J. *et al. Neuron* **87**, 1215-1233 (2015) PubMed **PubMed**
2. Iossifov I. *et al. Proc. Natl. Acad. Sci. USA* Epub ahead of print (2015) **PubMed**