

NEWS

Scan of whole genomes ties regulatory regions to autism risk

BY ALLA KATSNELSON

4 OCTOBER 2017

Children with autism have an excess of spontaneous mutations in DNA that controls the expression of autism genes, a new analysis suggests¹. This finding contradicts similar analyses from other teams.

The study also found that many children with autism carry multiple spontaneous mutations, some of them in autism genes. The results hint that a few mutations scattered throughout the genome underlie a significant number of autism cases, the researchers say.

“I think we have a handle on another major cause of autism,” says lead investigator **Evan Eichler**, professor of genome sciences at the University of Washington. The work appeared 27 September in *Cell*.

But some researchers are skeptical of the statistical approach and say the study is too small to link these mutations to autism risk.

“On balance, I suspect there is some truth to the claims in this paper, but I don’t see the evidence here as conclusive,” says **Jeffrey Barrett**, a human geneticist at the Wellcome Trust Sanger Institute in Hinxton, United Kingdom.

Eichler’s team analyzed whole-genome sequences from 516 children with autism, as well as their unaffected parents and siblings. (The sequences came from the Simons Simplex Collection (SSC), which is funded by the Simons Foundation, *Spectrum’s* parent organization.)

Overall, children with autism have the same number of spontaneous, or de novo, mutations as their unaffected siblings. But they have more missense mutations — in which one DNA base is swapped for another — and more mutations in regulatory regions of genes that are important in fetal brain development.

This finding barely met the threshold for statistical significance. But when the researchers restricted their analysis to 845 genes with known ties to autism, the difference between the children with autism and their siblings easily cleared the significance bar.

“Regulatory regions of genes that are already implicated in autism have an excess of de novo mutations,” Eichler says.

A 2015 study revealed that mutations in DNA that **boosts the expression of nearby genes** can increase autism risk. And a 2016 report from Eichler’s group suggested that children with autism have an excess of mutations in **stretches of noncoding DNA** thought to contain regulatory elements.

Multiple mutations:

However, the statistical evidence for the paper’s key findings is weak, several researchers told *Spectrum*.

This type of genetic analysis requires comparing many parts of the sequence information from the two groups. When scientists make these comparisons, they must perform additional statistical tests to eliminate chance findings. The new analysis did not adequately make these corrections, Barrett and others say.

“If we want to build a solid foundation on which to understand autism, we need to acknowledge, and correct for, multiple comparisons,” says **Stephan Sanders**, assistant professor of psychiatry at the University of California, San Francisco, who was not involved in the study.

Eichler and his team acknowledge in the study that some of the findings do not hold up after the necessary statistical checks. They also clarify which of the findings retain significance after these steps, Eichler notes. Still, he agrees that the conclusions must be confirmed in a larger sample.

Eichler’s team also found that children with autism are more likely than their siblings to have multiple, potentially harmful de novo mutations in any part of their genome. Again, the difference only became clearly significant when the researchers restricted their analysis to genes tied to autism.

Compared with their siblings, twice as many children with autism have two or more de novo mutations in regions that regulate autism genes, this analysis found.

“I think this tells us that, in fact, multiple de novo mutations are confronting kids with autism,” Eichler says.

Conflicting results:

Some of the new findings conflict with other analyses of SSC data. Sanders says his team has also analyzed the whole genomes of 519 people with autism and their unaffected parents and siblings from the SSC. After making the appropriate corrections, Sanders' group found that noncoding mutations do not have a robust effect on autism risk. Those results are **under review**.

Sanders estimates whole-genome sequences from at least 5,000 families are required to determine whether such mutations affect autism risk.

In another study under review, **Jonathan Sebat**'s team at the University of California, San Diego examined large mutations called **copy number variants** in sequences from more than 1,500 families. They found that rare, **inherited mutations in noncoding regions** of the genome up autism risk. "But there is no contribution from de novo mutations," says Sebat, chief of the Beyster Center for Genomics of Neuropsychiatric Diseases.

At a minimum, these disparate findings call for caution in interpreting results, researchers say. "Each group is describing what they see under their favorite lamp post," Sanders says. "We need to wait until we have sufficient samples to illuminate the entire landscape evenly."

Eichler and his colleagues are working through an additional 7,500 whole-genome sequences from the SSC to confirm the findings.

REFERENCES:

1. Turner T.N. *et al.* *Cell* Epub ahead of print (2017) **Abstract**