NEWS

‘Synonymous’ mosaic mutations may up autism risk

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A type of mutation long thought to be harmless has turned up in children with autism, and may play a role in the condition. Researchers presented the unpublished findings today at the **2016 American Society of Human Genetics Annual Meeting** in Vancouver, Canada.

So-called ‘synonymous’ mutations swap out a single nucleotide but generally do not alter the protein’s structure. The researchers discovered that children with autism have more of these mutations than their unaffected siblings do.

“That was really weird because those mutations aren’t supposed to do anything,” says lead investigator **Brian O’Roak**, assistant professor of molecular and medical genetics at Oregon Health and Science University. “We spent a lot of time looking at that data to see if we could make it go away.”

Instead, the researchers discovered that these mutations may influence autism risk by affecting how proteins are pieced together. The mutations occur in mosaic patterns, meaning they are present only in a subset of the body’s cells. Rebecca Barnard, a postdoctoral fellow in O’Roak’s lab, presented the findings, which the researchers plan to post on the **preprint server bioRxiv** later this week.

The findings highlight the diversity of mutations that underlie autism. They also hint at the need for diagnostic tests that can catch these subtle genetic changes.

The study makes “a significant contribution to our understanding of the genetic causes of autism,” says **Fereydoun Hormozdiari**, assistant professor of biochemistry and molecular medicine at the University of California, Davis, who was not involved in the work.

Mosaic mystery:

The researchers stumbled across their discovery while searching for mosaic mutations, which most genetic screens do not pick up. This type of mutation is thought to be involved in brain-related conditions such as **tuberous sclerosis**, **schizophrenia** and **autism**[1].

In recent years, scientists have devised **reliable methods of detecting** mosaic mutations. O'Roak's team wrapped three **existing methods** into a new tool that accurately detects mosaic mutations about 94 percent of the time.

The "state-of-the-art" tool will allow scientists to quickly scour massive datasets for mosaic mutations, Hormozdiari says.

The researchers used the method to search for spontaneous, or *de novo*, mosaic mutations in 2,300 families from the Simons Simplex Collection, a repository of genetic and clinical data from families that include one child with autism and unaffected parents and siblings. (The collection is funded by the Simons Foundation, *Spectrum*'s parent organization.)

The team examined more than 5,000 genetic variants in children with autism and their unaffected siblings and parents. They found mosaic mutations in all three groups. To their surprise, the most common mosaic mutations in children with autism turned out to be synonymous ones.

Convinced the finding was a fluke, they doubled back to search for an error in the analysis. They found nothing amiss.

Real findings:

The researchers then found that these mutations tend to occur near splice sites — where enzymes cut the messenger RNA that is made into protein — in children with autism, and farther away in the unaffected relatives.

Their findings suggest that synonymous mutations within 20 bases of the splice site may account for up to 6 percent of autism cases in simplex families.

The researchers also found non-synonymous mosaic mutations. Many of THESE occur in genes linked to autism, such as CHD2 and SYNGAP1.

"That's exciting because it tells you that these are bona fide risk genes. Otherwise, you wouldn't see every possible type of mutation affecting them," says O'Roak.

Commercial genetic tests cannot reliably detect mosaic mutations, he says, and may miss them in children with autism.

The researchers also found that parents pass some mosaic mutations down to their children. They

plan to search for mosaic mutations in twins and families with multiple affected children. Their findings may reveal whether the mutations contribute to the **broad autism phenotype**, a grouping of autism traits in people who do not have the condition.

*For more reports from the 2016 American Society of Human Genetics Annual Meeting, please **click here**.*

REFERENCES:

1. O'Roak B.J. *et al. Nature* **485**, 246-250 (2012) **PubMed**