NEWS

‘Silent’ mutations may contribute to autism, schizophrenia

BY **NICHOLETTE ZELIADT**

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Mutations in genes that seemingly don’t affect the corresponding proteins may still boost autism risk. These so-called synonymous, or ‘silent,’ mutations may change how genes are pieced together, suggests a study published in March in *Neuron*[1].

The first strong hint that this might be important in autism came from a 2014 study that showed that synonymous mutations seem to play a role in cancer[2].

“These mutations are potentially important but largely unexplored,” says study investigator **Bin Xu**, assistant professor of neurobiology at Columbia University.

Most genes consist of swaths of coding DNA called exons, separated by patches of noncoding DNA called introns. When a gene is translated into a protein, the exons are pieced together in various combinations. This process, called alternative splicing, can generate different proteins from the same gene. Problems with splicing are thought to **occur in autism**, and can lead cells to produce too much or too little of a particular protein.

The new study supports this notion by showing that people with autism and schizophrenia tend to have synonymous mutations in genomic regions that regulate splicing. The mutations occur near splice sites, the boundaries between exons and introns.

Precisely how the synonymous mutations affect their target genes remains unclear, however.

“It’s a nice study, but there is no experimental confirmation that any of these mutations actually affect splicing,” says **Lilia Iakoucheva**, assistant professor of psychiatry at the University of California, San Diego, who was not connected with the research.

Sequence sifting:

The researchers sifted through data from 11 sequencing studies published between 2012 and 2014 to identify synonymous mutations in 1,043 people with autism, 1,021 with schizophrenia and 731 siblings or unrelated people with neither condition. The studies focused on only the **exomes** — the collection of exons throughout the genome — and specifically on *de novo*, or spontaneous, mutations in those regions.

They analyzed 253 synonymous mutations in people with autism and 228 in those with schizophrenia, as well as 154 in controls.

There was no significant difference in the overall frequency of synonymous mutations in people with autism or schizophrenia compared with controls. But when the researchers restricted their analysis to short stretches of DNA surrounding splice sites, they found that synonymous mutations are about twice as common in people with autism as in controls. What's more, the mutations near the splice sites in people with autism are about 2.5 times more likely to disrupt regions that regulate splicing than those found in controls.

By contrast, synonymous mutations linked to schizophrenia tend to affect regions that serve as landing strips for proteins that turn genes on.

Blip boost:

When the researchers added data from two **massive sequencing studies**, the link between the mutations and autism weakened slightly.

This larger dataset included another 1,046 synonymous mutations in people with autism and 516 in controls. But the autism mutations were only about 1.5 times more likely to disrupt factors that regulate splicing than mutations in controls.

The drop is somewhat concerning, Iakoucheva says. "Who knows? If we add more mutations, maybe the signal would disappear completely."

The affected genes in the people with autism are enriched for those that help to maintain neurons' structure and function. Others control the expression of genes important for neuron growth and brain development. Eight of the genes also carry autism-linked mutations that obliterate protein function. This finding strengthens the idea that synonymous mutations play a role in autism.

Because most of the regions that control splicing reside outside exons, the next step is to look at the effects of mutations throughout the genome.

"There have been great delays and resistance funding this next step because funding agencies

thought there would not be disease-relevant variation in the noncoding genome or that it would be impossible to interpret," says lead investigator **Maria Karayiorgou**, professor of psychiatry at Columbia University. "Hopefully, our study can help put those worries to rest."

REFERENCES:

1. Takata A. *et al. Neuron* **89**, 940-947 (2016) **PubMed**
2. Supek F. *et al. Cell* **156**, 1324-1335 (2014) **PubMed**