

# Postconception Genetic Mutations Contribute to Autism Risk

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Mutations that occur after conception may play an important role in autism spectrum disorder (ASD), according to a study of nearly 6000 families that combined three genetic sequencing techniques.

"Our study has uncovered new mutations in ASD, as well as provided additional evidence for some genes that have been previously reported in ASD," first author, Elaine Lim, PhD, from Boston Children's Hospital in Massachusetts, told *Medscape Medical News*.

The study was [published online](#) July 17 in *Nature Neuroscience*.

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## "Striking Enrichment"

ASD has been linked to mutations to more than 60 different genes, including spontaneous noninherited (de novo) mutations, but the disorder remains largely unexplained. Dr Lim and colleagues delved into an emerging category of de novo mutation: postzygotic mosaic mutations (PZMs).

"There is increasing recent evidence that PZMs can contribute to brain malformations and epilepsy and that a fraction of clinically relevant PZMs can be detected in blood of affected individuals," they write.

The later PZMs occur during embryonic development, the fewer cells will carry them, making them harder to find. "If the mutation is in a very small fraction of all cells, it will be missed by whole-exome sequencing," Dr Lim said in a news release.

To dig deeper, Dr Lim, senior investigator Christopher Walsh, MD, PhD (from Boston Children's and the Broad Institute of MIT and Harvard), and colleagues obtained whole-exome sequencing data previously gathered from 5947 families with ASD.

They resequenced some of the DNA from these children using three independent sequencing technologies.

The researchers identified 7.5% of ASD patients' de novo mutations as PZMs, 83.3% of which had not been picked up in the original analysis of their genome sequence.

"Our analysis also revealed striking enrichment of PZMs within genes that are clinically relevant to ASD, including the bona fide ASD risk gene *SCN2A*," the researchers report. In addition, they say the identification of recurrent nonsynonymous PZMs in a small set of genes in ASD probands "also provides strong evidence for the clinical importance of PZMs."

Two genes known to be active in brain development (*KLF16* and *MSANTD2*) but not previously associated with ASD were significantly enriched for PZMs.

In addition, they found that loss-of-function and missense PZMs in critical exons in ASD probands showed enrichment in amygdala expression, which is "intriguing since the amygdala plays key roles in emotional and social responses.... An 'amygdala theory' of autism has been supported by recent work that found impaired neuronal responses in the amygdala in individuals with ASD," they write.

The researchers also tested the association of IQ with PZM carriers in 7 probands with recurrent PZMs for which IQ scores were available. Two of 7 (28.6%) had nonverbal IQs of at least 100, compared with 2 of 65 probands (3.1%) with recurrent de novo loss-of-function mutations having nonverbal IQs of at least 100, suggesting a 9.3-fold excess of probands with higher nonverbal IQs harboring PZMs ( $P = .01$ ).

"This preliminary observation would need replication in a larger number of individuals to test the hypothesis that individuals harboring PZMs might be less severely affected than individuals harboring gDNMs [germline de novo mutations], in terms of cognitive abilities such as IQ, and to test whether PZMs may be over represented in a subset of individuals with higher-functioning forms of ASD," the researchers note.

Overall, they say this research adds to prior evidence that complex brain disorders, such as epilepsy, intellectual disability, schizophrenia, and brain malformations, can arise from noninherited mutations that occur at some point during prenatal development.

"We have known that PZMs are an important cause of epilepsy, but this work provides the best evidence so far that they are relevant to autism as well. So it is now exciting to consider what other psychiatric conditions might have a role for PZMs," Dr Walsh said in the release.

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## Important Work Ahead

Potential clinical implications, Dr Lim told *Medscape Medical News*, include "the need for more sensitive approaches to identify potential mosaic mutations in affected children, as well as the need to identify such mutations in unaffected parents, which can inform us about the chances of passing any deleterious disease-associated mutations to their offspring."

"I think some exciting logical next steps include testing the hypothesis that differences in the ratios of mosaicism might be associated with varying degrees of phenotypic manifestations such as IQ, as well as studying the proportions of mutant alleles in phenotypically unaffected parents, and that can teach us about the number of mutant cells needed to result in a phenotype or readout," she said.

Commenting on the findings for *Medscape Medical News*, Gerard Schellenberg, PhD, from the University of Pennsylvania Perelman School of Medicine and director, Penn Neurodegeneration Genomics Center, Philadelphia, said the fact that "germline de novo mutations contribute to autism is well established, and it's not surprising and perhaps somewhat expected" that PZMs might also contribute to autism.

"This is almost entirely done with blood DNA, which is fine, but it would be interesting to look at brain DNA; if you had somatic cell events that increase the number of brain deleterious mutations, that would be interesting," Dr Schellenberg said.

"It's important to identify as many of the genes that contribute to autism as possible because our overall goal is to get the full genetic spectrum of autism and then try to put together pathways that these genes point to," he added.

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