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Researchers catalog dozens of mutations in crucial brain development gene

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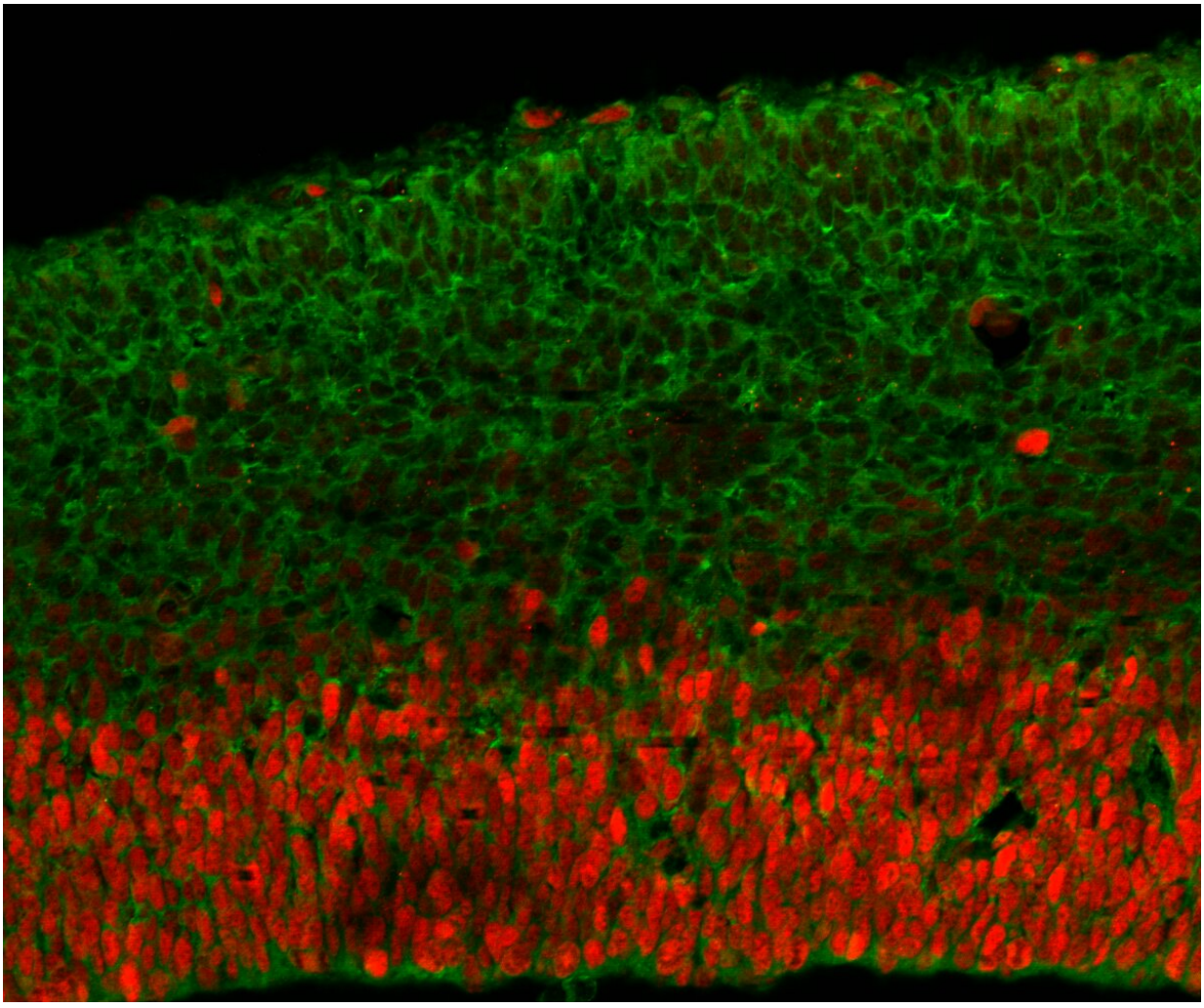

Genetic samples from developmentally disabled children have identified dozens of new mutations in the DDX3X gene that lead to smaller brains and intellectual disability because of the gene's essential role in neuron genesis and transport. Credit: Silver Lab, Duke University

An international team of researchers that pooled genetic samples from developmentally disabled patients from around the world has identified dozens of new mutations in a single gene that appears to be critical for brain development.

"This is important because there are a handful of genes that are recognized as 'hot spots' for mutations causing neurodevelopmental disorders," said lead author Debra Silver, an associate professor of molecular genetics and microbiology in the Duke School of Medicine. "This gene, DDX3X, is going to be added to that list now."

An analysis led by the Elliott Sherr lab at the University of California-San Francisco found that half of the DDX3X mutations in the 107 children studied caused a loss of function that made the gene stop working altogether, but the other half caused changes predicted to disrupt the function of the gene.

The DDX3X gene is carried by the X chromosome, which occurs twice in females and only once in males. Only three of the children in the study were male, indicating that an aberrant copy of the gene is probably most often a lethal problem for males who only have a single copy of X.

In humans, this syndrome often results in smaller brains and intellectual disability. Understanding how and why DDX3X mutations lead to developmental issues provides insight into how the gene functions normally.

With the finding that DDX3X was a common element in the developmental disabilities of these children, Silver's team "used a set of experimental tricks to see how it would lead to disease." In mice, her team manipulated levels of the gene to see how development of the

cerebral cortex would be altered.

Changes in the gene led to fewer neurons being produced in a dosage-dependent manner, Silver said.

In the most severe cases, Sherr's team showed that functional changes in DDX3X resulted in a smaller or even completely missing corpus collosum, the broad communications structure between the two halves of the brain. In some cases, identical genetic spelling errors that occurred in several children also led to polymicrogyria, an abnormal folding pattern on the surface of the brain.

"Not every mutation acts the same," Silver said.

The collaborative team also tested how 'missense' mutations, in which the protein is made but somehow defective, would impair brain development. In the most severe missense mutations, the way protein was made was affected, leading to the formation of 'clumps' of RNA-protein aggregates in neural stem cells, similar to the protein clumps found in Alzheimer's disease, Silver said.

Together, these issues point to a role for DDX3X in the genesis of developing neurons as the brain grows. "The way neurons are made and organized is disrupted," Silver said. "We know that this gene is required for early brain development which can cause a whole host of developmental problems."

Almost all of the mutations seen in the study children were 'de novo,' meaning they happened during the child's early development, rather than being inherited from a parent.

Parents of the children with these mutations have established the DDX3X Foundation to pursue better understanding of what causes the

disease, identify therapies, and provide a supportive community for families.

More information: "Pathogenic DDX3X Mutations Impair RNA Metabolism and Neurogenesis During Fetal Cortical Development," Ashley Lennon, Mariah Hoye, Debra Silver, Elliott Sherr. *Neuron*, March 4, 2020. DOI: 10.1016/j.neuron.2020.01.042 , www.cell.com/neuron/fulltext/S0896-6273(20)30099-4

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