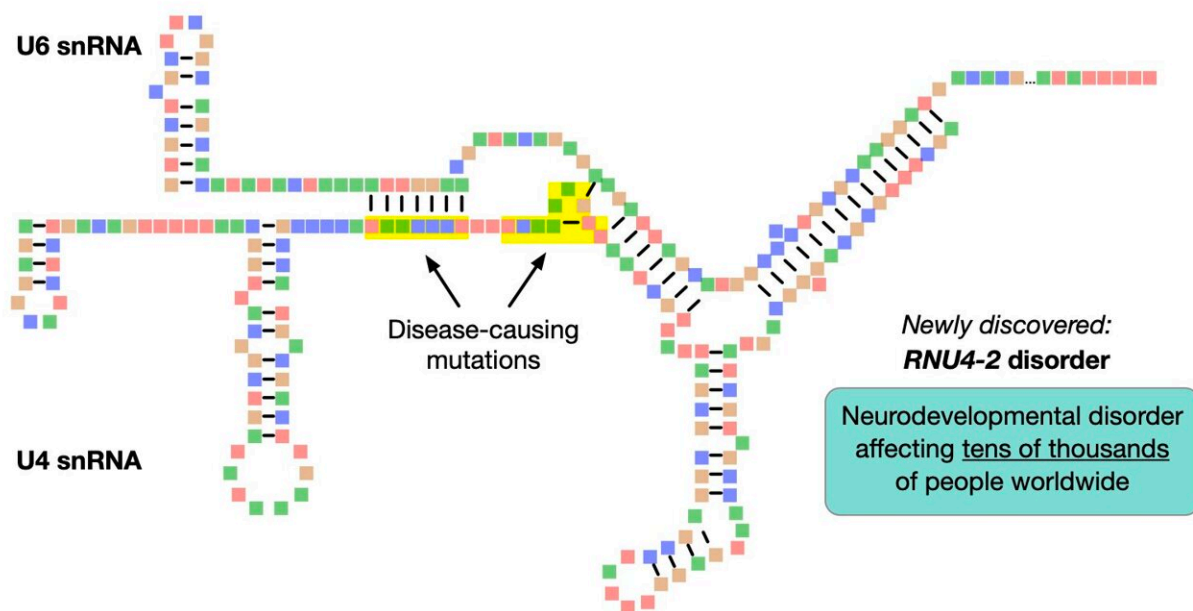


# Researchers identify a genetic cause of intellectual disability affecting tens of thousands

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Schematic showing the structures of U4 and U6 RNAs, and the interactions between them. Mutations in the highlighted regions of U4 cause a neurodevelopmental disorder that affects tens of thousands. Credit: Lab of Ernest Turro, Ph.D., at Icahn Mount Sinai.

Researchers at the Icahn School of Medicine at Mount Sinai and others have identified a neurodevelopmental disorder, caused by mutations in a single gene, that affects tens of thousands of people worldwide. The work, [published](#) in the May 31 online issue of *Nature Medicine*, was done in collaboration with colleagues at the University of Bristol, UK; KU Leuven, Belgium; and the NIHR BioResource, currently based at the University of Cambridge, UK.

The paper is titled "Mutations in the U4 snRNA gene RNU4-2 cause one of the most prevalent monogenic neurodevelopmental disorders."

The findings will improve clinical diagnostic services for patients with neurodevelopmental disorders.

Through rigorous genetic analysis, the researchers discovered that mutations in a small non-coding gene called RNU4-2 cause a collection of developmental symptoms that had not previously been tied to a distinct genetic disorder. Non-coding genes are parts of DNA that do not produce proteins.

The investigators used whole-genome sequencing data in the United Kingdom's National Genomic Research Library to compare the burden of rare genetic variants in 41,132 non-coding genes between 5,529 unrelated cases with [intellectual disability](#) and 46,401 unrelated controls.

The discovery is significant, as it represents one of the most common [single-gene](#) genetic causes of such disorders, ranking second only to Rett syndrome among patients sequenced by the United Kingdom's Genomic Medicine Service. Notably, these mutations are typically spontaneous and not inherited, providing important insights into the nature of the condition.

"We performed a large genetic association analysis to identify rare variants in non-coding genes that might be responsible for neurodevelopmental disorders," says the study's first author Daniel Greene, Ph.D., Assistant Professor of Genetics and Genomics Sciences at Icahn Mount Sinai and a Visitor at the University of Cambridge.

"Nowadays, finding a single gene that harbors genetic variants responsible for tens of thousands of patients with a [rare disease](#) is exceptionally unusual. Our discovery eluded researchers for years due to various sequencing and analytical challenges."

More than 99% of genes known to harbor mutations that cause neurodevelopmental disorders encode proteins. The researchers hypothesized that non-coding genes, which don't produce proteins, could also host mutations leading to intellectual disability.

Neurodevelopmental disorders, which often appear before grade school, involve developmental deficits affecting personal, social, academic, or occupational functioning. Intellectual disability specifically includes significant limitations in intellectual functioning (e.g., learning, reasoning, problem-solving) and adaptive behavior (e.g., social and practical skills).

"The [genetic changes](#) we found affect a very short gene, only 141 units long, but this gene plays a crucial role in a basic biological function of cells, called gene splicing, which is present in all animals, plants and fungi," says senior study author Ernest Turro, Ph.D., Associate Professor of Genetics and Genomic Sciences at Icahn Mount Sinai and a Visitor at the University of Cambridge.

"Most people with a [neurodevelopmental disorder](#) do not receive a molecular diagnosis following [genetic testing](#). Thanks to this study, tens of thousands of families will now be able to obtain a molecular diagnosis

for their affected family members, bringing many diagnostic odysseys to a close."

Next, the researchers plan to explore the molecular mechanisms underlying this syndrome experimentally. This deeper understanding aims to provide biological insights that could one day lead to targeted interventions.

"What I found remarkable is how such a common cause of a neurodevelopmental disorder has been missed in the field because we've been focusing on coding genes," says Heather Mefford, MD, Ph.D., of the Center for Pediatric Neurological Disease Research at St. Jude Children's Research Hospital who was not involved with the research.

"This study's discovery of mutations in non-coding genes, especially RNU4-2, highlights a significant and previously overlooked cause. It underscores the need to look beyond coding regions, which could reveal many other genetic causes, opening new diagnostic possibilities and research opportunities."

**More information:** Daniel Greene et al, Mutations in the U4 snRNA gene RNU4-2 cause one of the most prevalent monogenic neurodevelopmental disorders, *Nature Medicine* (2024). [DOI: 10.1038/s41591-024-03085-5](https://doi.org/10.1038/s41591-024-03085-5).  
[www.nature.com/articles/s41591-024-03085-5](https://www.nature.com/articles/s41591-024-03085-5)

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