A global collaboration involving University of Manchester scientists has discovered a gene whose variants potentially cause neurodevelopmental disorders (NDDs) in hundreds of thousands of people across the world.

The findings of the University of Oxford led study, published in Nature,
are an exciting first step towards the development of future treatments for the disorders which have devastating impacts on learning, behavior, speech, and movement.

While most NDDs are thought to be genetic and caused by changes to DNA, to date around 60% of individuals with the conditions do not know the specific DNA change that causes their disorder.

Nearly all genes known to be involved in NDD are responsible for making proteins. However, the team discovered that the gene RNU4-2 instead makes an RNA molecule that plays an important role in how other genes are processed in cells.

The study estimates that these specific changes in the RNU4-2 gene can explain 0.4% of all NDD cases globally, potentially impacting hundreds of thousands of families across the world.

While previous studies have only looked at genes that make proteins, data from the 100,000 Genomes Project, used by the team meant they could sequence entire genomes enabling changes in genes that don't make proteins, like RNU4-2, to be analyzed as well.

The study was led by Nicola Whiffin, Associate Professor at the Big Data Institute and Centre for Human Genetics at the University of Oxford. The team found mutations in RNU4-2 in 115 people with NDDs, many of whom had the exact same variant which adds a single extra base at an important position in the RNA.

Jamie Ellingford, Senior Research Fellow at The University of Manchester and Lead Genomics Data Scientist at Genomics England, said, "This is a really powerful discovery which shows just how far we have developed as a global scientific and clinical community. It provides evidence of how we now have the capability to pinpoint all types of
differences in people's DNA which can be drivers of disease, and can rapidly connect families and researchers from across the world."

This finding builds upon jointly led work at the University of Manchester and the University of Oxford to understand the impact of DNA differences in the part of the human genome that doesn't directly encode for proteins, once called "junk DNA" because of its unknown role.

Ellingford added, "The close alliances between computational science, genomics and clinical discovery at The University of Manchester will hopefully enable future discoveries like this that help families and other researchers better understand genomic diseases."

Nicole Cedor, mother to 10-year-old Mia Joy, said, "When Undiagnosed Network told us about three years ago that there was nothing else they could do, we resigned ourselves to the fact that we may never find out.

"So, you can imagine our shock to get this news. With the information we have gained, we are getting blood work to check iron levels, getting a DEXA bone scan next week, and we have a referral in for endocrinology.

"We are so grateful to each person on the research teams that worked tirelessly to find this diagnosis. It is one thing to write papers and crunch all that data, then another to see a family with a precious unique child who is living it day by day. This is where the data meets real life. We like to refer to RNU4-2 as 'renew,' as our family is being renewed by this new information and hope for the future."

Professor Whiffin said, "What is most remarkable about this discovery is how often changes in this gene result in NDD. Most protein-coding genes involved in NDD are thousands of DNA bases long. RNU4-2 is
around 50 times smaller but changes in this gene are almost as frequent a cause of NDD as these protein-coding genes. Including RNU4-2 in standard clinical genetic testing will end diagnostic odysseys for thousands of NDD patients worldwide and provide long-awaited hope to families."

[www.nature.com/articles/s41586-024-07773-7](http://www.nature.com/articles/s41586-024-07773-7)

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