New genetic variants lead to diagnoses for children with developmental disorders

June 3 2021

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By analyzing parts of the genome that do not code for proteins, researchers have identified seven variants linked to developmental disorders.

Non-coding regions of DNA could hold the key to diagnosing developmental disorders in children, new research suggests.

The study, by researchers at the Wellcome Sanger Institute, the Wellcome Center for Human Genetics at the University of Oxford, the University of Exeter, National Center for Cardiovascular Research (CNIC) in Madrid, and Imperial College London, found mutations in the non-coding regions of DNA that cause developmental disorders in children, giving 10 families a named diagnosis.

The paper, published in the *American Journal of Human Genetics*, identified seven variants that were previously unknown that cause developmental disorders, and six of these impacted the gene MEF2C. By also identifying two of these variants in other patient groups, the researchers were able to give a diagnosis to multiple families, ending the 'diagnostic odyssey' that many patients and their families face.

Globally, around 400,000 babies are born every year with new, spontaneous DNA changes—known as de novo mutations—that interfere with their development. These developmental disorders can lead to conditions such as intellectual disability, epilepsy or heart defects.

De novo mutations in genes that create proteins are a well-established cause of developmental disorders, but to date many of the genes linked to these disorders remain unknown. Every person is born with around 60 de novo mutations on average, though the vast majority do not lead to health problems.

It is a huge advantage to a patient and their family to know the genetic cause of their disorder. Not only does it provide answers, but it also allows risk prediction for other family members and potentially a gateway into personalized treatment. Given this, the majority of patients

with developmental disorders will undergo genetic testing as part of their clinical care, however, this leads to a genetic diagnosis in fewer than half of cases. This genetic testing normally identifies any variants that occur in the parts of the genome that code directly for proteins.

Ongoing initiatives, such as the Deciphering Developmental Disorders (DDD) study, have discovered associated genes by looking for patterns in the genomes of children with these disorders and comparing these to their parents' genomes.

In this study, which is part of the wider DDD study, the teams looked in regions of the genome that are immediately adjacent to protein-coding regions, known as untranslated regions, or UTRs.

These regions are not coded into the final protein, but instead regulate processes; such as controlling how much protein is made, when it stops and where the protein ends up in the cell.

Through computational and lab-based methods, researchers identified six variants in the UTRs that impacted the gene MEF2C, either by changing the levels of gene expression, reducing the amount of protein produced or disrupting the function of the MEF2C protein.

"By looking at parts of the genome that are found next to protein coding regions, we have been able to identify multiple variants that cause developmental disorders that would have been missed by current clinical screening. In fact, we found that nearly one quarter of diagnoses identified in the Deciphering Developmental Disorders study in one particular gene are due to non-coding region variants. While this this does not mean that one quarter of all developmental disease diagnoses are due to variants in non-coding regions, it suggests that it could be highly beneficial to analyze these regions in patients that remain genetically undiagnosed," says Dr. Nicky Whiffin, senior author of the

study and research Group Leader at the Wellcome Center for Human Genetics, University of Oxford.

By identifying further genetic links to developmental disorders, it is possible to give more people a diagnosis and an understanding of their condition, which can help family planning, as well as potentially opening up new treatment plans and support. This study has highlighted how important it is to look into UTRs and to possibly include them in routine clinical screening. It could also encourage more researchers to have another look at their existing data, possibly finding more important genetic variants in previously unanalysed UTRs.

"It's great to see that this genetic research translates directly into being able to give patients and families the diagnosis that they have been waiting for. Receiving a diagnosis can allow patients and their families to access support networks and gain a greater understanding of their condition, which can have a huge impact on their lives, as well as understanding the risk for any future children they might have," says Dr. Meena Balasubramanian,
author on the study and consultant clinical geneticist at Sheffield Children's NHS Foundation Trust.

"In recent years, spectacular advances in genomic analysis have ended the agonising diagnostic odyssey that so many children with developmental disorders and their families have endured. For many others though, a genetic diagnosis has remained elusive. This crucial research, through which reasons for some children's developmental disorders have been identified by analysing untranslated regions of the genome, brings hope and comfort to some families that their diagnostic odyssey too might come to an end, and could help more in the future. Receiving a genetic diagnosis offers families the possibility of information, support and finding others with a similar disorder, thus relieving their isolation and despair," says Dr. Beverly Searle, CEO at

Unique – the Rare Chromosome & Gene Disorder Support Group.

"Understanding more about the genetic cause of disease is incredibly important, especially when it can have such a large impact on a child's life and the life of their family. This research shows that even though many regions of DNA do not directly code for proteins, these regions still contain vital clues and information that can help many patients and their families get the answers that they are searching for," adds Professor Matthew Hurles, co-author of the study and lead of the Deciphering Developmental Disorders project at the Wellcome Sanger Institute.

More information: Caroline F. Wright et al, Non-coding region variants upstream of MEF2C cause severe developmental disorder through three distinct loss-of-function mechanisms, *The American Journal of Human Genetics* (2021). DOI: 10.1016/j.ajhg.2021.04.025

Provided by Wellcome Trust Sanger Institute