Discovery of new mutations may lead to better treatment

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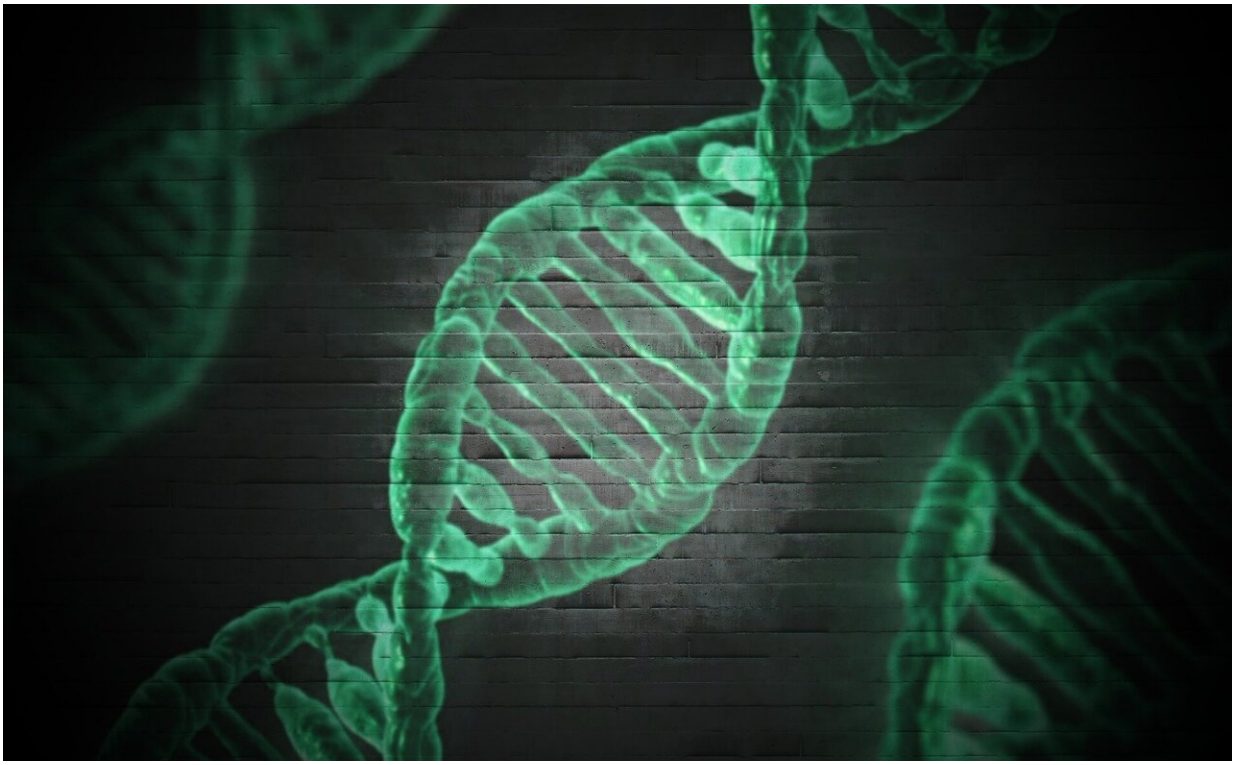

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Developmental disorders are neurologically-based conditions that affect the acquisition of specific skills such as attention, memory, language and social interaction. Although they have a genetic cause, this is often difficult to detect through standard genetic analysis of the parents. The

mutation found in the affected child is therefore termed a 'de novo' mutation (DNM).

"Although many new developmental disorders have been identified in recent years, there are many more to be discovered. Identifying them means that we will be able to give an accurate diagnosis to more patients and therefore allow them to have appropriate treatment and care," Ms Joanna Kaplanis, a Ph.D. student at the Wellcome Sanger Institute, Hinxton, UK, will tell the annual conference of the European Society of Human Genetics today.

In the largest study to date on developmental delay, the researchers analyzed genomic data from over 31,000 parent-child trios obtained from the UK's Deciphering Developmental Disorders Project, GeneDx, a U.S.-based genetic testing company, and Radboud University Medical Centre in Netherlands. Analysis of these trios yielded more than 45,000 DNMs. They developed an improved method to test for the enrichment (over-representation) of damaging DNMs in individual genes. "We found 307 significantly enriched genes, 49 of which are novel. With all of these genes we were able to explain about 51 percent of the DNM burden in our dataset. We then modeled different underlying genetic scenarios to get an idea of where the remaining de novo burden lies and how we can go about finding it," says Ms Kaplanis.

About 40 percent of developmental disorders are caused by DNMs, equivalent to about one birth in every 295 in the UK alone. The prevalence increases with the age of the parents. The disorders usually become apparent during childhood and include such conditions as autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), intellectual disability, and Rett syndrome. They may be mild, but in many cases they are severe, and those affected will need lifetime support. However, when they are unidentifiable making a decision on the best care for the affected child is difficult.

Given the size of the dataset, the researchers were not surprised to have been able to identify new genes. "However, we were expecting to be able to explain more of the DNM burden than we did. This means that half of the DNM burden in patients with developmental disorders still remains unexplained," says Ms Kaplanis. "This fact alone gives us clues about where the remaining burden lies and why we do not yet have the capacity to discover the remaining genes."

A possible explanation is that the DNMs in the genes as yet undiscovered are less penetrant, i.e. they present symptoms in fewer people. "We may need to adapt our system of gene discovery in order to capture these less penetrant genes," says Ms Kaplanis. " Incorporating more data from healthy populations may help to try and build a better picture of what they might be. "

The researchers also hope to increase their sample size in order to try to detect ever more genes associated with developmental disorders. However, the identification of 40 new genes already provides valuable information to clinicians and to drug developers. "Returning a genetic diagnosis is important when deciding on the best treatment and care for an individual, as well as providing new drug targets in rare diseases," Ms Kaplanis says.

Chair of the ESHG conference, Professor Joris Veltman, Director of the Institute of Genetic Medicine at Newcastle University, Newcastle upon Tyne, U.K., said: "Developmental delay is often caused by new mutations arising during the formation of sperm or eggs. By combining data on new mutations identified in the DNA of more than 30,000 patients, the scientists could implicate a role for 49 new genes in developmental delay. This study shows the power of large-scale international collaboration to advance our understanding of this disorder and improve diagnostics as well as patient management."

More information: Abstract no: PL2.4 Discovery and characterisation of 49 novel genetic disorders from analysing de novo mutations in 31,058 parent child trio exomes

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