Study linking 28 genes to developmental disorders to mean diagnoses for about 500 families

October 14 2020

Credit: Unsplash/CC0 Public Domain

Research into the causes of developmental disorders has identified 285 genes linked to these conditions, including 28 newly-associated genes. Published today (14 October 2020) in *Nature*, the study by researchers at

the Wellcome Sanger Institute, Radboud University Medical Center, OPKO Health's GeneDx and their collaborators will enable diagnoses for around 500 families living with children who have rare conditions.

The authors collated anonymised healthcare and research data to create the largest available genetic resource for developmental disorders. Analysis of the data estimates that around 1,000 genes linked to developmental disorders remain to be discovered. Finding them all will require ten times the amount of data currently available, which will only be possible with more open access to healthcare data.

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, autism or heart defects.

The 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.

Ongoing initiatives, such as the Deciphering Developmental Disorders (DDD) study, have discovered associated genes by looking for patterns in the genomes of people with these disorders. But because many conditions are extremely rare, the statistical analysis used to locate these genes requires large volumes of anonymised patient data that has not always been easily accessible.

For this study, the researchers analysed 31,058 exome sequence 'trios'. Each trio includes sequences from a child with a developmental disorder, plus both of their parents.

The sample was created by combining existing research and clinical datasets from the Wellcome Sanger Institute, Radboud University Medical Center and GeneDx.

The scale of the dataset greatly increased the statistical power available to search for previously undiscovered mutations. The authors then used an improved statistical test to determine whether individuals in the study had more mutations in the same gene than they would expect to occur by chance.

Dr. Kaitlin Samocha, a first author of the study from the Wellcome Sanger Institute, said: "From previous studies we know that certain genes and types of mutation are more strongly linked to developmental disorders, which has allowed us to narrow our search. Combined with a much larger dataset, this has enabled us to identify 28 novel genes associated with developmental disorders."

Dr. Helen Firth, Consultant Clinical Geneticist at Addenbrooke's Hospital, said: "Caring for a child with a developmental disorder can be extremely challenging for a family, particularly when their child's doctors don't know what is causing their condition and are unable to make a diagnosis. A diagnosis can help families to access support networks, inform treatment for their child and help them to understand the risk for any further children they might have."

The study also applied statistical modelling to the data to estimate that approximately 1,000 more development disorder-associated genes remain undiscovered. Around 60 percent of children born with a disorder do not have a diagnosis and the authors estimate that around 50 percent of these children will have a mutation in one of these unknown genes.

Professor Matthew Hurles, lead author of the study from the Wellcome Sanger Institute, said: "This study has really shown the benefits of access

to healthcare data, not least to the approximately 500 families living with a developmental disorder who had not been able to get a diagnosis until now. But our findings also estimate that we require ten times as much data to be able to identify all the genes linked to developmental disorders . As such, greater access to anonymised patient data is crucial to our understanding of these conditions and our ability to help the families living with them."

Kyle Retterer, Senior Vice President, Chief Technology Officer, and lead author of the study from GeneDx, said: "As a global leader in clinical exome sequencing and rare disease diagnostics, GeneDx is committed to helping end the diagnostic odyssey not only through diagnostic testing but through collaborative research projects like this one. By combining data and efforts across institutions, we are able to provide more patients and families with answers."

Professor Sir Mark Caulfield, Chief Scientist at Genomics England, said: "This study demonstrates the value of combining genomic data with healthcare data in gaining novel gene insights that improve patient outcomes. It also shows that, rather than being something that just takes place in a lab, genomics is bringing about tangible advances in healthcare that directly impact patients and their families. It should serve as a call to action that more must be done to make anonymised patient data available for research."

More information: Evidence for 28 genetic disorders discovered by combining healthcare and research data, *Nature* (2020). DOI: 10.1038/s41586-020-2832-5

Provided by Wellcome Trust Sanger Institute