News Data Science Human Genetics

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

News article by the Communications Team

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Researchers estimate that approximately another 1,000 genes linked to developmental issues have yet to be found

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.

"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 Kaitlin Samocha,

a first author of the study from the Wellcome Sanger Institute

"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."

Dr Helen Firth,

Consultant Clinical Geneticist at Addenbrooke's Hospital

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

“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.”

Professor Matthew Hurles,

lead author of the study from the Wellcome Sanger Institute

“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.”

Kyle Retterer,

Senior Vice President, Chief Technology Officer, and lead author of the study from GeneDx

“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.”

Professor Sir Mark Caulfield,

Chief Scientist at Genomics England

More information

* *De novo* mutations are spontaneous mutations in a child's DNA that are not carried by either parent. The mutations take place in the sperm or egg and are subsequently passed down to the child.

Publication

Joanna Kaplanis, Kaitlin E. Samocha and Laurens Wiel *et al.* (2020). Integrating healthcare and research genetic data empowers the discovery of 28 novel developmental disorders. *Nature*. DOI: 10.1038/s41586-020-2832-5

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Selected websites

The Deciphering Developmental Disorders study

The Deciphering Developmental Disorders (DDD) study aims to advance clinical genetic practice for children with developmental disorders. Children were recruited into the study between 2010 and 2015.

The DDD study is no longer recruiting new patients. If your child has an undiagnosed developmental disorder please speak with your paediatrician or GP about the most appropriate tests or referral into other studies.

The DDD team is absolutely committed to analysing and re-analysing all the genomic data from families in the study over the coming five years to try to find a diagnosis for as many children as possible.

More information about the DDD study can be found at www.ddduk.org

About GeneDx, Inc.

GeneDx, Inc. is a global leader in genomics, providing testing to patients and their families from more than 55 countries. Led by its world-renowned exome sequencing program, GeneDx has an acknowledged expertise in rare and ultra-rare genetic disorders, as well as one of the broadest menus of sequencing services available

among commercial laboratories. GeneDx offers a suite of additional genetic testing services, including diagnostic testing for hereditary cancers, cardiac, mitochondrial, neurological disorders, prenatal diagnostics and targeted variant testing. GeneDx is a subsidiary of BioReference Laboratories, Inc., a wholly owned subsidiary of OPKO Health, Inc. To learn more, please visit www.genedx.com.

The Wellcome Sanger Institute

The Wellcome Sanger Institute is a world leading genomics research centre. We undertake large-scale research that forms the foundations of knowledge in biology and medicine. We are open and collaborative; our data, results, tools and technologies are shared across the globe to advance science. Our ambition is vast – we take on projects that are not possible anywhere else. We use the power of genome sequencing to understand and harness the information in DNA. Funded by Wellcome, we have the freedom and support to push the boundaries of genomics. Our findings are used to improve health and to understand life on Earth. Find out more at www.sanger.ac.uk or follow us on Twitter, Facebook, LinkedIn and on our Blog.

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Quick links

- Kaitlin Samocha's profile
- Matt Hurles' profile
- Hurles research group
- Deciphering Developmental Disorders (DDD)
- DDD-NeuGen
- Jumping genes can cause rare developmental disorders in children
- Milestone reached in major developmental disorders project
- Rare genetic disorders more complex than thought