Study sheds light on causes of rare genetic diseases in 5,500 people

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Sofie Brogden with parents Dasha and Carl. Credit: Dasha Brogden

Around 5,500 people with severe developmental disorders now know the genetic cause of their condition, thanks to a major nationwide study in the U.K. that will help improve diagnosis across the world.

More than 13,500 families from 24 regional genetics services across the UK and Ireland were recruited to the Deciphering Developmental Disorders (DDD) study, a collaboration between the NHS and the Wellcome Sanger Institute.

All the families had children with severe developmental disorders that were undiagnosed despite prior testing through their national health service, and likely to be caused by a single genetic change. The Wellcome Sanger Institute sequenced all the genes in the children's and parents' genomes to look for answers, a search that is still ongoing.

Using with other high-tech methods, the team have so far been able to provide genetic diagnoses for around 5,500 children in the study, now published in the *New England Journal of Medicine*. The diagnoses were in over 800 different genes, including 60 new conditions previously discovered by the study. Around three-quarters of the conditions were caused by spontaneous mutations not inherited from either parent. The research team also found that the chances of success in getting a diagnosis was lower in families of non-European ancestry, reinforcing the imperative to increase research participation for under-represented groups.

Lead author Caroline Wright, Professor of Genomic Medicine at the University of Exeter, said, "Getting the right diagnosis is absolutely critical for families with rare conditions, which collectively affect around 1 in 17 people. Most of these conditions are genetic and can be diagnosed using the same genomic sequencing technology. The families in our study were desperate for answers, which can make a huge difference to clinical management and quality of life. We worked with hundreds of clinicians and scientists, as well as thousands of patients to try to find those answers. By sharing our findings, many more families in the future should get answers faster."

Senior co-author Matthew Hurles, incoming Director of the Wellcome Sanger Institute and Honorary Professor of Human Genetics and Genomics at the University of Cambridge, said responsible data sharing was critical for making the diagnoses.

He explained, "Undiagnosed patients with rare genetic diseases have the most to lose if they are not given an opportunity to participate in research and if their data are kept in silos. Many of these diagnoses were only made possible through combining data across all diagnostic centers in the UK and Ireland. For some diagnoses, it was only through sharing data with international colleagues that it was possible to make a diagnosis. As these genomic technologies move into routine healthcare, ensuring that undiagnosed patients can still benefit from research on their data will remain incredibly important."

Senior co-author Helen Firth, Professor of Clinical Genomics at the University of Cambridge and lead clinician for the study, emphasized the importance of the DECIPHER informatics platform for supporting recruitment of patients and return of diagnostic findings to clinical teams.

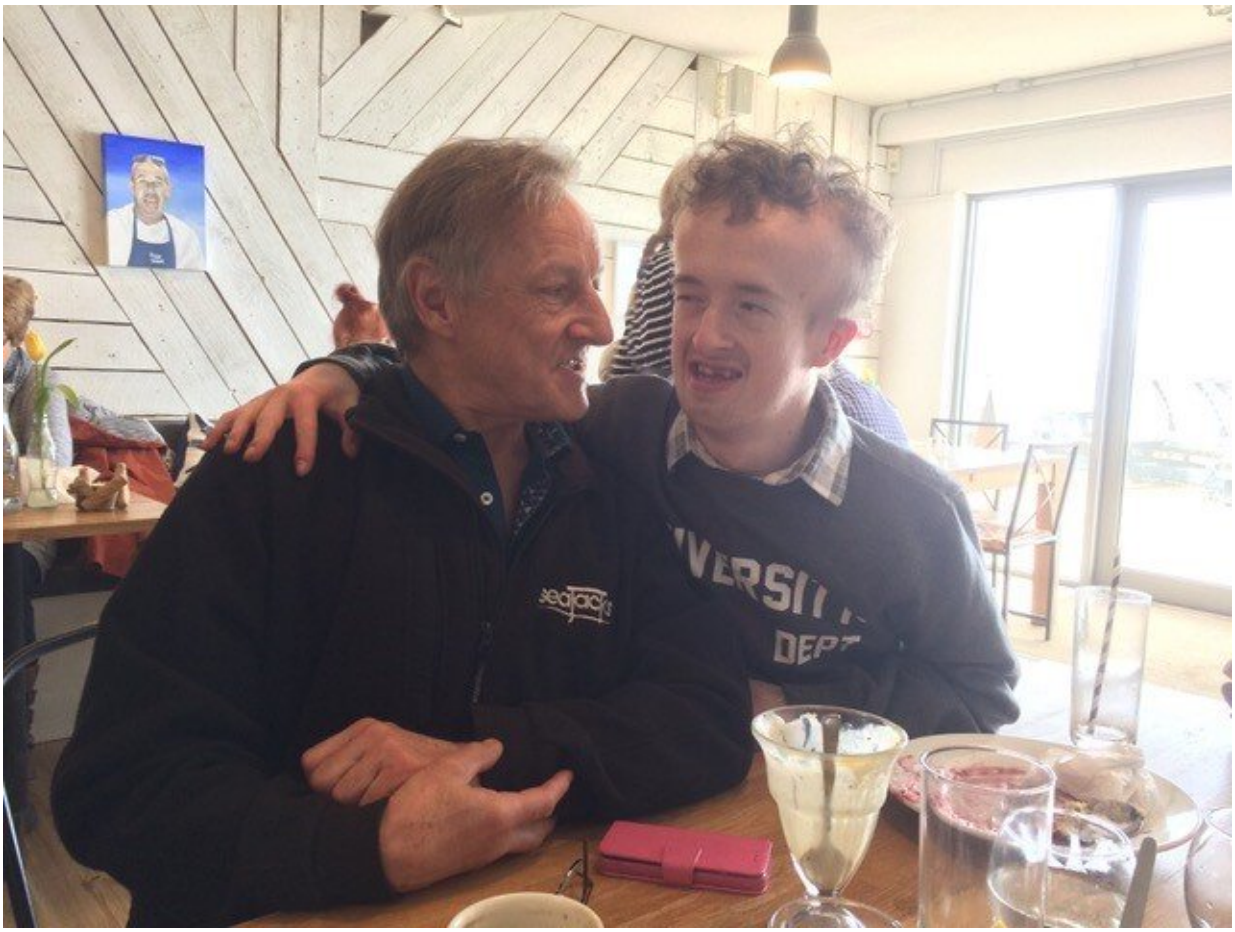
Professor Firth, who is also a Consultant in Clinical and Genomic Medicine at Cambridge University Hospitals NHS Foundation Trust, said, "Embedding a powerful informatics platform at the heart of this study facilitated the collaboration with families, clinicians and scientists engaged in the project, and played a crucial role in its diagnostic success and in the discovery and ultimately treatment of new causes of rare genomic disease. The Deciphering Developmental Disorders study has resulted in more than 290 publications and identified approximately 60 new disorders."

Senior co-author Michael Parker, Professor of Bioethics at the Ethox Centre at Oxford Population Health, University of Oxford, and ethics

lead for the study, highlighted the key role played in the success of the Deciphering Developmental Disorders Study of an integrated program of bioethics. He said, "From the initial design of the study, through the building and sustaining of collaborative partnerships with clinicians, to the identification and addressing of practical ethical problems in real time throughout the life of the project, the embedding of ethics research and advice into the Deciphering Developmental Disorders project has been crucial to its success and to building and maintaining well-founded trust and confidence of clinicians and patients."

A similar approach to diagnosing individuals with rare diseases is now being used in the NHS by the Genomic Medicine Service, the Scottish Genomics Laboratories Network Whole Exome Sequencing Service, and the Rapid Genome Sequencing Service for acutely unwell children with a likely monogenic disorder, which can provide a genetic diagnosis for babies and children in or facing critical care within just ten days. The genetic conditions identified in the current study will feed into the tests applied by the services, to help diagnose more people swiftly.

Health Minister Will Quince said, "We're creating the most advanced genomic healthcare system in the world and this study is yet another step forward to revolutionizing care for NHS patients. Using cutting edge, high-tech methods such as this offers the potential to better understand and more accurately diagnose rare genetic conditions so children can access treatment faster and potentially limit the impact of the disease on their life."



Mungo Fisher with his father. Credit: Jessica Fisher

How diagnosis impacts families

Getting the right diagnosis can guide clinical care, and brings together families in support networks that can help guide treatment and support pathways, reducing the isolation of having a child with an ultra-rare condition.

When Jessica Fisher was given a diagnosis for her son Mungo's rare genetic disorder, she initially felt it had all come too late. Mungo's

condition, called Turnpenny-Fry syndrome, was discovered in 2015 through the Deciphering Developmental Disorders study, in which he was a participant. But he was already 18, and Jessica, from St Austell in Cornwall, had been through years of uncertainty, not knowing how her son's development would unfold.

However, she took solace in being connected with another family recently diagnosed through the study, and forming a Facebook support group. Now, the group has connected around 36 families from across the world making it an invaluable community for those who are newly diagnosed.

"When I first saw a picture emailed to me of the other family's child, it was really emotional," Jessica said. "We'd always looked around for children who might look like Mungo—and here was a child in Australia who could have been his sibling. For a few months it was just us two families, but then it slowly started to grow. We now have families from countries including America, Brazil, Croatia, Indonesia… it's devastating to learn that your child has a rare genetic disorder, but getting the diagnosis has been key to bringing us together. The families are so appreciative to learn from our group, and being part of it does make us feel less isolated."

Turnpenny-Fry syndrome is caused by extremely rare changes in a gene called PCGF2. The disorder causes learning difficulties, impaired growth, and distinctive facial features that include a large forehead and sparse hair. Other common issues include feeding problems, severe constipation, and a range of potential issues in the brain, heart, circulation system and bones.

For Dasha Brogden, the support group has been a lifeline. Her daughter, Sofia, now nearly three, received a diagnosis at just one month old, when she was still in a neonatal unit. Dasha, who lives in Oxfordshire, said,

"For us, getting a diagnosis really helped us to understand what to expect. Compared to families who came before the condition had an official diagnosis, we were lucky. We were given a leaflet based on the experiences of other families, and through that we knew she would need physiotherapy and occupational therapy. We learned that Sofia may have heart conditions, and a heart scan revealed that she needed surgery. She had a heart operation at 2 months old, and after that she really started to make good progress, and we were able to take her home from hospital.

"We're also incredibly grateful to be part of this community. Very few people are living through this experience, and it feels like Jessica and Mungo are like family to us. It's invaluable, and it's only been possible because they took part in the study and got a diagnosis, which is now helping others to get there much faster."

More information: Genomic Diagnosis Rare Pediatric Disease in the United Kingdom and Ireland, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2209046

Jennifer E. Posey et al, Genomics in Clinical Practice, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMe2302643 , www.nejm.org/doi/10.1056/NEJMe2302643

Provided by University of Exeter

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