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Nationwide project paves way for clinical genetic diagnosis

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The first nationwide project to genetically diagnose rare diseases will pave the way for translating advances in genomics into patient care in the NHS. Deciphering Developmental Disorders (DDD), a collaboration between the Wellcome Trust Sanger Institute, the UK Department of Health and regional genetics services, is working with 12,000 families to diagnose their child's developmental disorder, demonstrating the feasibility and value of introducing large-scale sequencing diagnostics into health care.

The project, which will continue into next year, has so far found a diagnosis for nearly a third of the first 1000 families analysed, where previous genetic tests were unable to find the cause. The diagnoses have focused on the 1100 genes that have previously been recognised as a cause of developmental disorders. This success rate will continue to improve as more disease-causing genes are discovered.

"Each of these patient families has been through a long diagnostic odyssey before taking part in the DDD project," says Dr Helen Firth, an author from the Department of Clinical Genetics at Addenbrooke's Hospital. "For many, we are able to offer the diagnosis they have waited so long for. Sometimes this improves clinical management, but simply knowing the source of the problem can provide families with peace of mind."

Genome-wide microarray and whole exome sequencing is used to identify nearly 80,000 variants in each child, a handful of which

potentially hold the genetic key to their disorder. Filtering out benign changes and unrelated findings accurately and efficiently is the major challenge facing researchers. A key step in this process is to compare symptoms identified by clinicians, such as neurodevelopmental delay or abnormal growth, with an in-house database of all known genes associated with developmental disorders.

"This project requires the collaborative efforts of hundreds of NHS staff and researchers," says Dr David FitzPatrick an author from the Medical Research Council's Human Genetics Unit in Edinburgh. "Clinicians managing patients on the frontline, database curators ploughing through the latest research, bioinformaticians developing computational tools and genetics experts interpreting results are all working together towards the common goal of finding answers for these patients."

Most of the causative genetic changes are new mutations in the affected child that were not inherited from either parent. Where unaffected parents were sequenced as well as the child, researchers saw a 10-fold reduction in the number of variants needing clinical evaluation. This study shows the importance of using parental genetic data, where possible, for the diagnosis of rare disorders.

The DDD study will continue to recruit families until April 2015, and will continue to try to find a genetic diagnosis for all the remaining undiagnosed families. It is hoped that the approach developed in this study will be rapidly incorporated in standard clinical practice to maximise the diagnosis of rare genetic disorders.

"By pulling together 24 regional genetics services and more than 180 clinical geneticists, we've implemented one single exome sequence diagnostic pipeline for children across the country," says Dr Caroline Wright, lead author and Programme Manager for the Deciphering Developmental Disorders project. "The project has shown that large-

scale genetic testing, which brings such enormous benefits to patients and families, is both effective and affordable."

The research is published in *The Lancet*.

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