Every year, thousands of babies are born in the UK who do not develop normally because of errors in their genetic makeup. Currently, diagnosis is restricted to a small minority; up to half of children with severe developmental disorders of probable genetic origin remain without a diagnosis. Rare disorders, those with variable manifestations and those that are difficult to distinguish from other disorders can be particularly challenging to diagnose.

The aim of the Deciphering Developmental Disorders Study (DDD) is to determine if new high-throughput genetic technologies can determine the cause of developmental disorders, and to facilitate the use of these technologies in the NHS. The study involved taking 40,000 saliva samples from children with undiagnosed developmental disorders and their parents. Genome-wide microarray and whole exome sequencing was systematically applied to these samples. Results were returned to patients and their families via their local NHS clinical teams, with appropriate counselling.

The study investigated the cause of abnormal development in nearly 14,000 children from across the UK and Ireland, in whom conventional genetic testing did not yield a result. Samples were collected over 4 years, and the study involved all 24 regional genetics services. The NIHR Clinical Research Network supported recruitment in England, exceeding targets by recruiting 11,300 patients and their parents.
Outcomes and findings

A number of features led to the DDD study’s success:

- Recruitment was through Regional Genetics Services who had expertise in rare disease.
- Exome sequencing was far more cost-effective than genome sequencing, enabling greater rates of diagnosis and gene discovery on a limited budget.
- The study was delivered as a partnership between NHS Regional Genetics Services and the Wellcome Trust Sanger Institute with diagnostic results returned to individual patients by their own consultant clinician.
- DECIPHER (https://decipher.sanger.ac.uk) provides a platform for recruitment, phenotype upload, variant interpretation & proportionate data-sharing across NHS genetics services.
- The DDD study has a high international profile and DECIPHER enables a global reach for the study.

Although analysis of this data will continue until 2021, there have been a number of important findings to date. So far the team have achieved a diagnostic rate of ~35% in patients where previous genetic investigations had failed to identify a diagnosis. This rate may increase over time as knowledge increases and new genes are identified.

In addition to making diagnoses across many genes already linked to developmental disorders, more than 30 new developmental disorder genes have been identified as a result of this study.

"Deciphering Development Disorders offers a win-win to patients, clinicians and scientists alike. It could significantly improve our understanding and management of these rare conditions and provide new avenues of research into treatments for scientists to pursue."

Dr Helen Firth, Chief Investigator and Consultant Clinical Geneticist at Addenbrooke’s Hospital, Cambridge

Value to the NHS

The DDD study is the first nationwide exome sequencing study. It achieved a consistent diagnostic rate in children with undiagnosed developmental disorders and demonstrates that a robust translational genomics workflow is achievable within a large-scale rare disease research study. It allowed feedback of potential diagnostic findings to clinicians and participants and addressed key ethical issues around sharing results with patients.

- It has the potential to act as a prototype for translating diagnostic genome sequencing into the clinic for rare diseases.
- It demonstrated the value in sequencing parental DNA as well as the child’s DNA: a 10-fold reduction was seen in the number of variants that needed clinical evaluation when the child and both parents were sequenced, compared to sequencing only the child.
- Of the diagnostic variants identified in known genes, most were novel and not present in current databases.
- The DECIPHER platform enabled quick phenotyping by NHS clinicians, visualisation of variants in a real-time genomic context. This was coupled with proportionate and secure data-sharing to maximise diagnosis and discovery.

Key publications:

- Study site: www.ddduk.org
- Over 40 publications to date, including:
  - Large-scale discovery of novel genetic causes of developmental disorders. DDD Study, Nature 2015