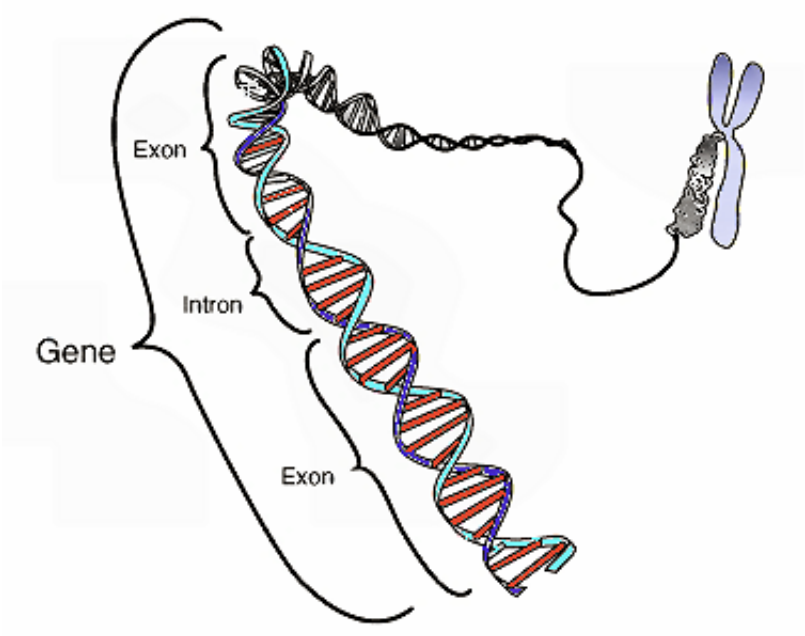
Project pinpoints 12 new genetic causes of developmental disorders

December 24 2014



This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

The first results to emerge from a nationwide project to study the genetic causes of rare developmental disorders have revealed 12 causative genes that have never been identified before. The Deciphering Developmental Disorders (DDD) project, the world's largest, nationwide genome-wide diagnostic sequencing programme, sequenced DNA and compared the clinical characteristics of over a thousand children to find the genes responsible for conditions that include intellectual disabilities

and congenital heart defects, among others.

DDD, which is a collaboration between the NHS and the Wellcome Trust Sanger Institute and is funded by the Department of Health and Wellcome Trust through the Health Innovation Challenge Fund, worked with 180 clinicians from 24 regional genetics services across the UK and the Republic of Ireland to analyse all ~20,000 genes in each of 1133 children with severe disorders so rare and poorly characterised that they cannot be easily diagnosed using standard clinical tests. The benefits of diagnosis include improving clinical management, helping parents obtain support, informing reproductive choice and providing a molecular basis for the disorder, which is the starting point in the search for new treatments.

The DDD project works by collecting together clinical information in a database along with the genetic variants from each patient's genome. If patients who share similar symptoms also have variants in common, it helps to narrow down the search for causative mutations across the genome. However, this can be challenging, since the chance of having a particular type of mutation can be as low as one in fifty million. DDD's nationwide secure data-sharing network has made it possible to find and compare these incredibly rare disorders; in fact, for four of the 12 newly identified genes, identical mutations were found in two or more unrelated children living hundreds of miles apart.

"Working at enormous scale, both nationwide and genome-wide, is critical in our mission to find diagnoses for these families," explains Dr Helen Firth, an author from the Department of Clinical Genetics at Addenbrooke's Hospital and Clinical Lead for the DDD study. "This project would not have been possible without the nationwide reach of the UK National Health Service, which has enabled us to unite a number of families who live hundreds of miles apart but whose children share equivalent mutations and very similar symptoms."

In one example, two unrelated children, both with identical mutations in the gene PCGF2, which is involved in regulating genes important in embryo development, were found to have strikingly similar symptoms and facial features. This constitutes the discovery of a new, distinct dysmorphic syndrome.

All of the newly discovered developmental disorders were caused by new, "de novo", mutations, which are present in the child but are not in their parents' genomes. The DDD project has shown that it is critical to use, where possible, genetic data from parents, most of whom do not have a developmental disorder, to help filter out benign inherited variants and find the cause of their child's condition.

"The DDD study has shown how combining genetic sequencing with more traditional strategies for studying patients with very similar symptoms can enable large-scale gene discovery," says Professor Sir John Burn, Professor of Clinical Genetics at Newcastle University. "This data-set becomes more effective with each diagnosis and each newly identified gene."

Originally, the DDD project focused on applying array technology to screen genes for deletions or duplications that cause the patient's disorder. However, this strategy enabled researchers to find a diagnosis for only 5 per cent of patients. Improvements in sequencing technology have allowed DDD to use genome-wide "exome" sequencing that searches through all protein-coding genes for all classes of genetic variants. This approach produces 100 times more data but delivers a diagnosis for 30 per cent of patients.

"The success of DDD has provided a valuable test bed for Genomics England," says Professor Mark Caulfield, Chief Scientist for Genomics England. "This research has shown that the Government's commitment to sequencing 100,000 genomes can produce powerful data that will

make a real difference to genetic research as well as to clinical diagnostics and treatment."

The DDD project, which started in 2010, will ultimately analyse data from 12,000 families. So far 10 per cent of the 12,000 families that will participate in the study have been analysed in detail, but already the discovery of 12 novel genetic causes of developmental disorders has increased the proportion of patients that can be diagnosed by 10 per cent.

Nonetheless, some DDD children will not be able to be diagnosed by looking at data from UK patients in isolation, and so to identify similar patients from around the world DDD is sharing limited anonymised genetic and clinical data on these undiagnosed DDD children through the DECIPHER database. Researchers hope that the project will inspire more clinical and research programmes around the world to deposit data in the DECIPHER database to pinpoint more genetic causes of developmental disorders and improve diagnostic rates internationally.

"There is a clear moral imperative for both clinical testing laboratories and research studies to share this information globally," says Dr Matt Hurles, senior author and principal investigator on the DDD project. "DDD and DECIPHER have demonstrated that large-scale data sharing can give families the diagnoses they so urgently need; diagnoses that simply cannot be made by looking at the data in isolation."

More information: Large-scale discovery of novel genetic causes of developmental disorders, *Nature*, DOI: 10.1038/nature14135" target="_blank">nature.com/articles/DOI: 10.1038/nature14135

Provided by Wellcome Trust Sanger Institute