

OCT  
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## DECIPHERING DEVELOPMENTAL DISORDERS THIRD ANNUAL FAMILY NEWSLETTER



Recruitment

Results

Publications

Beyond DDD

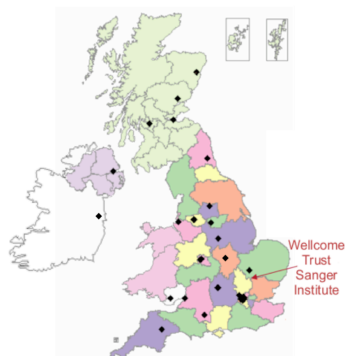
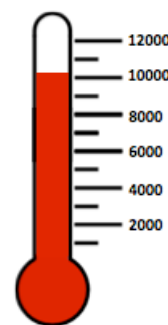
Questions

### Welcome to the third edition of the DDD Family Newsletter!

We have reached a very exciting phase in DDD. Nearly a third of families in our pilot study of the first ~1000 trios (Mum, Dad and Child) now have a diagnosis, and we discovered 12 new genes involved in developmental disorders. Much of this year has been spent making technical improvements to our analysis processes so that we can make faster diagnoses in the next 11,000 patients over the final 2 years of the study. *We hope to send back many more diagnoses soon, and will continue to revisit data generated from all DDD patients throughout the project in light of new knowledge.* Finally, we are committed to continuing to work with those families for which the genetic causes of their condition remain elusive. DDD is the biggest project of its kind and has attracted interest and admiration worldwide. **Thank-you for being part of DDD!**

### RECRUITMENT

We have recruited over 10,000 patients into the study and have received over 30,000 samples! We have also extended recruitment to include adults with developmental disorders who are able to give consent themselves. Please do continue to send us your saliva samples as quickly as possible as we need to reach our target of 12,000 patients.



Our annual DDD meeting brings together many of the clinicians, genetic counselors, research nurses and scientists from around the country who are working hard to recruit and collect all your samples, as well as core team members based at the Wellcome Trust Sanger Institute who are processing and analysing your data to find as many genetic diagnoses as possible.

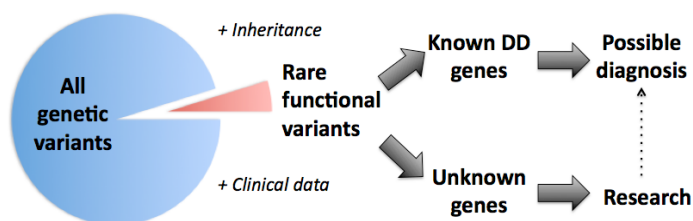


*The primary objective of the DDD project is to improve clinical genetic practice for children with developmental disorders within a 5 year period by the systematic application of the latest microarray and sequencing methods to patients with disorders of development while addressing the new ethical challenges raised.*

## RESULTS

**Sample Processing.** Our DDD laboratory scientists continue to use the most up-to-date methods to analyse your samples. Our main technique, exome sequencing (sequencing all ~20,000 genes in your genome), allows us to detect almost all the types of genetic changes that are currently known to cause disease, including chromosome imbalances previously only detectable using microarray technology. As a result, we are winding-down the use of microarrays and aim to exome sequence every patient in DDD.

**Data Analyses.** We have developed methods to help us sift through large volumes of data and identify only DNA changes in your child that are likely to be responsible for the developmental disorder (DD). As a pilot, we have focused our attention initially on the first ~1000 family trios (Mum, Dad and child).



**Results so far.** We have reported over 300 likely diagnoses in the first ~1000 trios. These have been found in over 130 genes of the ~1200 genes that are already known to be involved in developmental disorders and most of them are new genetic changes that occurred spontaneously in the child ('*de novo*' mutations). By applying statistical methods to the remaining ~19,000 genes in the human genome, we have also identified an additional 12 genes not previously associated with developmental disorders. The clinical genetics team caring for your children have been informed of all our findings to date.

**Results for the Remaining Families.** Exome sequence data provides more diagnoses but takes longer to check and analyse than microarray data. Moreover, we are better able to understand our microarray data if we review it at the same time as the sequencing results. This has caused substantial delays in returning results compared with our initial expectations, and we ask for your patience and understanding as we try to find accurate diagnoses for as many children as possible. We have learnt lessons from our pilot study and have improved our analysis methods accordingly. We are working hard to roll out results for all DDD children over the next 2 years, starting with the next ~3000 trios in the coming months.

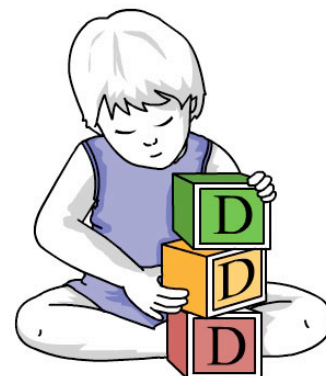
## PUBLICATIONS

Data sharing is a fundamental part of DDD to aid diagnoses and discoveries in the future, and includes sharing a small number of anonymised variants via the publicly viewable DECIPHER database (<http://decipher.sanger.ac.uk>). **Every DDD researcher must sign an agreement to protect patient anonymity and data security.** We also aim to publish as much of our research as possible, either performed by the core team or local clinical teams, to increase international understanding of developmental disorders. For example, papers describing our findings and methods in the first ~1000 trios have recently been accepted for publication in two top journals, *Nature* and *The Lancet*. Clinical members of the DDD team have also published papers on individual genes in the *European Journal of Human Genetics*, *Clinical Genetics* and the *Journal of Medical Genetics*. A full list of publications is available online ([www.ddduk.org](http://www.ddduk.org)).

## BEYOND DDD

The DDD team is absolutely committed to trying to find a diagnosis for every participating child. We are also committed to ensuring that this new form of genetic testing is adopted by the NHS for future families. As a result, DDD will stop recruiting new families in April 2015 in order to focus on our existing families. Having demonstrated the value of the careful application of these genomic technologies in clinical diagnosis, we are working with the NHS to do this type of genetic testing in the future.

**Beyond April 2015:** After the recruitment of new families to DDD ceases, the DDD team will continue to analyse the genetic data on all recruited families. We expect to make more diagnoses, even in the first ~1000 trios, because our ability to make diagnoses increases with the number of families in the study (which is why we are so anxious to achieve our goal of 12,000 families). However, it is likely that there will still be many DDD children without a genetic diagnosis. Work on these families is set to continue beyond the original 5-year period of the study, with the DDD team actively seeking additional funding to extend the project to focus on more detailed research in these children (such as whole genome sequencing – see **Questions** below). With the support of DDD families and their doctors, we are optimistic about obtaining this additional funding. We are absolutely committed to continuing our work with DDD families over the coming years to apply the latest available technologies to understand the causes of their childrens' conditions.



### Ethics Survey

*We have received nearly 7000 responses from the online DDD Genomethics survey investigating public attitudes towards genomic results.*  
([www.genomethics.org](http://www.genomethics.org))

*One key finding is that although most people are in favour of receiving 'incidental findings' that are unrelated to the original purpose for testing, they do not believe this should be done at the expense of primary research.*

*The Genomethics survey has already had a far reaching impact! As well as resulting in multiple publications, it has also been translated into Danish, Urdu and Spanish, and is being used as a teaching aid in Britain, Australia and the USA.*



### **Fascinating Facts**

*The DDD study has now generated exome sequence data on 13,000 of the 30,000 samples we have received, costing over £2.5 million and making DDD one of the largest sequencing projects in the world!*

*The data require over 750,000 Gb of computer storage. Processing the raw DNA sequence data into 'variant files' has taken the equivalent of a single computer running over 45 years!*

*Once we obtain the exome sequence data for a trio, it takes around 8 hours of computing time to look for new mutations in each child!*

For more information about DDD, please talk to your clinical geneticist, or visit our website for updates:  
**[www.ddduk.org](http://www.ddduk.org)**

## **YOUR QUESTIONS ANSWERED**

***We can't get saliva from our child what shall we do?*** If it is too difficult to obtain a saliva sample from your child we can use DNA extracted from your child's blood sample instead. Please do make sure to send your parental saliva samples though, as these are key to finding a genetic diagnosis!

***What happens if we are a single parent family?*** The assessment of your child is likely to be delayed, as we have focused initially on complete family trios where we know the inheritance of each genetic variant in the child. However, we aim to sequence and analyse every child in DDD.

***What's the difference between exome sequencing and whole genome sequencing?*** The exome of an individual is the genetic sequence of just ~1% of DNA, which contains all ~20,000 genes that code for proteins. Since almost all disease-causing DNA changes we know about and can interpret are in genes, it is currently much more cost effective than sequencing the whole genome (which also includes the other ~99% of DNA).

***How many genes are analysed?*** We are sequencing **ALL** (~20,000) genes in the genome of each individual. There are ~1200 genes that are already known to cause developmental disorders in children, and we focus our initial analyses on this set first. However, we are also analysing the remaining (~19,000) genes to help us discover new developmental disorder genes.

***It has been over a year since we joined DDD, why haven't we received a result yet?*** At the outset, DDD was focused on microarray analysis, but as the project has progressed we have shifted over to exome sequencing because of its increased ability to find diagnoses. This is a fairly new technique, which generates large amounts of data, and we are still developing tools to analyse the data correctly. **We realise that the wait is difficult and we are deeply grateful for your support and patience.** Every family should receive a report by the end of October 2016. However, it is likely that many families will remain without a diagnosis. **You are not alone!** There is an excellent support group for those families whose children continue to be genetically undiagnosed called *Syndromes Without A Name* (SWAN) UK ([www.undiagnosed.org.uk](http://www.undiagnosed.org.uk)).

***Are there other children in DDD with the same diagnosis?*** For those families who do obtain a genetic diagnosis, it is possible to find out about other families with similar conditions from the fantastic support group, *Unique* ([www.rarechromo.org](http://www.rarechromo.org)).