Oct 2013

Deciphering Developmental Disorders

Second Annual Family Newsletter

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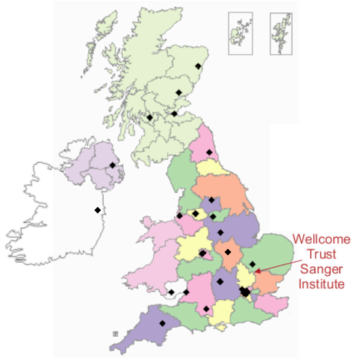
Welcome to the second edition of the DDD Family Newsletter!

After a concerted effort to set up the complex system of recruitment, technology and analysis needed to deliver diagnoses, this infrastructure is now in place. We are now entering a very exciting phase of the project as everything is now in full swing. As a result, we have reported back more than 300 likely diagnoses to the Regional Genetics Services for patients where standard approaches to investigation have been unable to find a genetic diagnosis. We will keep revisiting the data generated from patients recruited earlier in the project and are certain that new diagnoses will come to light on existing data as new discoveries are made. Any relevant findings will then be reported back to families by their clinical geneticist.

There is a lot of interest both nationally and internationally in the DDD study, which is now one of the largest projects of its kind in the world. *Thank you for being part of it.*

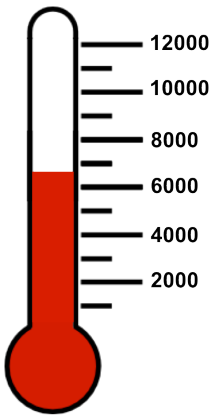
Recruitment

We have now introduced DDD to the republic of Ireland, taking our total to 24 active recruitment sites in regional genetics services covering the whole of England, Wales, Scotland, Northern Ireland and Eire. We have also extended recruitment to the start of April 2015, and to include adults with severe neurodevelopmental disorders. Our dedicated teams of clinicians, research coordinators and scientists around the country are working hard to collect and process all your samples, and find diagnoses for as many families as possible. Here we all are at our annual meeting:



Since April 2011, we have recruited over 6,000 families into DDD, so we are well on the way towards our target of 12,000.

Please do make sure to send all your saliva samples back as quickly as possible to the Wellcome Trust Sanger Institute in the FREEPOST white envelopes provided. If you need new samples packs, please get in touch with your local research nurse or genetic counsellor.



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.

Although we have not been able to get a result back to everyone within a year, as initially hoped, we are continuing to work on all the data and will get in touch with the clinical teams as soon as possible. Please bear with us, and thank you for your patience.

Results

We have now reported over 300 likely diagnoses to clinical teams, including over 100 variants identified through exome sequencing (see final page). The majority of these are new mutations that occurred spontaneously in the child (so-called '*de novo*' mutations) in genes known to cause developmental disorders. We have also identified a few cases of uniparental disomy (UPD), where the child inherits both copies of a chromosome from just one parent, instead of one from each as usually happens.

We have also sent back around 1500 'normal' array reports, which mean that we have not found a likely diagnosis yet. Many families will not have any results from our initial analysis. This may be because we have not yet completed all the genetic analyses for your child, or because we need to request a new DNA sample. Even if these analyses are complete, and we have not found the cause of your child's difficulties, please be reassured that we will continue to analyse and re-analyse all the genetic data periodically until the end of the study, so you may receive results later. Your clinician or research nurse/genetic counsellor will be alerted if we need another sample, or as soon as we report a new result, so that they can re-contact you, check the result and discuss it with you.

We are working hard to produce results that are both accurate and clinically relevant. Because of the enormous volume of genetic data, and the rapidly changing science of genomics, this inevitably takes time. However, the power of the DDD study lies in its size, so the more data we have, the better our chances of finding the cause of your child's developmental disorder.

Sponsored Bike Rides

At the end of September 2013, around 100 scientists and clinicians involved in DDD took part in one of nine bicycle rides around the country. The rides were up to 60 miles in length, and were typically between Regional Genetics Centres. We raised around £10,000 for two patient support charities, Unique and Syndromes Without a Name (SWAN UK), and forged new friendships across the project.

Scientific Research

We regularly present at scientific conferences, and are now working on our first few publications – keep an eye on www.ddduk.org for updates. Our first big publication will examine the results from the first 1000 child-mother-father trios, led by the scientific team at the Wellcome Trust Sanger Institute. Many of the clinical teams are also leading research projects focusing on specific disorders using DDD data, sometimes in combination with data from other studies. Projects include investigating the genetic causes of:

- Cleft lip and palate
- Seizures
- Growth failure
- Intellectual disability
- Autism and schizophrenia

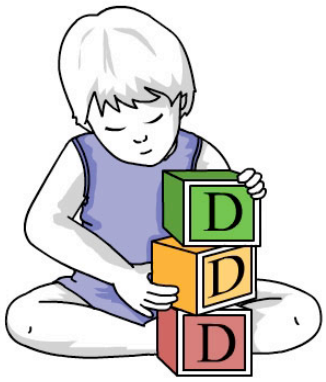
We are also starting to work on a computational method for examining photographs in collaboration with the University of Oxford. We hope this will improve our ability to identify similar children within the study and ultimately help make diagnoses. Rest assured that the photos themselves will remain completely anonymous, and will only be analysed within a secure environment at the Sanger Institute.

Every DDD researcher must sign a legally binding data access agreement that guarantees patient anonymity and data security.

Ethics Research

Thank you to everybody who took part in the ethics online survey. Your contribution was very welcome and much appreciated. From 11,336 initial hits on the survey website we now have 6944 more or less fully completed questionnaires (74% of people answered every single question) - this is a great dataset and will allow us to provide some robust information to guide policy on the sharing of genomic information from future research studies. Participants came from every walk of life and we had responses from 91 different countries, including as far a field as Malaysia, Qatar, Zimbabwe, India, China as well as the UK, North America and Europe. The online discussion forum, *Mumsnet*, picked up the survey and over 1400 mums (and dads) took part from there.

From September onwards the first set of results from the ethics study will be delivered as spoken presentations, first at the British Society of Genomic Medicine and second at the American Society Human Genetics. Shortly after that the first written publications should appear in the medical and social sciences literature. Interviews with interested participants should start in 2014. As and when the results from this arm of the study are ready, we'll let you know what we've found.



Ever feel alone, isolated, or in need of some support?

There are two fantastic patient support groups involved with DDD:

Syndromes Without A Name (SWAN UK), a project run by Genetic Alliance UK offering support and information to families of children with undiagnosed genetic conditions www.undiagnosed.org.uk

Unique, the rare chromosome disorder support group for families with a diagnosis of a chromosomal change that caused their child's developmental disorder. www.rarechromo.org

Fascinating Facts

Although most children in the study will have different conditions, some unrelated children will have a mutation in the same gene

Finding these mutations helps us understand more about the function of the gene and the future for the child

To date, we have found over 50 recurrent genes in the first 1000 families

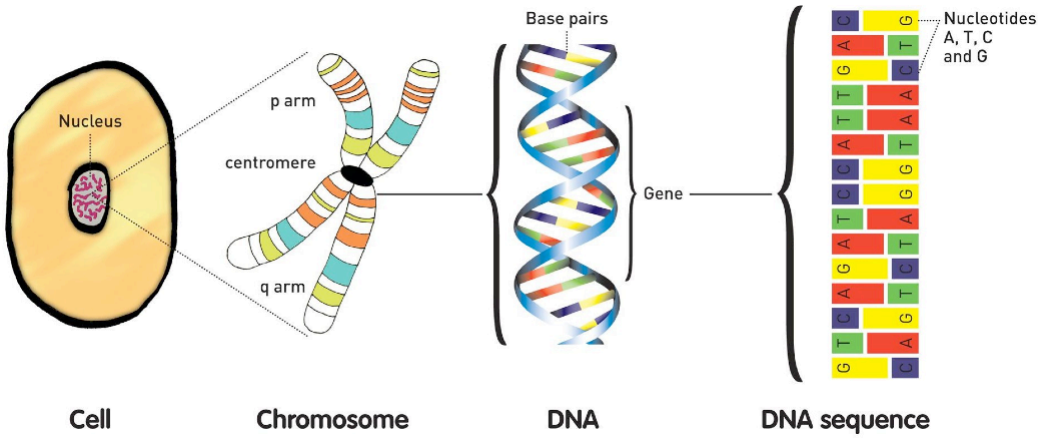
The most commonly mutated genes in DDD are ARID1B (linked with intellectual disability) and SATB2 (linked with cleft palate) – already, six families have received diagnoses in each of these genes.

For more information about DDD, please talk to your clinical geneticist, or visit our website for updates:

www.ddduk.org

Genome Sequencing

The DDD study initially started out using arrays to look for copy number changes in the genome – where a chunk of DNA has been lost or gained. However, scientific and technological advances over the last few years have caused us to rethink how to make the most diagnoses possible in the study. We are now focusing more on sequencing every gene in the genome, ideally of the child and both parents, in order to look for small changes in the genome – even a single letter change in the genetic code. Unfortunately, although it is a very powerful technique, there are many thousands of differences between every genome so finding the relevant one(s) can take a long time.



Unique has produced a leaflet about genome sequencing for families: http://tinyurl.com/genomicsequencing

FAQs

Q. We can't get blood from our child – is just the saliva sample OK?

A. Yes. We will do as much as we can with whatever sample(s) we receive, and in due course will let your clinical team know if we run out of DNA and need more sample from you.

Q. We can't get saliva from our child – is just the blood sample OK?

A. Yes. See above!

Q. We are a single parent family – will my child still get sequenced?

A. Yes. Although we have started sequencing complete child-mother-father trios, as this improves our ability to find a diagnosis much faster, we plan to sequence every child in the study.

Q. When will we receive some results?

A. Unfortunately it is not possible to give an exact answer. We try hard to get likely diagnoses back to clinical teams as quickly as possible. However, analysis of genome sequences is still very new, and the science is continually evolving, so making diagnoses takes time. We are currently completing our analysis of the first 1000 trios in the study, and hope to move on to new patients in the New Year.