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Understanding Chromosome & Gene Disorders

DNA sequencing:

whole genome and exome sequencing

What are chromosomes and DNA?

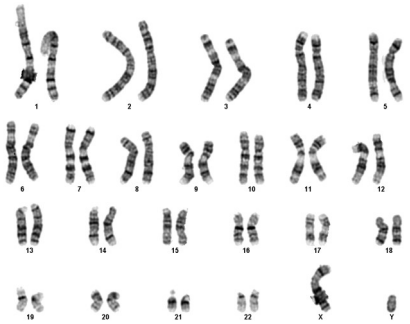
Chromosomes are the structures in the body's cells that carry the genetic information (DNA) that tells the body how to grow, develop and function. Chromosomes usually come in pairs, with one of each pair being inherited from each parent. Humans have 23 pairs of chromosomes giving a total of 46 individual chromosomes. Of these 46 chromosomes, two are the sex chromosomes that determine biological sex, usually two X's for a girl and an X and a Y for a boy. The remaining 44 chromosomes (called autosomes) are grouped in 22 pairs, numbered 1 to 22 approximately from the largest to the smallest. Each chromosome has a short (p) arm and a long (q) arm. The full set of genetic information, packaged within the chromosomes, is called a genome and small sections of this information code for genes.

DNA is a code written in only four 'letters' known as bases, called A, C, G and T. There are around six billion bases in every human genome, and the largest chromosome (chromosome 1) contains around 250 million bases. The meaning of this code lies in the sequence of the letters A, C, G and T in the same way that the meaning of a word lies in the sequence of letters of the alphabet.

A gene is a functional region of DNA. The human genome contains around 20,000 genes, meaning each chromosome contains tens to hundreds to thousands of genes. Genes may be thought of as individual instruction booklets (or recipes) that together contain all the genetic information necessary to tell the body how to develop and function. Most genes provide the instructions to make ('code' for) a protein. Proteins play many important roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Looking at chromosomes (chromosome and genomic array analysis)

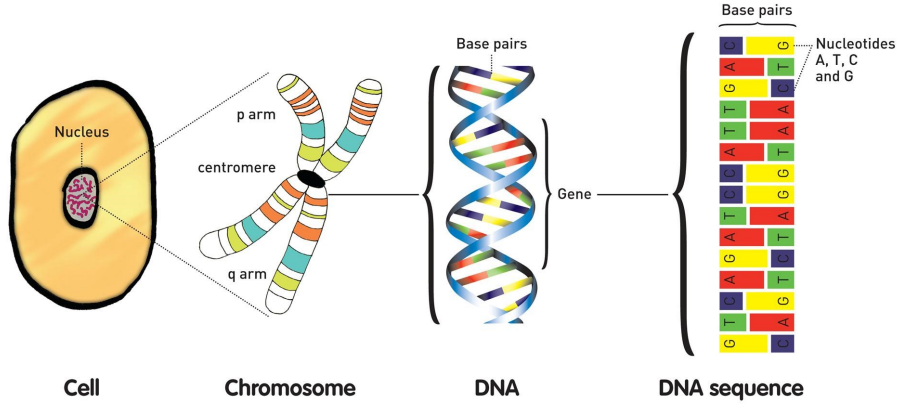
Chromosomes cannot be seen with the naked eye, but if you stain them and magnify them many hundreds of times under a microscope, you can see that each one has a distinctive pattern of light and dark bands. Looking at chromosomes in this way is often referred to as karyotyping. Using this technique, it is possible (if the change is large enough) to see if there is a chromosome imbalance [a loss (deletion) or gain (duplication) of chromosome material] or if any of the chromosome material has been rearranged.



Chromosomes pairs 1-22, X and Y (male)

A more recent enhanced test is called a genomic array test or chromosomal microarray test (CMA). This type of test includes microarray-based comparative genomic hybridisation (array CGH, also known as CMA-HR), single nucleotide polymorphism array (SNP array, also known as SNP-chip or CMA-SNP) or a combination of both. Genomic array tests allow the detection of chromosome deletions or duplications that are smaller than can be detected by looking down a microscope. Smaller alterations are often called microdeletions or microduplications. Unique has separate guides on Array CGH, 'deletions and microdeletions' and 'duplications and microduplications'.

Even more recent advances in technology have allowed the development of a more precise test that can detect even smaller genetic changes, this is called DNA sequencing. Sequencing can detect alterations as small as a change in a single base ('letter').



What is sequencing?

Sequencing involves reading the exact order of letters – the As, Cs, Gs and Ts - along a piece of DNA. This is the most detailed genetic test possible. It allows us to read a person's genome from start to finish (whole genome sequencing), or to just read selected variants or regions of particular importance (whole exome, panel and single gene sequencing). An individual's sequencing result will then be compared to standards and references of what is common in the population and the results are interpreted by laboratory and clinical genetics specialists. Using sequencing, it is possible to detect single base changes, as well as pieces of missing or duplicated genetic information (deletions/microdeletions or duplications/microduplications). This technology means that almost any change to the DNA that might have caused a child's developmental disorder can potentially be found. However, interpreting the sequence data is a highly complex task and it will be some years before the full diagnostic potential of this technology is realised.

What are the different types of sequencing?

There are several possible ways to undertake sequencing for clinical purposes:

Whole genome sequencing (WGS)

This involves a person's entire ('whole') genome being sequenced. The results will include the sequence of all of that person's genes as well as all of the non-coding DNA that doesn't code for a gene (quite remarkably, less than two percent of our genome codes for genes). Non-coding DNA is made up of the same four letters as coding DNA but it doesn't have the same meaning. We are not sure what all of this non-coding DNA is for but we do know that some of it controls when genes are switched on or off, while other bits are important for determining or maintaining the structure of chromosomes. Although the whole genome is sequenced for a WGS test, often only part of the data is used for analysis. A virtual panel is applied to the sequencing data so that analysis is focused on variants in genes linked to the clinical features of the child or adult being tested.

Whole exome sequencing (WES)

It is known that most of the changes that occur in DNA sequences that lead to genetic disorders are located in the coding part of the genes (exons). Therefore, sequencing the exome (exome sequencing), rather than whole genome sequencing, is currently a more efficient and economical way to sequence a person's DNA to discover most of the genetic causes of diseases, disabilities or developmental delay. As with WGS, a virtual panel is often applied for sequence analysis.

Panel sequencing

It is also possible to sequence just a subset of specific genes, such as all those known to be involved in certain features, for example epilepsy. This test is less expensive than exome sequencing, but limits the possibility of finding new genetic diagnoses.

Single gene sequencing

The sequencing of individual genes was a traditional approach in the past but requires a clinician to select which one of the ~20,000 genes to sequence. This is possible for some disorders, for example cystic fibrosis where there is a single causative gene, but not for the majority where a similar clinical condition can be caused by changes in a variety of genes, making it difficult to select which gene to sequence.

How do I request sequencing for my child?

Previously, genome sequencing was usually only available as part of a research project. However, with the decreased cost and increased knowledge now available, sequencing technologies are being offered by clinical genetics departments of some national health services. The NHS genomic medicine service in England is now able to offer whole genome sequencing to individuals who meet the eligibility criteria as part of a routine diagnostic pathway. The situation in the rest of the UK and other countries varies but it is expected that sequencing tests will become increasingly available for those with a suspected genetic condition. If you would like your child to have a genome sequencing test, you might like to discuss with your doctor, paediatrician or genetics specialist to see whether this would be appropriate for your child and, if so, what is currently available for you.

What is the NHS Genomic Medicine Service (GMS)? (England only)

In England, the National Health Service (NHS) has recently made huge investments to ensure consistent, fair and impartial access to genetic testing across the country. This initiative has been named the Genome Medicine Service (GMS) and includes a national genomic laboratory network and genomic test directory together with centres providing whole-genome sequencing and clinical services. The GMS aims to routinely use WGS and other recent genomic technologies to drive more personalised treatments and interventions. The initial roll out of this service will take place between 2020 and 2025.

Can I have prenatal testing using sequencing?

Since sequencing is a relatively new and emerging technology it is not yet commonly offered before a baby is born, however, occasionally, sequencing will be offered as part of prenatal testing. Specifically, rapid exome (RE) sequencing, with analysis limited to a panel of genes known to cause problems that may present prenatally, has recently been introduced in England when an ultrasound scan finding suggest a baby may have a genetic condition. Once a pathogenic genetic variant has been identified through sequencing in a family member, then for any future pregnancy, prenatal testing or pre-implantation genetic diagnosis may be possible.

Will sequencing change my child's treatment?

Detecting a DNA change by sequencing might offer a genetic explanation for any learning or developmental difficulties that affect your child but does not necessarily lead directly to immediate improved treatment. However, if a gene or a region of a chromosome that is associated with a specific clinical feature has been shown to be duplicated, deleted or changed in your child, this may have an impact on your child's care or it may give you an indication of health problems to watch out for that may be have been identified in other people with the same or similar chromosome or gene change.

What else can sequencing reveal about me?

Each human genome contains many changes, some of which are relevant to current or future diseases and other personal characteristics. Like a microarray, a sequencing result may raise unexpected genetic risks in you or your child that are unrelated to your child's original reason for referral. These findings are often called 'incidental' or 'unexpected' findings as they do not relate to the reason your child was tested but they may have implications for your child's future health or development, or the health of other family members. Currently these results are not usually shared with patients because it is hard to know what they mean.

What if the sequencing does not give a diagnosis for my child?

Your geneticist or genetic counsellor will be able to discuss this outcome and advise whether other tests may be appropriate for your child. In this case, the geneticist would discuss if any additional screening might be recommended for your child. There is currently a lot of research being done to understand genomes, so it is possible that a diagnosis will be found in the future if your child's DNA sequence is reanalysed.

What samples are needed for sequencing?

Sequencing can be performed on any DNA sample from an adult or child. The most commonly used DNA samples are those prepared from the cells of a blood sample. Sometimes, saliva or cells from a cheek swab are used (buccal swab) and, depending on why the test is being performed, cell samples from other tissues can be used.

Why has sequencing been offered for our child?

A sequencing test is particularly valuable for serious undiagnosed disorders where a small genetic change(s) is likely to be the cause of the disorder. In such cases, older technologies, such as karyotyping and array CGH analysis, may be unable to find the DNA change.

In the past, sequencing was not routinely offered to families, although some families were offered exome sequencing or whole genome sequencing as part of a research project, such as the Deciphering Developmental Disorders (DDD) project in the UK (www.ddduk.org) or the 100,000 genomes project (www.genomicsengland.co.uk).

More recently, in the UK, NHS England has launched the Genomic Medicine Service (GMS), making England the first country in the world to integrate whole genome sequencing into routine clinical care for a range of indications. Thanks to this initiative, it is expected that many undiagnosed children and adults will have a better chance of discovering the genetic change(s) underlying their clinical features or disorder.

How will we be given the results?

The results are likely to be given to you by the doctor who ordered the test and they will be able to talk you through them, at least in outline. You will almost certainly then receive a follow-up letter summarising the consultation. Alternatively, you may receive a preliminary result from the doctor doing the test and then referral to a geneticist (if appropriate) if interpretation is complex or once family studies (if needed) are completed.

How long do the results take?

As DNA sequencing is an emerging technology, results could take time to be reported back and passed on to parents. Previously, sequencing results from research projects generally took a long time to be reported because, although the test itself is quite quick, analysis of the resulting sequence data can involve a number of specialists and take some time. The technology and expertise in sequence analysis has improved tremendously over the last few years and results are now likely to be reported back more quickly.

Interpretation of the results

Sequencing is a way to find changes in a person's DNA, including small losses or gains of parts of chromosomes and/or genes [sometimes known as copy number variants (CNVs)], or changes in a single nucleotide (each nucleotide includes a base) within a gene [known as single nucleotide variants (SNVs)]. Many of these changes are very common and seem to have little or no effect on an individual's health and development. However, some are relatively frequently seen and have been associated with well understood patterns of medical features. Some changes are emerging as rare genetic variants that are being associated with a spectrum of features and difficulties experienced by different individuals. Other sequencing results are even more rare and, in some cases, this means it is not yet possible to work out if that particular DNA change is causing the features and difficulties apparent in a child or adult. Parental testing can sometimes help to clarify this type of uncertain result (this is called Trio analysis). Sharing potentially diagnostic findings through a platform such as DECIPHER (www.deciphergenomics.org) can also be helpful to see whether other people around the world who have the same variant have similar clinical features.

My geneticist says my child has a change in a specific gene. How do I find out what this gene does?

At present, we only understand the role of a small minority of genes and their association with particular features. When a gene's association with a clinical feature is known, it can be informative for the care and management of a child's health to know which gene is affected. A simple 'one gene-one disorder' model does not apply to all genes; some genes are more complicated and variants in different parts of the gene, or different variant types, may cause different clinical disorders. If you would like further information on the specific gene(s) involved in your child's disorder, you may wish to request an appointment with your geneticist or genetic counsellor who will be able to discuss this with you more fully.

With the help of clinical geneticists and other medical professionals, *Unique* also publishes a growing library of freely available single gene disorder guides (www.rarechromo.org/disorder-guides/).

What are the advantages of sequencing?

Sequencing provides the most comprehensive analysis of genes and chromosomes available to date. Therefore, many more children are likely to get a diagnosis from sequencing than from other genetic tests. Additionally, sequencing can detect changes in genes and chromosomes when there are no obvious genetic explanations for an individual's health or developmental concerns, meaning there are no gene/chromosome specific tests that could be used to help with diagnosis.

Receiving a diagnosis from sequencing may prevent your child from having to undergo many other tests in order to discover a reason for their difficulties. A diagnosis may help you and your doctor to watch for common health problems that may be associated with your child's particular DNA change(s) and may help predict what to expect as your child gets older. If the gene(s) has been associated with a particular feature or health problem, it may help to guide management or treatment for your child.

Also, some parents find it helpful to share their child's diagnosis with the school system and other services involved with the care of their child to help them better understand their child's difficulties and to help obtain additional services. Some parents choose to join a support group to meet other parents facing similar challenges and possibly be connected with other families with a similar diagnosis.

Additionally, when a specific DNA change is detected, the parents (and some other family members) may be offered a genetic test to see if they are carriers of changes in their DNA that put them at risk of having (more) children with a chromosome or DNA change. For some genetic disorders, it may be helpful for adult carriers to be aware of their diagnosis so their health can be monitored for possibly conditions that could appear later in life. The availability of genetic testing of extended family members varies within and between countries and for different genetic diagnoses. You may wish to discuss which options are available to you with your genetics specialist.

What are the limitations of sequencing?

Unlike single gene diagnostic sequencing, interpreting the results from whole genome or exome sequencing is very complicated. Every person has a unique DNA sequence, meaning there are lots of tiny genetic differences, called variants, between all of us that won't be associated with the features for which an individual is being investigated. Some variants are common, some are rare and this makes finding the genetic difference(s) that cause a particular developmental disorder especially challenging. These DNA changes include copy number variants and single nucleotide variants that are common in the general population and are often completely harmless, these are known as benign. However, sometimes a CNV or SNV can affect health or development, these are called pathogenic. Some sequencing results may include a DNA change for which the significance is not yet known, these are called variants of uncertain significance (VUS or VOUS). These variations can make interpreting the test results very difficult. In addition, some DNA changes, such as changes to the number of highly repetitive DNA sequences (for example as found in Huntington's disease), are hard to detect using current genome sequencing technologies. For disorders caused by these sorts of changes, a different technique is used.