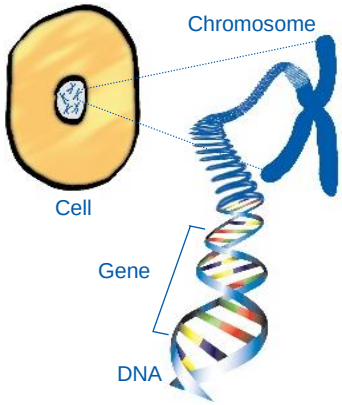
Interpreting Genetic Test Results

Each time a person has a genetic test, their genetic test result will be documented in a **genetic report**. A genetic report is a formal document from a genetics laboratory that records the result of an individual's genetic test. Genetic reports are written by scientists in the genetics laboratory who perform the genetic testing and interpret the results. Genetic reports can be difficult to understand and can contain lots of complicated scientific information, as well as symbols and abbreviations of key terms. This guide has been written to explain the different types of genetic change found in families and how to interpret a genetic report.

Types of genetic test

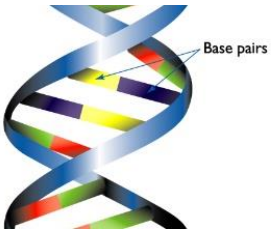
There are many types of genetic test available that can detect different genetic changes. How the information is presented in a genetic report will depend on the laboratory and which genetic test was carried out.

Studying chromosomes - chromosome analysis



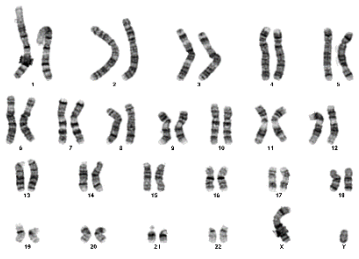
Our genes are carried in structures called **chromosomes**, which consist of a complex chemical called **DNA**. Chromosomes usually come in pairs, with one chromosome inherited from each biological parent. Each chromosome has a short (**p**) arm and long (**q**) arm, which are joined at the **centromere**. We typically have **46** chromosomes in total: two chromosomes 1-22 (**autosomes**) and two of the **sex chromosomes** (X and Y). Usually, males have one X and one Y chromosome (XY), and females have two X chromosomes (XX).

Chromosomes cannot be seen with the naked eye, but if they are stained and magnified under a microscope using a type of test called a **karyotype**, it is possible to see that each one has a distinctive pattern of light and dark **bands** that look like horizontal stripes. Each band contains millions of **base pairs** of DNA. Base pairs can be used as a measure of the size of a section of DNA.

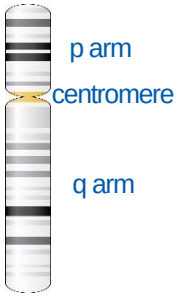


1 base pair = bp
1,000 base pairs = 1kb
1,000,000 base pairs = 1Mb

DNA



A male karyotype
(XY sex chromosomes)
with 46 chromosomes in total



Chromosome 9
The short (p) arm, long (q) arm, centromere (in yellow) and distinctive pattern of light and dark bands of chromosome 9

Carrying out a karyotype means that it is possible to see a chromosome imbalance (loss or gain of chromosome material) or if a chromosome(s) is rearranged in some way, if the change or rearrangement is large enough (approximately 5 – 7 mega bases (Mb)). Some changes are too small to be seen on a karyotype so a test that can detect smaller changes, called a **microarray**, is needed**.** Sometimes an even more in-depth test is needed so **sequencing analysis** is performed rather than chromosome analysis.

Studying the genome - genomic analysis

The **genome** is the complete set of genetic information in an individual - this means the genome includes a person's chromosomes.

Recent advances in technology have allowed for the development of a more precise test that can detect even smaller genetic changes than those that can be detected by a karyotype or microarray. This type of test is called **DNA sequencing**.

Our DNA is made up of **four chemical building blocks** called **nucleotides** that are represented by the letters **A**, **C**, **G** and **T**. DNA sequencing involves reading the exact order of these letters along a piece of DNA in an individual's genome, and then comparing this to what is common in the population. The findings are interpreted by genetic laboratories and specialists.

By using sequencing, it is possible to detect **single base changes** (a change in one letter), as well as pieces of **missing or duplicated genetic information** that may not be visible in a karyotype or array.

To learn more about microarrays and sequencing please see our **array CGH**, **SNP array** and **DNA sequencing** guides.

Types of Genetic Change

Chromosome changes

The type of genetic change will be recorded in the genetic report.

Aneuploidy

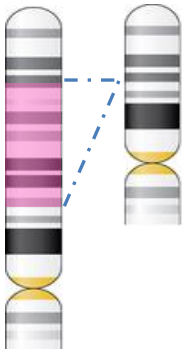
This means **the presence of a lower or higher number of chromosomes** than expected. For example, instead of the usual 46 chromosomes, some people have 45 or 47 chromosomes or more. Examples of aneuploidy include trisomy 13; trisomy 18; Turner Syndrome (45, X); Klinefelter syndrome (47, XXY); 47, XXX; 47, XYY and 48, XXXY.

To learn more about specific aneuploidies, please see our guides for specific aneuploidies e.g. XYY, XXXY

Deletion 'del'

To learn more about deletions, please see our Deletions and microdeletions guide

This means a **piece of chromosome is missing**. Deletions can vary in size from one base pair to tens, hundreds, thousands (kb) or millions (Mb) of base pairs. Those too small to be seen using karyotype testing are known as **microdeletions** and are identified using microarray testing or sequencing.



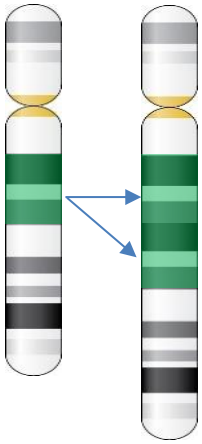
An example of a deletion in the short (p) arm of chromosome 2

A region (pink) in the p arm of chromosome 2 has been lost.

Duplication 'dup'

To learn more about duplications, please see our Duplications and microduplications guide

This means **an extra copy of a piece of a chromosome is present**. As with a deletion, a duplication can vary in size from one base pair to millions (Mb) of base pairs. Some duplications are tiny and are called **microduplications**. Microduplications will not always be visible on a karyotype but can be identified using microarray testing or sequencing.



An example of a duplication in the long (q) arm of chromosome 18

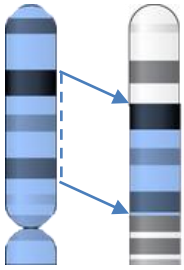
A region (green) in the q arm of chromosome 18 has been duplicated.

Copy Number Variant 'CNV'

This means there is **a difference in the number of copies of a specific piece of DNA in a chromosome**. We normally have two copies of each chromosome, but if a piece of DNA is duplicated in one chromosome but not the other, the new copy number is 3. A deletion usually results in a new copy number of 1. It is possible to have a copy number of more than three if the piece of DNA is duplicated many times. For example, if the piece of DNA has been duplicated several times and is present as five copies, the copy number would be 5. A copy number of 0 means the specific piece of DNA is not present in the chromosomes.

Insertion 'ins'

This means a **piece of one chromosome is inserted into another chromosome**.



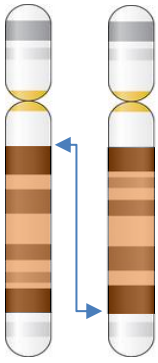
An example of an insertion in chromosome 10

An insertion of a piece of chromosome 8 (blue) into chromosome 10 (white).

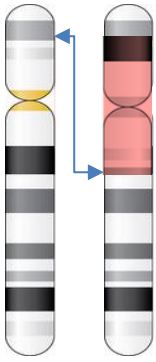
Inversion 'inv'

To learn more about inversions, please see our Inversions guide

This means a piece of a chromosome has **rotated by 180 degrees** and then **reinserted itself into the gap left in the chromosome**. If an inversion occurs within the same arm of the chromosome, this is called a **paracentric inversion**. If the inversion occurs across the short arm and long arm of the chromosome, this is called a **pericentric inversion**.



An example of a paracentric (away from the centre) inversion

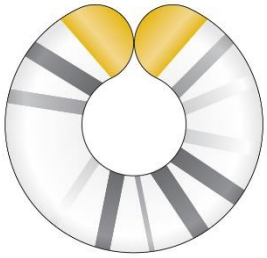


An example of a pericentric (around the centre) inversion

Ring chromosome

To learn more about ring chromosomes, please see our guides for specific ring chromosomes e.g. Ring chromosome 17

A ring chromosome is formed when the **tips of a chromosome are lost, and the two broken ends join together to form a closed ring**.



Ring chromosome 17

A small amount of genetic material is lost from the ends of chromosome 17, and the chromosome bends to form a closed ring instead of the usual bar-like structure.

Uniparental disomy (UPD)

To learn more about UPD, please see our Uniparental disomy guide

Uniparental disomy or UPD occurs when **both copies of a specific chromosome (or part of that chromosome) are inherited from one parent** and no copy is inherited from the other parent. When both chromosomes (or part of a chromosome) of a pair are inherited from the mother it is known as **maternal UPD** (or mUPD / UPDmat). When both copies are inherited from the father it is known as **paternal UPD** (or pUPD / UPDpat).

Isochromosome & Isodicentric (Idic) chromosome

An **isochromosome** is an unusual chromosome that forms when **two** short (p) or two long (q) **arms of the same chromosome join at a centromere** and are arranged as a 'mirror image' of each other. An **isodicentric chromosome** is an isochromosome that has **two centromeres.**

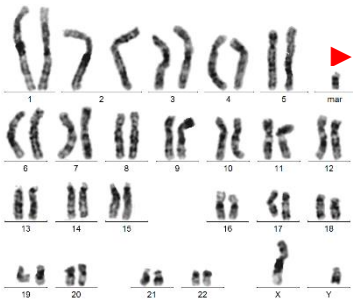
An example of isochromosome 12
An isochromosome made from two opposite facing p arms of chromosome 12.

An example of Idic[15]
An individual has a small additional isodicentric chromosome derived from chromosome 15, as well as two regular chromosomes 15. They therefore have 47 chromosomes, rather than the usual 46.

Small supernumerary marker chromosome (sSMC)

To learn more about these, please see our Small supernumerary marker chromosomes (sSMC) guide

This means that there is an **extra chromosome** in all or some of the cells of the body. In addition to the 46 chromosomes that we usually have, people with a supernumerary marker chromosome have a **small extra 47th chromosome that contains part(s) of one, or more, regular chromosome(s)** (47,XX, + mar (for a female) or 47, XY, +mar (for a male)). Examples of sSMCs include the presences of a dicentric/isodicentric chromosome or ring chromosome.



A karyotype for a male with an sSMC derived from chromosome 15 (marked ▶)

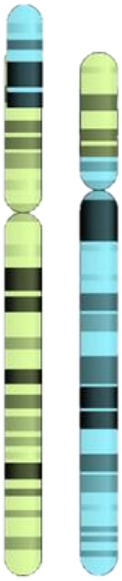
5

Translocations 't'

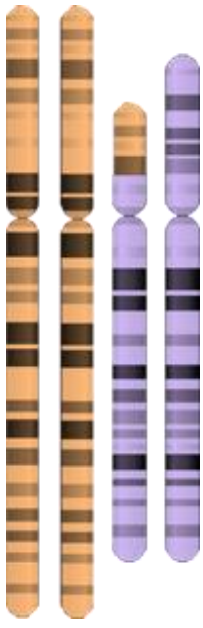
To learn more about translocations, please see our different guides: Balance Translocations; Balanced Insertional Translocations; Unbalanced Translocations; Robertsonian Translocations

A translocation happens when **a section from one chromosome of a particular pair changes places with a section from a chromosome of another pair**. They include reciprocal translocations, Robertsonian translocations and insertional translocations. Translocations can be balanced or unbalanced. The rearranged chromosomes that result from a translocation are referred to as derivative (der) chromosomes.

- **Reciprocal translocations** – when two pieces of chromosomal material (usually from different chromosomes) change places but no chromosomal material has been lost or gained and the break points have not impacted a gene (the translocation is balanced).
- **Unbalanced/imbalanced translocation** – when two pieces of chromosomal material (usually from different chromosomes) have changed places and some genetic material has been lost and/or gained. The amount of genetic material gained or lost can vary in size.
- **Robertsonian translocation ('Rob')** – when two of the five "acrocentric" chromosomes (13, 14, 15, 21 or 22) have broken at the beginning of the short arm near the centromere. The short arms are lost and the remaining long arms fuse together. Loss of these short arms should not cause symptoms. A person with a Robertsonian translocation has a total of 45 chromosomes (instead of 46).



A balanced reciprocal translocation
A section of one chromosome has changed places with another chromosome but no chromosomal material has been lost or gained.



An unbalanced translocation
A section of one chromosome 10 (purple) is deleted and there is a duplication of a section of chromosome 6 (orange).

A Robertsonian translocation
The long (q) arms of a chromosome 14 (bottom) and chromosome 22 (top) are attached at the centromere (yellow).

Sequence variants

Using a test called DNA sequencing, it is possible to detect even smaller genetic changes in our DNA, including **single nucleotide variants** (SNVs), as well as missing or duplicated material. Single nucleotide changes are referred to as **'sequence variants'** as they represent a change from the expected DNA sequence. For example, instead of AACCG, the variant may change the sequence to A**T**CCG.

Some of our genes (specific sections of DNA) provide instructions for making **proteins**. Proteins are made of building blocks called **amino acids** and play important roles in allowing our bodies to grow, develop and function. **Sequence variants in a gene may change the instructions that gene gives**. This can have an impact on the protein made by that gene, which can have consequences for our health and development.

Types of sequence variant:

Loss of function (LOF) – some variants prevent the formation of a functional protein.

Altered function – some variants cause the gene to produce a protein that functions **but not as expected**. Such proteins may behave in different ways and cause different symptoms depending on how their function has been changed.

Missense – these variants are like a 'typo' in the genetic code (one letter changed in the nucleotide sequence) that changes one amino acid to another and so can **alter the way a protein is made**. This can cause loss of function of the protein, gain of function, or no change.

Nonsense – these variants cause a 'full-stop' to appear in the genetic code, meaning the **part of the protein coded for after the stop signal will not be made**. This can cause loss of function.

Frameshift – these variants cause a **'shift'** in the genetic code. This means the information is **misread** and the protein is not made properly. This can cause a loss of function or altered function.

Sequence variant classification

When a sequence variant is found through the genetic testing process, scientists will determine the type of genetic change, how it affects the function of the gene, and if the variant has been identified before. They can use this information to classify the sequence variant as either **benign**, **pathogenic**, or a **variant of uncertain significance**. **The variant classification will be recorded in the genetic report**.

• **Benign** – a genetic change that is **not expected to cause any features or symptoms of a related condition**. Benign changes to DNA are common and nothing to worry about and are not usually included in genetic reports.

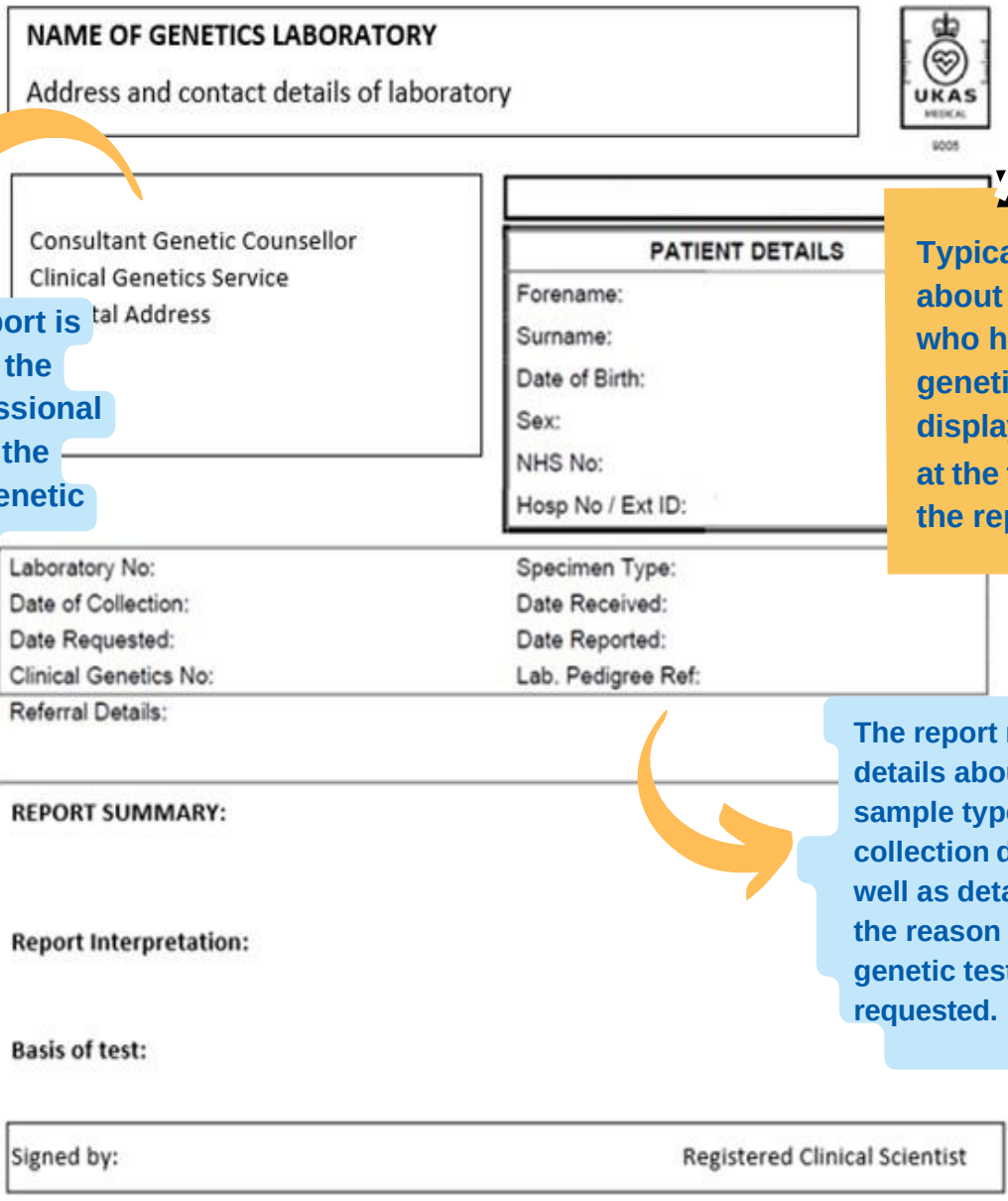
• **Variant of uncertain significance** (‘VUS’/'VOUS') - VUS is used to describe a genetic change that is **different from the standard genetic code and could either be a natural difference (benign) or the likely cause of a condition (pathogenic) in an individual.** However, currently there is not enough evidence for classification so it's uncertain whether it is benign or pathogenic.

• **Pathogenic (‘disease-causing’)** – a genetic change that is the likely **cause for an individual to have or be at risk of developing a certain genetic condition**.

Sometimes a sequence variant is called **‘likely benign’** or **‘likely pathogenic’**. This is because there is some evidence that points to the genetic change being either benign or pathogenic with **90% certainty**. Sometimes, a VUS will be **re-classified** to **likely benign/benign or likely pathogenic/pathogenic** if new knowledge about the genetic change is found through research, or more people with features or symptoms of a condition are found to have the same VUS. This information will **be recorded by the scientists in the genetic report** as part of their interpretation of a genetic result. Reclassification of a VUS is not automatic and **may take time**.

What does a genetic report look like?

All genetic reports contain the same type of information, but the layout of this information may vary between different genetics laboratories. Here is an example of what a genetic report may look like:



The genetic report is addressed to the healthcare professional who referred the individual for genetic testing.

Typically, details about the person who had the genetic test are displayed at the top of the report.

The report records details about the sample type and collection date, as well as details about the reason why genetic testing was requested.

The genetic result is clearly stated in the genetic report and is written in scientific language that is universal to genetic healthcare professionals across the world.

In the **interpretation** section of a report, the clinical scientist will record information about **the specific genetic finding(s) and the potential impact on the individual, as well as the chance of future pregnancies being affected**. Information about how the genetic finding is inherited through a family and implications for wider family members may also be included.

The report will also include some technical information about how the genetic test was performed in case it needs to be repeated. At the end of a genetic report is the name and signature of the clinical scientist who interpreted the genetic result and wrote the report.

Reading a genetic result

Sequence variants

Below is an example of a genetic result from DNA sequencing of multiple genes associated with childhood syndromes. This testing identified a sequence variant in a single gene.

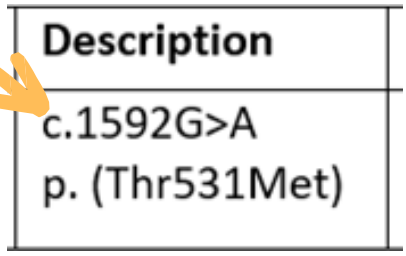
Referral Details: Child with epilepsy and behavioural problems. ? syndrome. Please test paediatric disorders panel

Result:

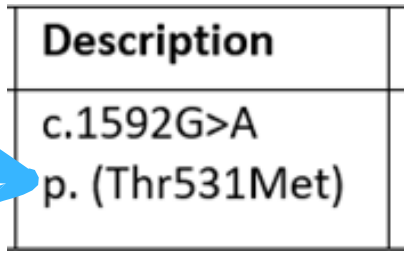
Gene	Description	Genomic Coordinates	Zygosity	Classification
GRIN2A	c.1592G>A p. (Thr531Met)	Chr16.hg19:g.933456316	Heterozygous	Pathogenic

Summary: heterozygous for a pathogenic GRIN2A sequence variant consistent with a diagnosis of GRIN2A-related speech disorders and epilepsy

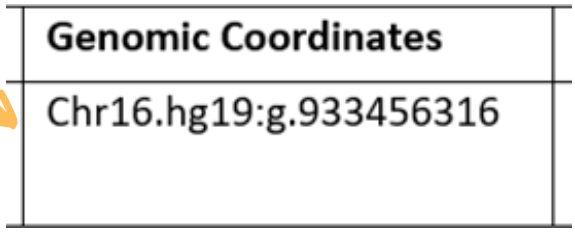
c.1592G>A demonstrates that a single nucleotide change has taken place (**c.** refers to the reference sequence used). The nucleotide at position **1,592** which is usually a **G (guanine) has been changed to an A (adenine)**.



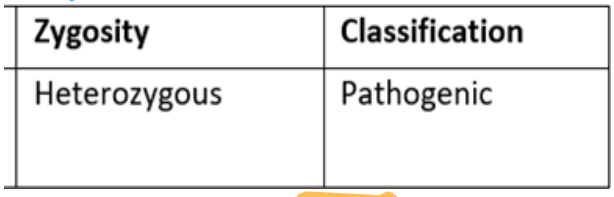
p.(Thr531Met) demonstrates the protein change as a result of this single nucleotide change. In this example, the nucleotide change c.1592G>A has caused the **Threonine (Thr) at amino acid position 531 to be replaced by a Methionine (Met)**. Threonine and Methionine are two types of **amino acid** (the building blocks of proteins). Most genetic reports will record the changes at both the DNA (nucleotide) and protein (amino acid) level.



The **genomic coordinates** specify the exact location where this genetic change can be found in the DNA (like a map), in this case in **chromosome 16**.



We generally have two copies of each gene as we inherit one from our biological mother and one from our biological father. **Zygosity** refers to whether the sequence variant is present once or twice. **Heterozygous** means there is one copy.



After reviewing the information about this sequence variant in the literature and using special bioinformatic programmes, the scientists have classified this variant as '**pathogenic**' (disease-causing).

Chromosomal findings

The results of chromosome studies will look like a long string of numbers and letters that are specific to the genetic change that has been identified during testing. The description of the result can look very confusing, but each part includes a useful piece of information. A few examples are explained below:

Karyotype result

Below is an example of a **karyotype** that identified an extra chromosome: chromosome 18. This is called trisomy 18 as there are three copies of chromosome 18.

Referral Details:	Ultrasound scan findings. First trimester screening.
Result:	**KARYOTYPE: 47,XX,+18**
Summary: Chromosome analysis shows an abnormal female karyotype with an additional chromosome 18, trisomy 18, which is diagnostic of Edwards syndrome.	

'47' signifies the number of chromosomes this individual has (usual number is 46); **'XX'** signifies that this individual is female; **'+18'** signifies that there is one additional copy of chromosome 18.

Microarray result

Below is an example of a microarray result in a **male without any unusual genetic changes**.

Result:	**arr(X,Y)x1(1-22)x2**

'arr' signifies that an array test was carried out; **'(X,Y)x1'** signifies that a single X and a single Y chromosome were identified, signifying that the individual is male. **'(1-22)x2'** signifies that two of each chromosome number 1-22 were identified in the sample. This is a **typical male result**.

Microarray result with a deletion

Below is a microarray result which identified that an individual **has a 16p11.2 microdeletion**.

Result:	**arr[hg19] 16p11.2(29,673,954-30,198,600)x1**

'arr' signifies that an array test was carried out. **'hg19'** means Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made, and the base pair numbers may be adjusted.

'16p11.2' signifies that a change was found in chromosome **16** in the short "**p**" arm in band **11.2**. **'(29,673,954-30,198,600)'** signifies the base pairs that are missing. The **first base pair shown to be missing is 29,673,954**. The **last base pair shown to be missing is 30,198,600**. If you take the first long number from the second number, you get 524,646; this is the number of base pairs that are missing. **'x1'** means that **there is one copy of these base pairs and not two** – as you would normally expect - **so this is a deletion**.

To find out more about how to interpret a microarray result, please see our **SNP array** and **array CGH** guides.

Reciprocal Translocation

Here is an example of a genetic test result which identified an individual had inherited a **balanced translocation involving chromosomes 11 and 22.**

Referral Details:	Mother carries an 11;22 translocation. Partner pregnant
Result:	**t(11;22)(q23;q11.2)mat**

Summary: this patient has an apparently balanced reciprocal 11;22 translocation which has been inherited from his mother. Prenatal diagnosis should be offered to his partner in the current and any future pregnancy.

The **referral details** explain that the patient's partner is pregnant, and his mother carries a translocation. Since the patient's partner is pregnant, he has been referred for testing. **'t'** refers to the type of genetic finding which is a '**translocation**'. Next, the chromosomes that are involved are recorded, which are **11 and 22 (11;22)**. **(q23;q11.2)** indicates which '**arm**' of the chromosomes are involved, in this case the **q** arm, and the **band location** where the chromosomes have broken **(11q23 and 22q11.2)**. **'mat'** means this translocation has been **maternally inherited.** If a parent has not had a genetic test, this information may not be known and so is not included in the report. This translocation is **balanced** as there is no gain or loss of genetic material.

Robertsonian Translocation

Below is an example of a genetic result that identified an individual as a carrier of a **Robertsonian translocation involving chromosomes 13 and 14**.

Referral Details:	Father has a 13;14 Robertsonian translocation. For targeted karyotyping
Result:	**der(13;14)(q10;q10)pat**

Summary: this patient has a balanced Robertsonian 13;14 translocation, which has been inherited from her father. Prenatal genetic diagnosis should be offered in any future pregnancy.

'der' refers to a **derivative chromosome** which is a **chromosome that is rearranged**. In this example, this derivative chromosome involves one chromosome **13** and one chromosome **14 (13;14)** that are **attached together by their long arms (q)**. The breaks have occurred in the middle of both chromosomes at **band 10 (q10;q10)**. **'pat'** or 'paternal' refers to how this chromosomal change has been inherited (in this case from the biological father). If a parent has not had a genetic test, this information may not be known and so is not included in the report.

Mosaicism

In genetics, the term mosaicism describes a condition in which a genetic change is found in some, but not all, of the body's cells.

Result:	**mos dup(5)(q32.2q35.3)[11]/46,XX[22]**

This is an example of **mosaicism** (**mos**), meaning that **different cells in this individual have different numbers or arrangements of chromosomes**. This is a girl or woman **'XX'**. Thirty-three cells have been tested. **Eleven ([11]) of the tested cells** had a **duplication of chromosome 5** (**dup(5)**). **(q35.2q35.3)** shows the part of the chromosome that is duplicated; in this case, there is a gain of a chromosome segment from **q35.2 to q35.3**. **Twenty-two ([22]) of the tested cells** showed a **typical karyotype** for a girl or woman **(46,XX)**.

To find out more about mosaicism, please see our **mosaicism** guide.

If you have any further questions about interpreting a genetic report or would like help interpreting your/your child's genetic report, please get in touch with Unique (help@rarechromo.org) or contact your local Genetics service. You may also find Unique's Glossary of Genetic / Genomic terms helpful.

Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West,
Oxted, Surrey, RH8, 9EE, UK,
Tel: +44(0)1883 723356
info@rarechromo.org I www.rarechromo.org

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This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management, and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. This guide was written by Lucy Dowden (trainee genetic counsellor), Beth Hughes (trainee genetic counsellor) and Unique (CA) and was verified by Dr Abhijit Dixit, Consultant Clinical Geneticist, School of Medicine, University of Nottingham, UK.

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