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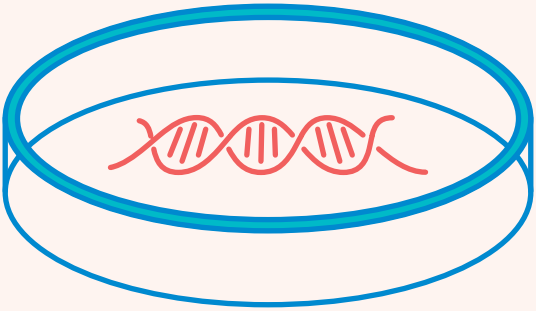
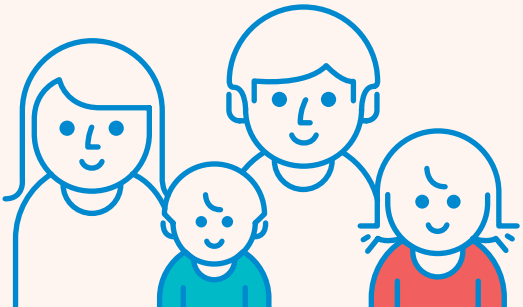
ACADEMIC MEDICAL CENTRE

Genomic
Medicine Centre

Genetic Testing





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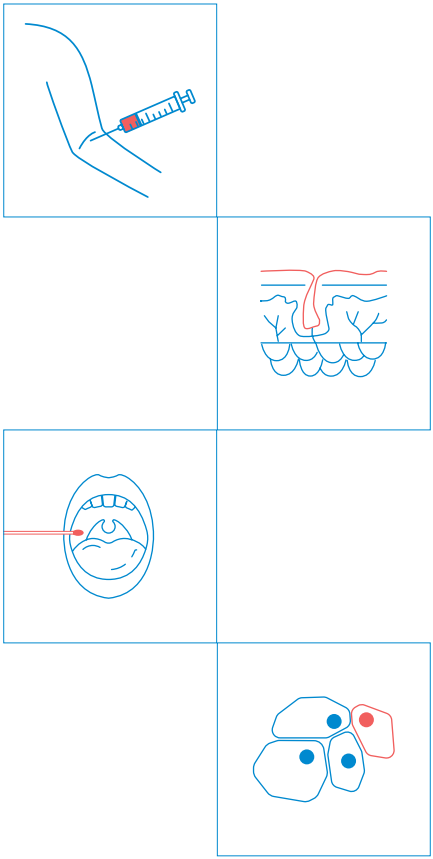
Introduction

Your or your child's doctor has recommended genetic testing in order to find out if you or your child has an underlying genetic condition.

This booklet provides further information to assist you and your family with making an informed decision.



What is genetic testing?

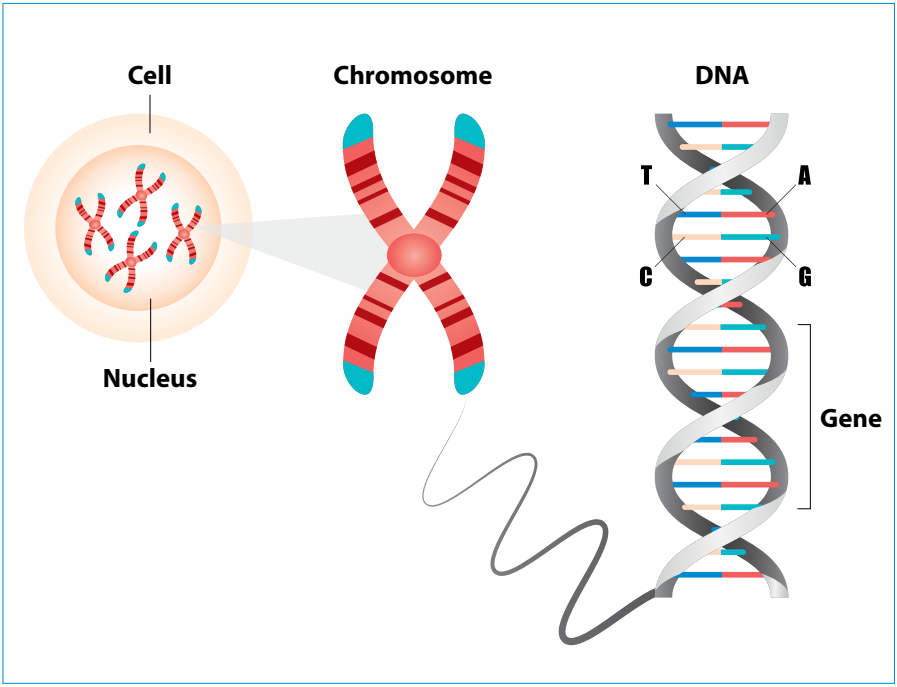
Genetic testing is the process of analysing a person's genetic material. It is performed to look for genetic changes that may help to explain a person's health problems.

Genetic testing is often performed on a blood sample. Skin, saliva or other tissue types may sometimes be used.

A person may undergo genetic testing for one or more of the following reasons:

- Search for a genetic diagnosis
- Improve the management of a person's condition
- Determine the best approach to their medical care
- Provide information about the chances of having another child with the same condition

There are different types of genetic tests available. Depending on your or your child's condition, the doctor will discuss the appropriate test(s) with you and your family.



What does 'genetic material' consist of?

A **genome** refers to the genetic material of a person. Your genome is like your body's instruction manual – it contains information that is needed to make you, and to enable your body to function correctly.

Your genome is made up of **DNA** (deoxyribonucleic acid). DNA is found in the cells of your body and is tightly packaged into structures called **chromosomes**.

Genes are specific sections of the DNA that contain instructions in the form of a genetic code. The genetic code consists of four chemical 'letters' (A, C, G and T) that build the entire genome of over three billion letters!

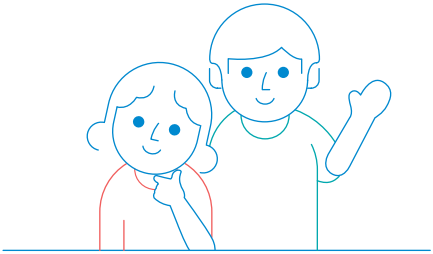
Similar to how different combinations of letters make up words, different combinations of A, C, G and T make up different instructions for your body. The order of these letters (the DNA sequence) determines if the right instruction is made.

How are genetic disorders inherited?

A genetic disorder arises when significant changes in a person's genetic material lead to problems with development and functioning of the body.

As a person's genetic material is inherited from their parents – half from the mother and half from the father – genetic changes that cause health problems may also be passed down through families.

While genetic changes may be inherited from parents, some are not inherited and occur as a new change (*de novo*) within the affected individual.



Types of genetic inheritance

Inheritance is the passing of genetic material from parents to their children (offspring). Genes come in pairs – one comes from the mother, and one comes from the father.

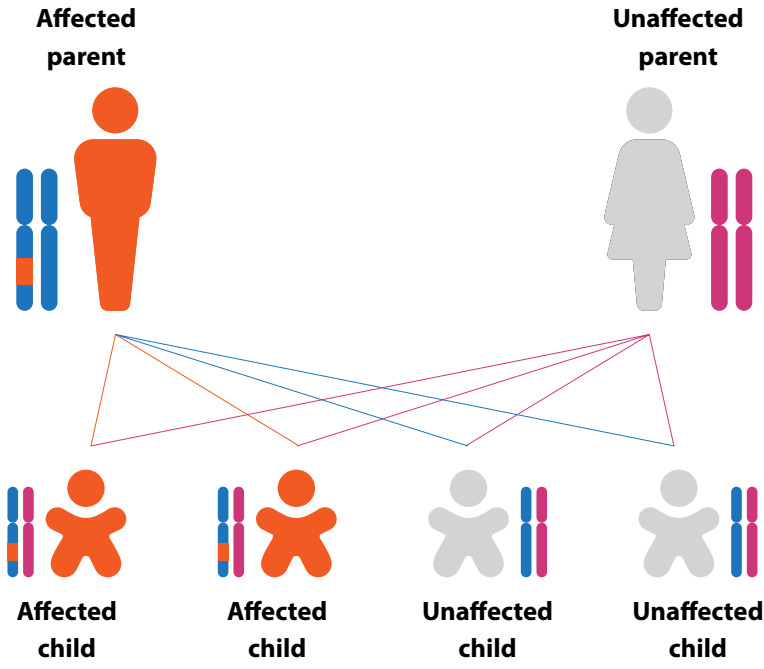
The risk of an offspring inheriting the affected gene copy depends on the type of inheritance of the genetic disorder.

The main types of inheritance patterns include:

1. **Dominant inheritance**
2. **Recessive inheritance**
3. **X-linked inheritance**

1 Dominant inheritance

In disorders with dominant inheritance, **one copy of the gene is affected and sufficient to cause disease**. The affected individual has a 50% chance of passing on the affected gene copy to his/her offspring.

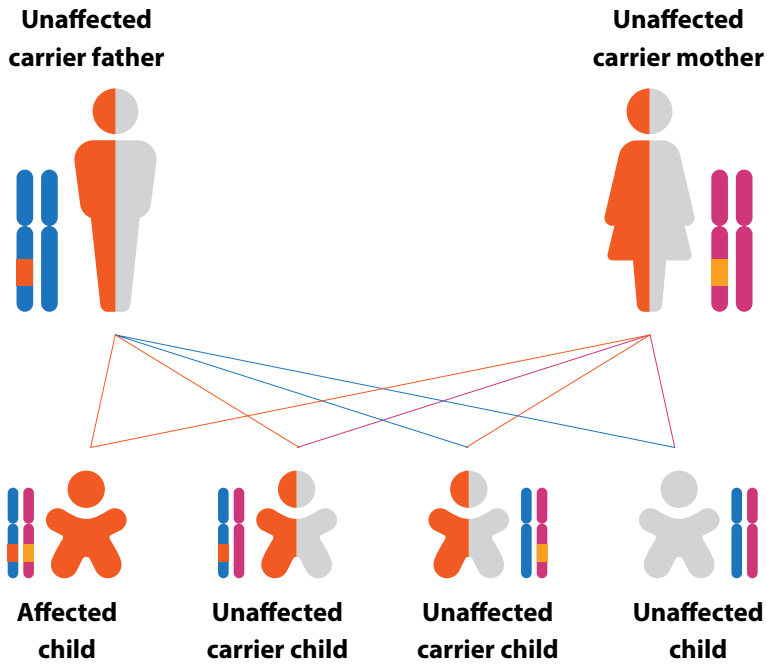


2 Recessive inheritance

In disorders with recessive inheritance, **both copies of the gene are affected in individuals who have the disorder**.

Individuals with only one affected copy of the gene are known as carriers, and often do not have any symptoms of the disorder.

The affected individual (both copies affected) has a 100% chance of passing on the affected gene copy, while a carrier (one copy affected) has a 50% chance of passing on the affected gene copy to his/her offspring.



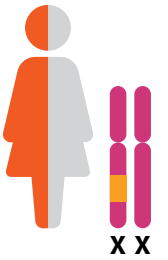
3 X-linked inheritance

In diseases with X-linked inheritance, **the affected gene is located on the X chromosome**.

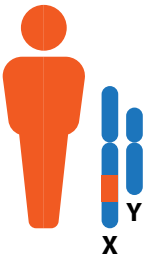
Typically, females have two X chromosomes, and males have one X and one Y chromosome. As such, females have two copies of X chromosome genes, while males only have one copy of X chromosome genes.

In X-linked recessive conditions:

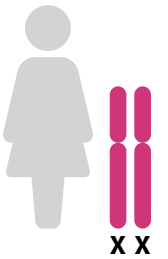
Females	Males
Females with one affected and one normal copy of X chromosome genes are known as **carriers**. Some carriers may have mild manifestations of the genetic disorder.	As males only have one copy of X chromosome genes, males with one affected copy are **affected** with the genetic disorder.



Female carrier



Affected male



Female unaffected

Male unaffected

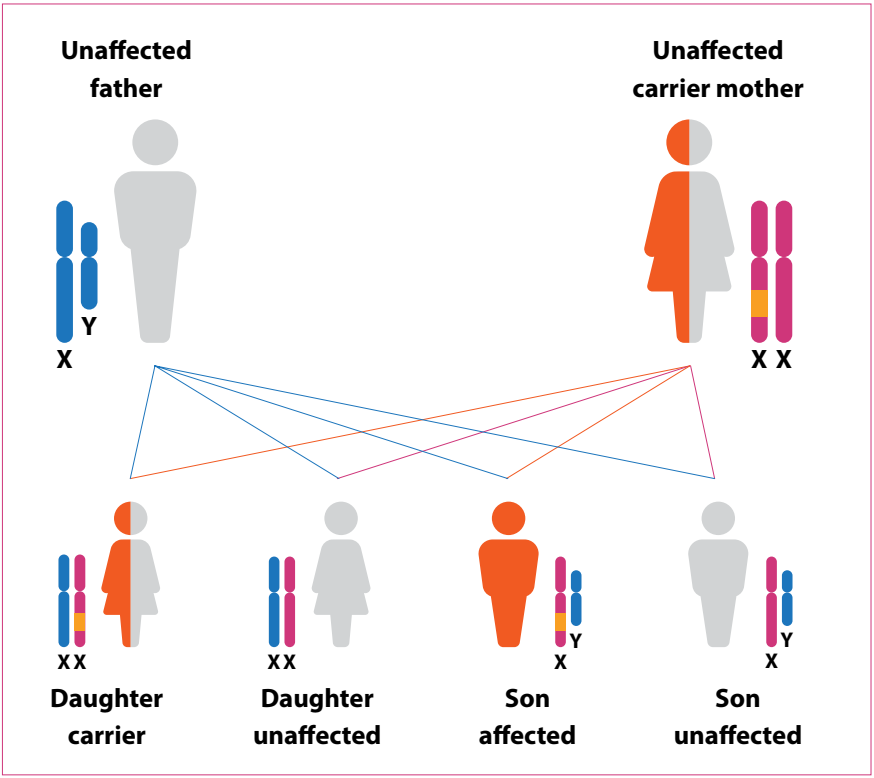
3 X-linked inheritance (continued)

Female carriers (one copy affected)

A female carrier with one copy affected has a 50% chance of passing on the affected gene copy to her offspring.

If her child is female:
There is a 50% chance that her daughter will be a carrier, and a 50% chance she will be unaffected.

If her child is male:
There is a 50% chance that her son will be affected, and a 50% chance he will be unaffected.



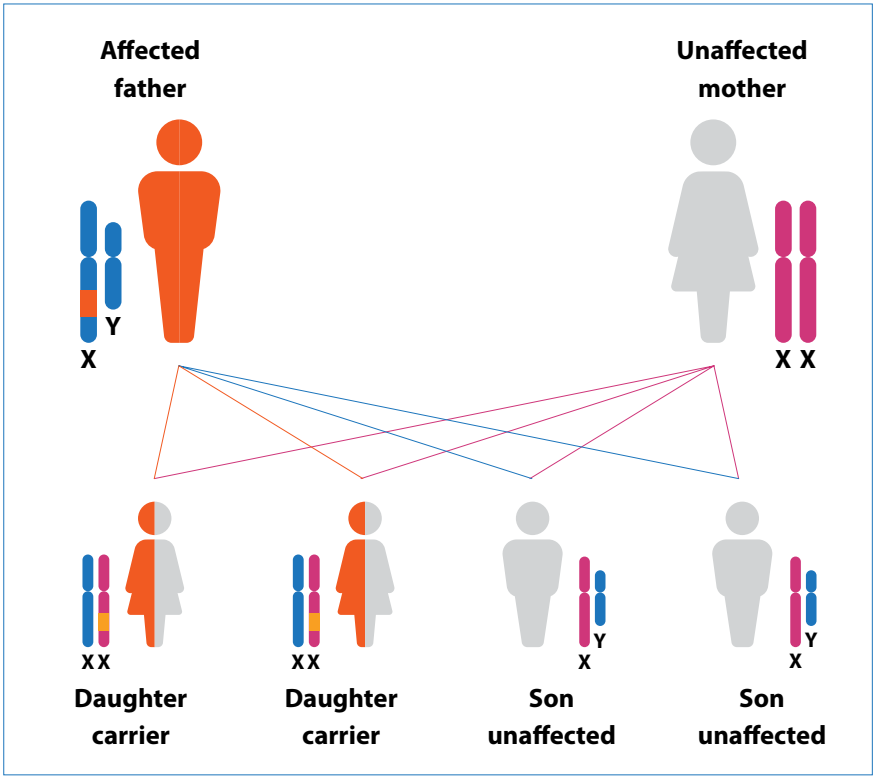
Chromosome with an unaffected gene

Chromosome with an affected gene

Affected males (one copy affected)

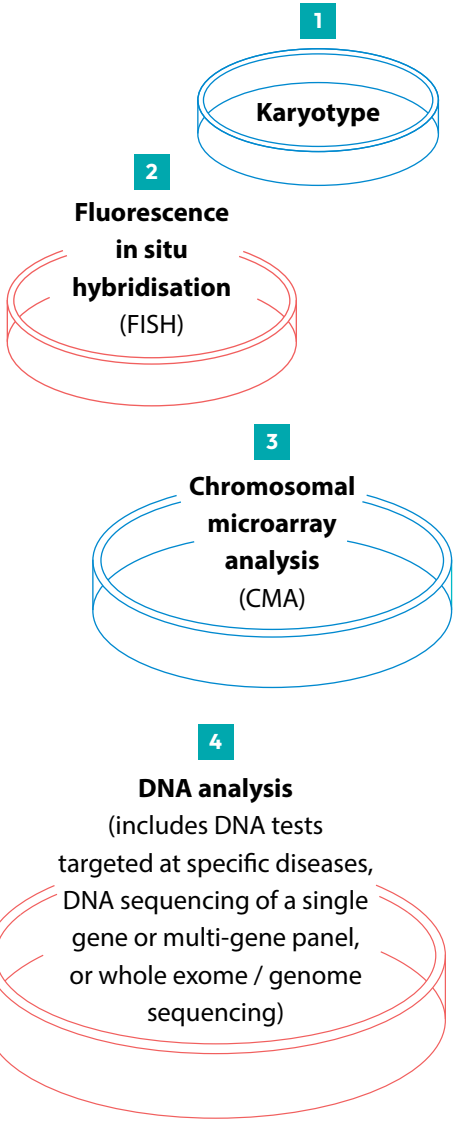
If his child is female:
Affected fathers, with one copy affected, have no normal gene copy and will pass their affected copy to all their daughters (100% chance). They will be female carriers.

If his child is male:
Affected fathers do not pass on the affected copy to their sons, as sons inherit their X chromosome from their mothers.



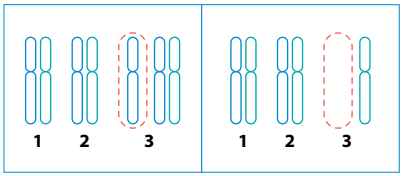
Types of genetic tests

Depending on your or your child's condition, the doctor may recommend one or more of the following genetic tests:

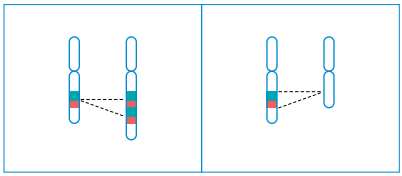


These genetic tests are used to look for changes in genetic material, which can result in problems in areas such as the development and functioning of an individual. These changes may include:

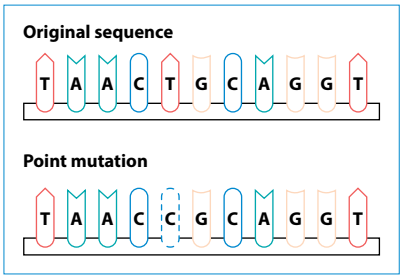
- Extra or missing entire chromosomes



- Extra or missing parts of chromosomes

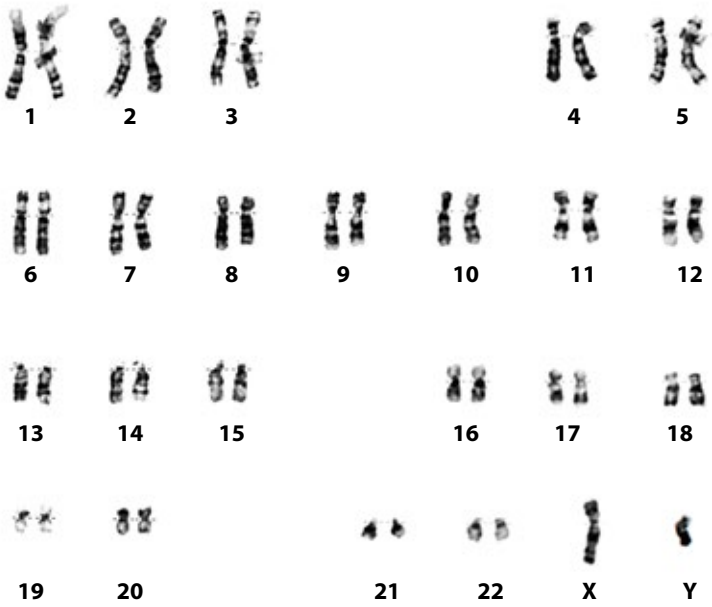


- Changes in DNA sequence



1 Karyotype

A karyotype is a test used to check the number, size and structure of a person's chromosomes. It produces an image of a person's chromosomes.

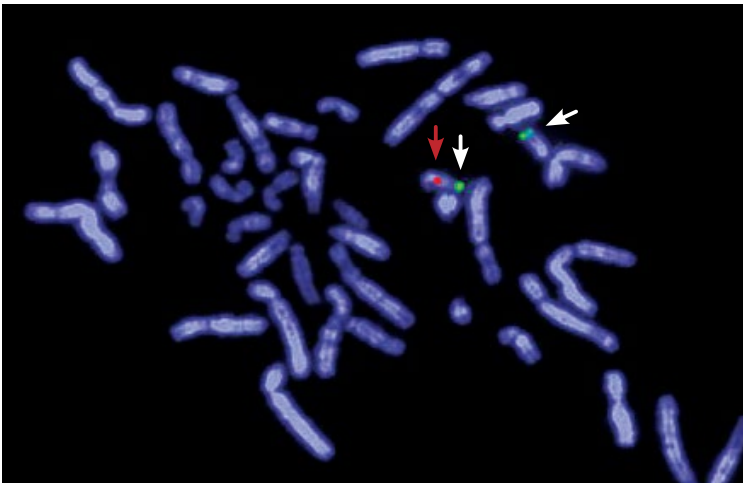


A normal karyotype consists of 23 pairs of chromosomes (46 chromosomes). Each chromosome pair is numbered 1 to 22, and the 23rd pair is named X and Y. Females have two X chromosomes (XX), and males have an X and Y chromosome (XY).

A karyotype can detect extra or missing parts of / whole chromosomes, as well as pieces of chromosomes that are located away from their original position.

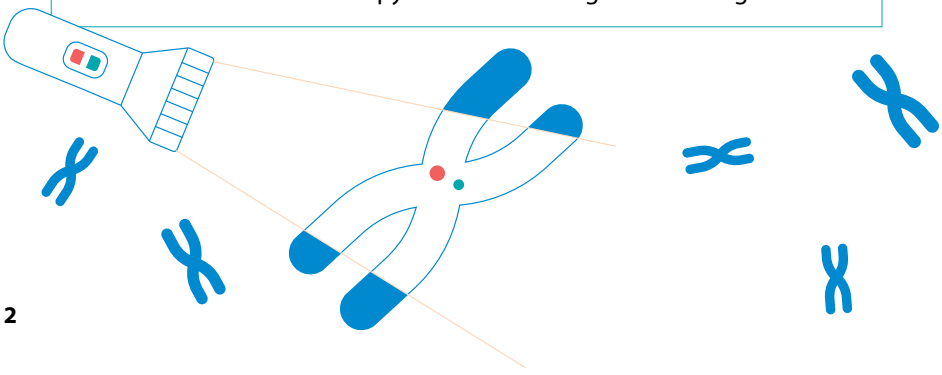
2 Fluorescence in situ hybridisation (FISH)

FISH is a test used to look for specific parts of a person's chromosomes. It makes use of fluorescent dyes to highlight specific parts of a chromosome. It can detect specific additional or missing material that may not be detected on a standard karyotype.



In the FISH example above, the green and red dyes are used to highlight respective regions of chromosome 22 – the green dye highlights a far-end region, while the red dye highlights a region nearer to the centre of chromosome 22.

Two copies of green dye (indicated by the white arrows) are seen, and this tells us that both copies of the far-end region are present. Only one copy of red dye (indicated by the red arrow) is present, which tells us that one copy of the central region is missing.



3 Chromosomal microarray analysis (CMA)

CMA is a test used to look for extra or missing segments of a person's genetic material. It detects changes in the number of copies of each DNA segment (copy number variants).

As there are usually two copies of each DNA segment, extra or missing segments lead to changes in the number of copies. If a copy number variant is detected, that segment is analysed to identify the genes that are extra or missing.

These changes are too small to be detected on a karyotype. As such, it is possible for a person with a normal karyotype report to have copy number variants in their genetic material.

4 DNA analysis

DNA analysis is a test that determines the specific order of the chemical letters (A, C, G and T) in our genome.

These chemical letters form three-letter combinations that make up a person's genetic code. Our genetic code carries specific instructions for the body to function correctly.

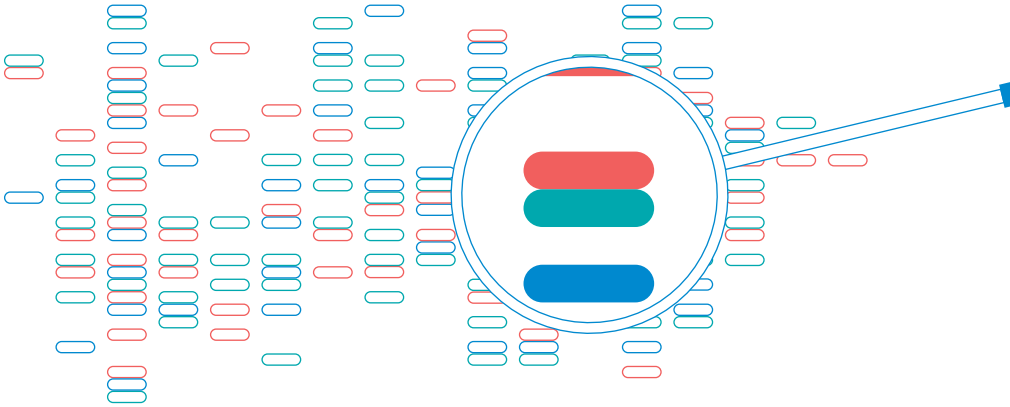
We all have changes (variants) in our DNA sequence, which give rise to our unique individuality. Although most variants are not harmful, some have serious consequences and can result in diseases.

DNA analysis can be used to analyse one or many genes simultaneously. These tests may be categorised as:

- DNA tests targeted at specific diseases
- Single gene sequencing (one gene)
- Multi-gene panel sequencing (multiple genes)
- Whole exome / genome sequencing (all known genes in the genome)

In summary:

Genetic test	Used to look for	Limitations
1 **Karyotype**	• Whole or large segments of chromosomes that are extra or missing • Large segments of chromosomes that are rearranged	• Unable to detect segments that are too small
2 **FISH**	• Specific segments of chromosomes that are extra or missing	• Detects only the specific segments ordered
3 **CMA**	• Small segments of chromosomes that are extra or missing (too small for detection by karyotype)	• Unable to detect rearrangements
4 **DNA analysis**	• Specific order (sequence) of the gene(s) ordered	• Less accuracy in detecting extra, missing or rearranged segments



What are the possible results of genetic testing?

There are several outcomes of genetic testing. These include:

Possible genetic results	Interpretation
Disease-causing variant(s) identified	Variants (genetic change[s]) known to cause disease are identified.
Disease-causing variant(s) not identified	No variants (genetic change[s]), which the genetic test is set out to detect, are identified.
Variant(s) of unknown significance (VUS)	Variants (genetic change[s]) are identified, but current evidence is unclear whether these change(s) result in a person's disorder. As our knowledge of genetic disorders increases, VUS may be reclassified over time.

Acknowledgements

Genetics Service, KK Women's and Children's Hospital

Information contributed by:

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