

**Genes contain the instructions for growth and development. A variation in a gene that causes the gene to not work properly is called a mutation or pathogenic variant.**



### IN SUMMARY

- A pathogenic variant alters the gene message so that it no longer sends the right information to the cells
- Pathogenic variants are present in all of us however, there are other factors which affect how they impact on our health
- Some variants are passed down through a family, while others may be acquired throughout life
- Genes are made up of a DNA code
- There are different types of variants that cause a health condition when you look closely at the DNA code.

Our body is made up of billions of cells, and in each cell there are instructions, called **genes**, that make all the necessary structural components and chemicals for the body to work. These genes are packaged onto long strands known as **chromosomes**.

We all have 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as **autosomal chromosomes**. The 23rd pair is made up of the **sex chromosomes** called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

### A CLOSE LOOK AT DNA, GENES AND CHROMOSOMES

DNA makes up the chromosomes and is an extremely long chain, made up of chemical units called bases. There are four different types of bases, **A**denine (A), **C**ytosine (C), **G**uanine (G), and **T**hymine (T).

The bases that form DNA are grouped together in groups of three, which makes it possible for the cell to read the instruction sequence.

Each three letter sequence forms what is called a **codon**. An example of the code in a very small part of a gene may be TAC GCC CAG CAG TCA CTG.

When these codons are read as part of a gene, they provide the cell with the instructions to build a **protein**.

Proteins are important in controlling specific functions in the cells, muscles, organs and many other parts of the body.

It is important that the right gene message is read in order for the right protein to be built.

The way that a protein is made depends on the DNA message in the gene.

The three letter codons code for specific amino acids. It is these amino acids which build up to form the proteins.

Codons do not always code for an amino acid.

Some have other specialised messages for the cell such as to *stop* or *start*, and to help the cell recognise where the actual gene messages begin and end.

Only about 1-2% of the entire DNA in the human cell (the human genome) is made up of genes that contain the information for making proteins.

The coding DNA sequences within a gene are called **exons** (because they are expressed).

Other sections of DNA do not code for proteins and are referred to as **non-coding DNA**.

Genes are strings of codons arranged in a specific order.

- Just like in a recipe for a cake, the ingredients must be right and added together in the right order. A codon is therefore like a word in a recipe for a protein
- If the recipe is different, the protein may not be made in the right amount or it may not be able to work as it should in the cell. In some cases, this can cause a genetic condition.

The sequence of letters in a gene, in sets of three, contain the instructions for our cells to start making a protein, to put the amino acids into the protein in the right order and to stop when the protein is complete.

### LOOKING FOR VARIANTS IN THE GENETIC CODE

If the sequence of DNA letters in a gene is not able to be read in the right way, the protein:

- May not be made in the right amount
- May be made in a form that will not work properly
- Is not made at all.

This can lead to health concerns and may be recognised as a genetic condition.

The first step in determining the cause of a genetic condition is to locate the gene involved. The location of many of the genes in humans is now known.

The next step is to study the sequence of letters in the gene or surrounding the gene in a person's cells. It is important to determine if the sequence of codons in the recipe of that gene is correct.

Genetic testing aims to work out whether someone has or does not have a variant in a particular gene that may cause a health condition. This can be important information for both that person and their family for a number of reasons:

- Genetic testing can lead to the diagnosis of a genetic condition in that person or other members of their family
- For some common conditions, the results of a genetic test may show that a person has an increased chance of developing a particular condition. This is known as **predictive testing** for conditions such as familial breast cancer
- More rarely, a genetic test can determine whether a person will develop a condition, based on the presence of a particular variant. This can be identified long before any symptoms are present, and is called **presymptomatic genetic testing**. An example of a condition where this is possible is called Huntington disease.

The effect that a variant has on a person's growth, development or health is because of a number of reasons, including how it affects the gene product (the protein); which cells in the body carry the variant; and when the variant first happened in that person.

### TYPES OF VARIANTS

There are a number of different types of variants that have been discovered.

#### a) Spelling changes in the code

Changing the spelling of a word in the message by substituting one letter (base) with another may be called a **single nucleotide variant** (*Figure 3.1a*).

DNA variations that cause a different amino acid to be included in the protein are called **missense** variants.

DNA variations that cause an early stop message in the protein are called **nonsense** variants.

**Figure 3.1:**

Examples of variants which lead to a gene message not working properly

	Working message	Non-working message
a. Single nucleotide variant	TAG GCC CAG CAG TCA CTG	TAG GCC CAG CAG TAA CTG
b. Deletion variant	TAG GCC CAG CAG TCA CTG	TAG GCC CAG CAG CTG
c. Insertion variant	TAG GCC CAG CAG TCA CTG	TAG GCC CAG CAG TCC TCA CTG
d. Repeat expansion	TAG GCC CAG CAG TCA CTG	TAG GCC CAG CAG CAG CAG CAG TCA CTG

### b) Deletion of code

A variant can also occur when part of the gene is 'deleted' (or missing) from the genetic code (*Figure 3.1b*). If this happens, the message may be too short or not read properly, and therefore may not make the right protein.

### c) Insertion of code

An insertion variant occurs when extra DNA is 'inserted' (or added) into the genetic code (*Figure 3.1c*).

If this happens, the message may be too long or not read properly and therefore may not make the right gene product or protein.

### d) Repeated code words

Another type of gene variant is called a trinucleotide repeat expansion, where certain code words are repeated in a sequence more often than usual (*Figure 3.1d*).

A number of genes contain repeated sequences of three letter DNA codes as part of the usual message.

The number of code words that are repeated within the message controlling how the message is being made, is important for the way a gene works.

For example, if the number of repeats increases over a critical level, the gene can become **unstable** and may develop even more repeats of the code words as the gene is copied.

An increase in the number of repeated code words may occur during the production of the egg or sperm.

There are different reasons for why a gene copy does not work. For some people, the condition may be due to a **single nucleotide variant**, while in others it may be caused by a **deletion** in the same gene.

### HOW A VARIANT MAY AFFECT THE BODY

Since the chromosomes come in pairs, there are also two copies of each of the genes. An exception to this rule applies to the genes carried on the sex chromosomes called X and Y.

A pathogenic variant may affect the body differently depending on how much it changes the resulting protein, which cells in the body have the variant, how critical that protein is to the body and how much of that protein is needed in the body. The impact of other genes and environmental factors may also play a part.

If a DNA variant happens in only one gene copy in the pair of genes and this causes a health condition, it is inherited in a **dominant** way.

If a health condition only happens when both copies of the gene are not working, the variant is inherited in a **recessive** way.

**We all have a number of recessive gene variants, which we may not be aware of as we have a backup working copy of the gene and therefore the right gene product is made.**

An **autosomal** gene is a gene located on a numbered chromosome and usually affects males and females in the same way.

A **sex-linked** gene is located on the X or Y chromosome and affects males and females differently.

Both recessive and dominant variants can be found on autosomal or sex-linked chromosomes.