

Important points

- Genes are made of DNA
- The information in the DNA is in the form of a chemical code made up of four letters (A, T, C and G). Each 'word' in the information is made up of three of these four letters
- Genes are strings of these letters arranged in a specific order
- This information in a gene is like a recipe for a specific protein
 - just like in a recipe for a cake, the ingredients must be right and added together in the right order
- It is possible to 'read' the genetic code to see if there are variations in the information
 - some variations make a gene faulty
 - these variations are called mutations
- There are a number of different ways in which the coded information in a gene can be changed so that the gene becomes faulty
- How the variation in the genetic information affects the gene message and the gene product depends on:
 - the chromosome on which the gene is located (an autosome - one of the numbered chromosomes 1-22 or a sex chromosome (X or Y)
 - the position of the gene on the chromosome
 - the position of the variation along the length of the gene
 - whether the cell can still work with the variation present in only one copy of the gene i.e. having one faulty copy and one working copy does not usually cause a problem (a recessive mutation)
 - whether the cell requires both copies of the gene to be sending the right message i.e. having one faulty copy and one working copy of the gene causes a problem (dominant mutation)
- Everyone is born with several genes that are faulty due to recessive mutations but which usually do not cause a problem (the back up system is in place)

Genes are made of the chemical DNA.

DNA is like an extremely long thin string, made up of a sequence of chemical sub-units called nucleotides. Each nucleotide is made up of three chemical parts.

- Two of these parts, called a 'sugar' and a 'phosphate', are the same in every nucleotide
- The third part of the DNA nucleotide is called a 'base' and there are four different bases. The bases in the DNA nucleotides are referred to by the letters A, T, C and G according to the first letter of their name: Adenine; Thymine; Cytosine; and Guanine.

The DNA can be thought of as a chemical code made up of four letters (A, T, C and G)

Within the DNA code, the four different types of nucleotides, each having one of the bases A, T, C or G, are grouped together to form a trinucleotide eg TAG, GCC, TCA

- A gene is a string of trinucleotides arranged in a particular sequence
- An example of the code in a very small part of a gene may be TAC GCC CAG CAG TCA CTG

A trinucleotide of three letters can be thought of as a code word. It is therefore called a **codon**.

The genetic code contains the recipes for proteins

Proteins are made up of chemicals called amino acids. The amino acids are the building blocks of proteins; they are arranged in a specific order that determines the shape of the protein and how it functions in the cell.

- A codon may be a code word for an amino acid
- Other codons contain the information for the cell to start or stop reading the DNA message

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 does not work properly or is faulty, the protein may not be produced in the right amount or it may not be able to function 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, provides the code for the amino acid sequence of the protein produced by that gene. This sequence makes up the 'genetic code'.

The genetic information in the code contains 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.

Genes contain both coding and non-coding DNA

The information in a gene is not read from the beginning to the end without stopping.

Genes are actually made up of segments of lengths of coding DNA that are expressed in the form of a protein product, interspersed by segments of lengths of non-coding DNA (an intervening DNA sequence).

- There are 'stops' and 'starts' in the information in each gene determined by the sequence of the letters in the codon
- Genes are therefore read in a start stop fashion rather than continuously

This means that the whole message that results from a particular gene is made up of separated 'sentences'. As shown in *Figure 5.1*, the information in the gene results in a message that is made up of three 'sentences'.

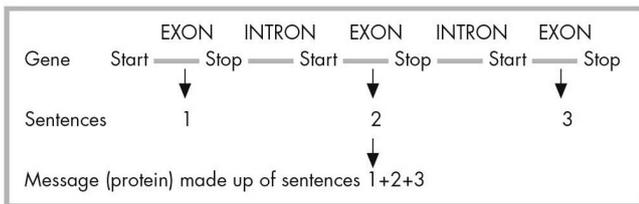


Figure 5.1: Representation of the message (the genetic code) sent to the cell from a gene, made up of 3 separate ‘sentences’. The sentences are first read and then translated into a protein

Coding DNA

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

- The coding DNA sequence within a gene is called an *exon* (because it is expressed)
- Each exon results in a sentence in the message read by the cell (Figure 5.2).

Variations to the sequence of letters within exons can change the amino acids that are produced to make up the proteins.

Non-coding DNA

The remaining 98% of the DNA in the human genome does not contain the information for proteins and was therefore thought (incorrectly) of as ‘junk’ DNA. The non-coding DNA separates genes from each other along the chromosomes as well as separating each sentence within the gene message.

- The non-coding DNA sequence within a gene that separates the sentences is called an *intron* (because it is an intervening sequence).

Variations to the sequence of letters within introns can have an effect on the way the gene is read from beginning to end. If the instructions for where to start and stop reading are interrupted or changed, the gene product may be faulty or reduced in amount.

The non-coding DNA that separates genes has a role in turning genes ‘on’ and ‘off’ according to their role in the cell and how much of a particular protein the gene produces. This non-coding DNA therefore has a control function within the genome.

‘Reading’ the genetic code to identify variations making a gene faulty

The first step in determining the cause of a genetic condition is to locate the gene involved. The location of most of the genes in humans is now known (see Genetics Fact Sheet 24).

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 ‘words’ in the recipe in the gene or the controlling non-coding DNA is right, if it contains a variation that makes the gene faulty (mutation) or does not affect the gene function at all.

Genetic testing aims to identify a particular faulty gene in a person, and define the exact type of mutation making the gene faulty.

- Can lead to the diagnosis of a genetic condition in that individual or their baby (see Genetics Fact Sheet 21)

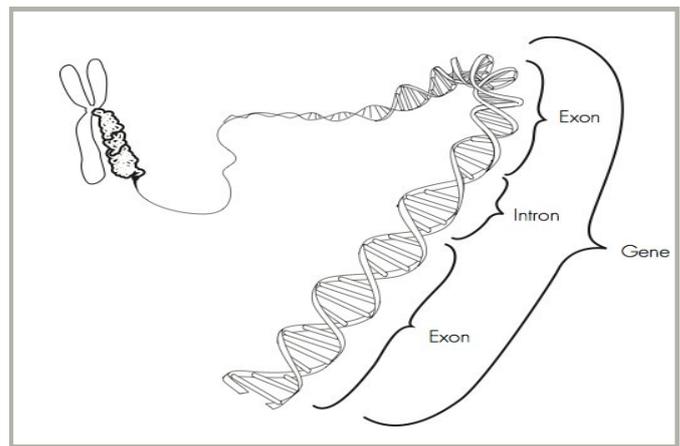


Figure 5.2: Genes are made up of a string of exons (expressed DNA sequences) and introns (intervening DNA sequences)

- For some common conditions, the results of the genetic test may show that a person is susceptible (‘predisposed’) i.e. at increased risk of developing a particular condition, e.g. ‘predictive genetic testing’ for breast cancer (see Genetics Fact Sheet 48).
- More rarely, a genetic test can determine with certainty that a person will develop a condition, based on the presence of the faulty gene, long before any symptoms are apparent, e.g. ‘presymptomatic genetic testing’ for Huntington disease (see Genetics Fact Sheet 44)

The effects of inheriting a faulty gene on a person’s growth, development or their health is also determined by the type of mutation in the gene and its impact on the gene product.

Types of variations in the genetic information—mutations

There are a number of different ways in which variations in the genetic information can become faulty as shown in Figure 5.3. Variations that make the genetic information faulty are called mutations.

These variations can occur in either the exon or the intron of a gene or in the associated surrounding non-coding DNA that has a role in the gene’s activity.

If the variation is in the exon and affects the sentence that is produced, it may cause a problem with the way the gene works.

Since the introns do not produce sentences that are contained in the message, variations in an intron can be present and cause no problem. If however, the variant in the intron changes the start and stop instructions, the message produced may be affected.

(a) Spelling changes in the code

Changing the spelling of a word in the message by substituting one letter with another is called a point or base mutation (Figure 5.3a). These are also referred to as *missense* or *nonsense* mutations.

- Examples of conditions that are due to changes at a point along the coded message include cystic fibrosis, Tay-Sachs disease and haemophilia (see Genetics Fact Sheets 33, 35 & 40).

	Correct message:	Faulty message:
(a) Point mutation	TAG GCC CAG CAG <u>TCA</u> CTG	TAG GCC CAG CAG <u>TAA</u> CTG
(b) Deletion mutation	TAG GCC CAG <u>CAG TCA</u> CTG	TAG GCC CAG <u>CAG</u> CTG
(c) Insertion mutation	TAG GCC CAG <u>CAG TCA</u> CTG	TAG GCC CAG <u>CAG TCC TCA</u> CTG
(d) Increased repeat mutation	TAG GCC <u>CAG CAG</u> TCA CTG	TAG GCC <u>CAG CAG CAG CAG</u> CAG TCA CTG

Figure 5.3a to d: Ways in which the genetic information can be changed so that the gene becomes faulty (gene variants)

(b & c) Insertions and deletions of code words

A mutation can also occur when part of the gene is ‘deleted’ or another word ‘inserted’ into the genetic code (Figures 5.3b and 5.3c). The message will either be too short or too long and therefore will not work properly or the protein may not be produced in the right amount.

- Examples of conditions that are due to deletions or insertions in the gene involved include haemophilia and Duchenne and Becker types of muscular dystrophy (see Genetics Fact Sheets 40 & 41).

(d) Repeated code words

Another type of gene variant is called a ‘trinucleotide repeat’ mutation where certain code words are repeated in a sequence more often than is usual (Figure 5.3d).

Many genes, or the associated non-coding DNA, contain repeated sequences of the three-letter code words (triplet repeats) as part of their normal message. The number of code words that are repeated within the message or in the information controlling the message’s production is important for the way a gene works.

If the number of repeats increases over a critical level, the gene can become ‘unstable’ and liable to develop even more repeats of the code words as the gene is copied.

The increase in the numbers of repeated code words may occur during the production of the egg or sperm. Sometimes, a gene containing code words repeated more times than usual can be inherited from a parent.

A genetic condition may occur if the number of repeats within the gene or in the non-coding DNA associated with the gene, is over a certain critical level or range.

- Fragile X syndrome and Huntington disease (see Genetics Fact Sheets 42 & 44) are genetic conditions due to the inheritance of genes containing an increased number of repeated code words within the gene message.

The same genetic condition can be caused by different gene variants

Many genetic conditions can be caused by several different types of gene variants (mutations) that occur in the same gene in different people. In some people, a condition may be due to a “point mutation”; in others it may be a “deletion” that makes the gene faulty.

As people have two copies of each gene, they may have a point mutation in one gene copy and a deletion in their other gene copy.

Nevertheless, the result is that both genes will be faulty and no working message will be produced from either gene copy.

- The same mutation will be present in the genes in all affected members of a family (*family-specific mutations*).

(a) Faulty genes located on an autosome (chromosomes numbered 1-22)

Genes located on the autosomes (chromosomes that are numbered by scientists as 1-22), are in pairs (see Genetics Fact Sheet 1). The impact in males and females of a mutation in a gene located on an autosome will usually be the same.

- Both copies of the gene pair send a message to the cell to make a particular product (a protein)
- A mutation in one copy of the gene makes that gene copy faulty
- The faulty gene’s message may lead to the production of a protein that does not work properly, a reduced amount of protein or perhaps no protein at all
- The information for the gene product, however, will still be sent from the working copy of the gene to the cells

Autosomal recessive mutations

If the body can still work as it should with less than the usual amount of the working gene product available, the person will be **unaffected** by having a gene in which one copy is faulty and the other working properly. The person is therefore an unaffected ‘carrier’ of the faulty gene copy.

- In these cases, the mutation causing the gene copy to be faulty is hidden or ‘recessive’ to the unchanged information in the working copy of the gene
- If both copies of a gene are faulty, there may be only an incorrect gene product, no gene product or the wrong amount produced in the cells of the body, which can result in the person being affected by a condition

A child can inherit a gene copy that is faulty due to a recessive mutation from a parent and be an unaffected carrier of the faulty gene copy just like the parent.

- If both parents carry the same faulty gene copy, there is 1 chance in 4 (25% chance), in every pregnancy, that their child will inherit both faulty copies of the gene and be affected by a genetic condition
- Genetics Fact Sheet 8 describes this pattern of inheritance in families, called autosomal recessive inheritance

- Genetics Fact Sheets 33, 34, 35 & 36 describe conditions that are directly caused by a recessive mutation in both copies of the gene that makes them faulty

When parents are close blood relatives, the chance is higher that they will share the same faulty gene (see Genetics Fact Sheet 16).

A recessive mutation can also occur in a gene for unknown reasons in the formation of a single sperm or egg cell or during or shortly after conception.

- Terms to describe these are 'new', 'spontaneous' or 'sporadic' recessive mutations making the gene faulty
- If the faulty gene arising from that spontaneous mutation is located on autosome, that person will not be affected by having the faulty gene copy, i.e. they will be an unaffected carrier of the mutation. They still have a working copy of the gene to provide the information for the cell to work normally

Autosomal dominant mutations

If the body cannot work as it should with less than the usual amount of working gene product, the person will be affected by having a gene in which one copy is faulty and the other copy is working.

- The mutation making the gene copy faulty appears to override or 'dominate' the information in the working copy of the gene
- Where a person has a dominant mutation that causes a genetic condition, they will usually be affected or susceptible (predisposed) to develop the condition

The 'dominant' mutation can be passed to a child from the parent (inherited).

- If a parent has the condition, or is predisposed to develop the condition, there is 1 chance in 2 (50% chance), in every pregnancy, that their child will inherit the faulty gene copy containing the dominant mutation from the affected or predisposed parent
- Genetics Fact Sheet 9 describes this pattern of inheritance in families, called autosomal dominant inheritance
- Genetics Fact Sheets 38 & 44 describe conditions that are directly caused by a dominant mutation in one of the copies of a gene that makes the gene faulty (achondroplasia and Huntington disease)
- Genetics Fact Sheet 48 describes an inherited susceptibility (predisposition) to breast and ovarian cancer where an inherited dominant mutation in one of the gene copies makes the person susceptible (predisposed) to develop the condition. In these conditions, the expression of the condition requires interaction with certain environmental factors (see Genetics Fact Sheet 11)

A 'dominant' mutation can also occur in a gene for unknown reasons in the formation of a single sperm or egg cell or during or shortly after conception.

- Terms to describe these are 'new', 'spontaneous' or 'sporadic' dominant mutations making the gene faulty
- If the faulty gene results in a genetic condition in that person arising from the fertilised egg, the affected person will be the first in the family to have the condition
- There will be no history of the condition in the family: the condition is described as 'sporadic'

- He or she, however, may then pass the faulty gene causing the condition on to future generations

(b) Faulty genes located on the X chromosome

Males have one Y chromosome and one X chromosome; males therefore only have one copy of the genes that make up most of the X chromosome. Females have two copies of these X chromosome genes.

The effects of mutations in genes carried on the X chromosome are different in males and females.

- Shortly after conception, most of one of the X chromosome copies in each female cell is 'switched off' or inactivated. This means that both males and females have only one active X chromosome copy in each cell, i.e. only one copy of each gene on the X chromosome in each cell is active in both males and females
- Usually the process by which the X chromosome is 'switched off' is random. Therefore, some cells will have the X chromosome coding for the working product, while other cells will have cells producing the wrong or reduced amount of product, or no product at all, due to the faulty gene
- This system of inactivating one copy of the X chromosome in females is discussed in Genetics Fact Sheet 14 and is an example of *epigenetics*

Genes that are not 'switched off' in this process are located at the end of the short arms of both the X and Y chromosome. These regions are called the pseudo-autosomal regions. The genes located in these regions behave just like the genes on the autosomes. The impact of variations in these genes that make the gene faulty will be the same as autosomal recessive or autosomal dominant mutations despite their location on the X and Y chromosomes.

Recessive mutations in most genes on the X chromosome

A female who has a mutation in a gene on one of her X chromosome copies but a working copy of the gene on the other X chromosome, is a 'carrier' of the gene mutation (X-linked genetic carriers).

- Due to the process whereby one of the female's X chromosome copies is inactivated, some of her cells will contain the X chromosome on which the working copy of the gene is located; other cells will contain the X chromosome on which the faulty gene is located
- Some cells will have the information to make the working gene product, while other cells will produce the wrong product, in reduced amount or no product at all, due to the faulty gene

A **woman** who is an X-linked genetic carrier will have:

- 1 chance in 2, or a 50% chance, **in every pregnancy**, of passing the recessive X-linked mutation on to her sons who may be affected by a condition due to the faulty X-linked gene copy as they will not have any cells that make the working gene product
- 1 chance in 2, or a 50% chance, **in every pregnancy**, of passing the recessive X-linked mutation on to her **daughters** who will generally be an unaffected X-linked genetic carriers just like their mother

- Genetics Fact Sheet 10 describes this pattern of inheritance in families, called **X-linked recessive inheritance**
- Genetics Fact Sheets 40, 41 & 42 describe conditions that are directly caused by a recessive mutation in a gene on the X chromosome that makes the gene copy faulty

While the process by which the X chromosome copy is 'switched off' is usually random:

- In some cases females will show the effects of the X-linked recessive mutation that they are 'carrying'. This is because the process of 'switching off' the X chromosome has become non-random and is skewed strongly towards switching off the X chromosome carrying the working copy of the gene
- So, more cells in the woman's body would have the active X chromosome containing the faulty gene. This would lead to less of the working gene product being available and the woman will show the effects of the faulty gene, though usually less severely than males

Dominant mutations in most genes on the X chromosome

Some gene products must be present in all the cells of the woman for the body to work normally.

A mutation in a gene on the X chromosome that impairs the cell's ability to make a product will therefore show an effect and so the mutation is described as 'dominant'.

A woman who is an X-linked carrier of a dominant mutation will have, 1 chance in 2, or 50% chance, **in every pregnancy**, of passing the recessive X-linked mutation on to **both her sons and daughters** who may be affected by a condition due to the faulty X-linked gene. Conditions due to an X-linked dominant mutation are rare.

Genetics Fact Sheet 10 describes this pattern of inheritance in families, called **X-linked dominant inheritance**.

Everyone is born with several genes that are faulty due to recessive mutations but which usually do not cause a problem

Each gene located on an autosome has a partner or 'back-up' copy.

Even though we are all born with several of our 20,000 genes containing recessive variations that make them faulty, the working copy usually protects us from showing any effects of these faulty genes. This depends on the type of mutation that is present and the effects on the gene and its product.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 8, 9, 10, 11, 14, 16, 21, 24, 33, 34, 35, 36, 38, 40, 41 42, 44, 48, 50

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