

Important points

- The information in the genes that are made up of DNA is in the form of a chemical code, called the genetic code
- There are small variations between every individual in their genetic information that makes each of us unique
- Some variations in the genetic information do not significantly alter the gene message so the information is still understood by the cell. These changes are common and are called neutral gene variants or polymorphisms
- Other variations in the genetic information cause the message to be changed so that it is no longer understood by the cell. These changes are called pathogenic variants or mutations
 - Genes with a mutation can be described as impaired or faulty
 - Language to describe mutations needs to be sensitive but also reflect the impact of the gene variation
- Faulty genes (mutated genes) may
 - Cause a problem with the development and functioning of different body systems or organs and result in a genetic condition
 - Be beneficial eg. having a faulty copy of the gene that tells the body to make haemoglobin makes a person more immune to malaria
- Some gene variants (neutral variants as well as mutations)
 - Are inherited from our parents
 - That occur in the egg, or sperm, or during or shortly after conception are described as 'new' or 'spontaneous' gene variants
 - Build up in our body's cells during our lifetime (not inherited)
- Some faulty genes directly or indirectly cause genetic conditions that run in families (inherited)
- Everyone is born with several faulty genes that usually cause no problem

The cells in the body contain a complete copy of a person's genetic plan or blueprint contained in our genes and located on chromosomes. The chromosomes, and therefore the genes, are made up of DNA.

The genes contain the information necessary for our bodies to grow and work. The information in the genes is in the form of a chemical code, called the genetic code, as described in Genetics Fact Sheet 1.

Each gene contains the code to make a message to tell the cells how to make a particular product such as a protein. The message can be thought of as a recipe for a protein.

The 'Genetic Book of Life' described in Genetics Fact Sheet 1 is like a recipe book for our bodies. There are small variations between every individual in their genetic information that makes each of us unique – we all have a slightly different recipe.

Chromosomes can be thought of as strings of genes as shown in Figure 4.1.

The genes are made up of coding DNA since they send coded messages to the cells to make proteins. The messages are made up of the letters A, T, C and G. 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 remaining 98% of the DNA in the human genome does not contain the information for proteins and was therefore (incorrectly) thought of as 'junk' DNA. This **non-coding DNA** separates genes from each other along the chromosomes and there is increasing evidence that it has a role in turning genes 'on' and 'off', depending on their role in the cell and how much of a particular protein the cell needs. This non-coding DNA therefore has a control function within the genome.

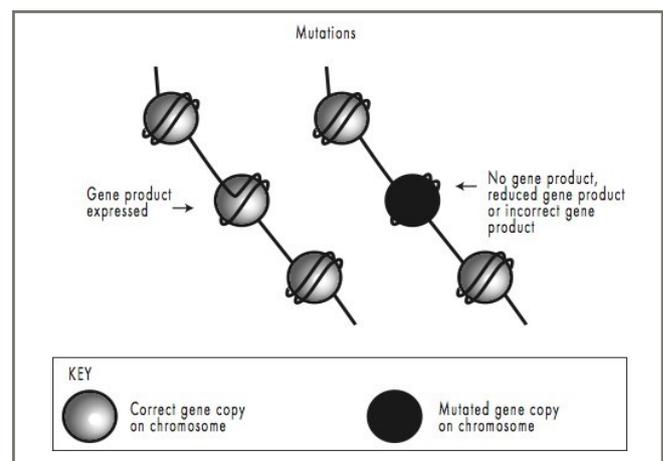


Figure 4.1—Mutations: variants in genes that make them faulty

Over the centuries, variations in the original sequence of letters have built up in our non-coding DNA and have been passed down through the generations. So the non-coding DNA can vary by as much as 1-4% between individuals. Variations also build up in our DNA as our cells grow, develop and work. Therefore everyone, even identical twins by the time they are born, has a unique genome.

This uniqueness is used in tests to identify us from everybody else as well as identify us as part of a family. These differences in the genetic code between us all may also be used in forensic investigations by the police (see Genetics Fact Sheet 22). Studies of the non-coding DNA are increasingly being used to identify people where there is no other means to do so, such as following natural disasters.

Variations in the information in our genes

We generally all have the same number and type of genes so that the same messages are sent to the body. However

- There are often small variations between individuals in the information contained in our coding DNA (that is, in our genes) and in our non-coding DNA
- If we did not have these differences, everyone would look the same
- Members of the same family tend to be similar, as they are likely to have fewer differences in their genes than unrelated individuals

While we all have the genes which tell us to have eye colour, some people's eye colour genes will say 'make the eyes blue' and some people's will say 'make the eyes brown'. The information in the eye colour genes is different between blue and brown-eyed people.

Similarly, there may be small variations in the genes which affect how our bodies grow and develop. Generally these variants do not have any impact on our health and are called *neutral variants* or *polymorphisms* (poly means many; *morphisms* means forms). They are quite common.

- We all have many different variants in our DNA that do not appear to cause a problem
- While the genetic code in a person may be slightly changed by having a variant, the change has not significantly altered the gene message: the information is still understood by the cell
- Some variants, however, to the genetic code cause the message to be changed so that it is no longer understood by the cell: the gene is impaired or faulty. These variants are called pathogenic variants
- Pathogenic variants make the genes faulty and are called **mutations**
- If the message to the cell comes from a faulty gene (mutated gene), the cell will either not make the right protein product, make it in reduced amounts or not make it at all (see *Figure 4.1*)
- Faulty genes may cause a problem with the development and functioning of different body systems or organs and result in a genetic condition (see Genetics Fact Sheet 2)
- Further information about mutations is provided in Genetics Fact Sheet 5

The language to describe a mutation

Words can be interpreted in different ways by different people. The term 'mutation' has been used to describe a change or variant in a gene for a very long time. In some communities, there is stigma associated with this term and so we are sensitive to using an alternative term to describe these changes or variations, while at the same time, maintaining the scientific meaning of such changes to the genetic code.

Studies performed by the Centre for Genetics Education with the general community and with family members affected by particular genetic conditions, have shown that the term faulty gene is preferable to describe a mutated gene. A number of other terms are commonly used to describe a mutation such as 'altered gene' or 'changed gene'.

We do not think, however, that these terms make it clear that some variations in a gene do not affect the gene function (*polymorphism/neutral variant*) while other variations cause the gene not to work as it usually does (*mutation/pathogenic variant*).

We believe that the term *faulty gene* describes the result of the variant on the function of the gene in the cell.

Variants that make a gene faulty (mutations) may be beneficial

Everyone is born with several faulty genes out of their 20,000 or so total number of gene pairs. Most of the time these faulty genes cause no problem because the genes come in pairs: even when one gene copy is faulty the other gene copy can still send the right message to the body (see Genetics Fact Sheet 8).

Sometimes it is essential to have both gene copies working correctly as the amount of gene product may be critical. So in these cases, even though only one copy of the gene is faulty and the other is a working copy, a problem may still occur (see Genetics Fact Sheet 9).

Other faulty genes make a person susceptible to particular conditions but they will never develop the problem unless they are exposed to particular environmental triggers (see Genetics Fact Sheet 11).

In fact, scientists know that in some cases, having particular faulty genes can be beneficial to a person. For example, in regard to the condition called thalassaemia (see Genetics Fact Sheet 34):

- The severe form (*thalassaemia major*) is due to having two copies of the faulty gene involved in the production of haemoglobin, the blood protein that transfers oxygen throughout the body. People with this severe form do not produce enough working haemoglobin and have severe anaemia
- People who are carriers of the faulty gene for thalassaemia (*thalassaemia minor*) have a faulty copy of the haemoglobin gene and a working copy. They produce enough haemoglobin although they may have very mild anaemia
 - Importantly, those who are carriers of the faulty haemoglobin gene are less likely to be affected by malaria: by not producing the right amount of haemoglobin, the body is more resistant to malaria. Perhaps this is because the pale, small red blood cells that are present in those who carry the faulty haemoglobin gene provide a poor environment for the growth of the mosquito-borne malarial parasite.

Everyone is born with several faulty (mutated) genes that usually cause no problem

Evolution depends on survival of the fittest. As an example, populations where malaria is common have a high frequency of people who are carriers of the faulty haemoglobin gene. More people who were resistant to malaria survived to have children and pass on their faulty genes.

Humans have evolved over the centuries by having faulty genes that increased their ability to adapt to their environment.

In our cells, from birth, we all have several genes in which variations in the information have made them faulty. Most people are unaffected by these gene mutations.

Variations in the genetic information

Variations in the usual sequence of letters in our genetic information may cause no problem (*polymorphisms/neutral variants*); others make the gene faulty (mutations).

These variations can be present when we are born because we have inherited them from our parents. Everyone inherits gene variants that include polymorphisms (neutral variants) as well as mutations (pathogenic variants).

Most of the time inheriting these gene variants does not cause a problem.

Other variations in the genetic information in our cells can occur in the formation of the egg or sperm, during or shortly after conception, or during our whole lifetime. See Genetics Fact Sheet 5 for more information about changes to the genetic information.

Variations that build up in the genes in our body cells during our lifetime cannot be passed on to our children

Variations in the DNA can be due to exposure to radiation such as that produced by the sun or by certain chemicals in our diets and in our external environment. Variations may also occur as our cells are copied to enable us to grow or repair damaged cells throughout life (as we age). Although the body has an efficient system to repair these changes in the DNA as they occur, sometimes there is a breakdown in the cell's repair system.

If a change to the DNA occurs and is not repaired, it will be copied into all the cells arising from the cell containing the DNA change (see *Figure 4.2*). If the variation in the usual information causes the gene to be faulty, all the cells copied from that cell into other cells in the body during the person's life will contain the faulty gene and will receive a faulty message.

For example the cells containing the faulty gene may be in a small part of our skin. These skin cells may become cancerous because of the number of faulty genes (mutations) that have built up over time with sun exposure. In other cases, the cells containing the mutation may be in breast tissue and can lead to breast cancer (see Genetics Fact Sheet 48 and 50).

- Faulty genes build up in the cells of our bodies as we age. These are called **acquired** or **new mutations**
- New faulty genes that build up in our body cells (the *somatic cells*), excluding the egg or sperm cells, over our lifetime are called **somatic** gene mutations. This type of mutation cannot be passed on to our children, as they are not in the egg or sperm. In *Figure 4.2* the mutation has arisen in a gene in a cell of the breast tissue only and so cannot be passed on to a child

Gene variants that occur in the egg or sperm cells can be passed on to children (inherited)

It is only when a variation in the genetic information is in a man's sperm or a woman's egg cells that the gene variant can be passed on to the next generation (inherited). This is only a potential problem if the gene variant makes the gene faulty (a mutation).

As sperm and egg cells are called 'germ cells', mutations that occur in the genes of the egg or sperm are called **germ cell** or **germ-line mutations**. Passing on the germ-line faulty gene (mutation) to a child may cause the child to be born with, or will develop or may be susceptible to developing a genetic condition.

- When the condition first appears in a family member it can be due to a 'spontaneous' ('sporadic') variation in the gene which makes the gene faulty. The mutation occurred in the egg or the sperm or during or shortly after conception, for unknown reasons. In those cases: The family member will usually have that faulty gene in every cell of their body (see *Figure 4.3*). That faulty gene may or may not cause a problem for that person
- As their egg or sperm cells will also usually contain the faulty gene, they in turn can pass it on to their children and their children's children. The faulty gene will now 'run in their family'
- Other blood (genetic) relatives of the affected person are not usually at risk for having the same mutation that causes the genetic condition as the 'spontaneous gene variation' would have occurred in the formation of the egg or sperm, during or shortly after conception of the affected family member

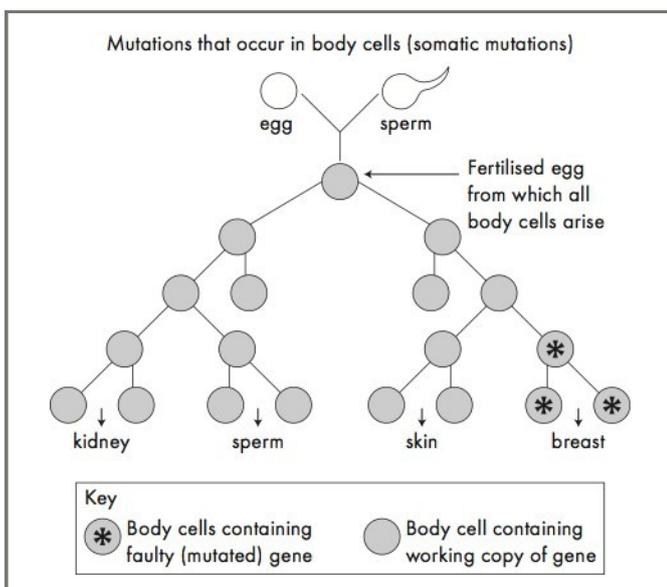


Figure 4.2: Mutations in somatic cells cannot be inherited

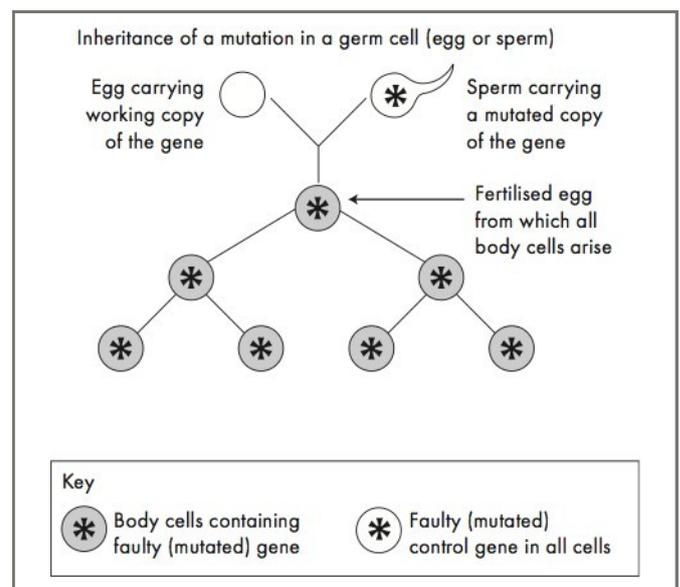


Figure 4.3: Inheritance of a mutation that is in an egg cell or sperm cell (called 'germ cells')

A parent who has inherited from his or her parents, a variant that makes a particular gene faulty, has a chance of passing that faulty gene on to their children.

Whether their children are affected at birth or later in life by a condition due to the mutation in either one, or both copies of a single gene, out of the approximately 20,000 different genes, depends on the type and amount of protein that is usually produced from the working copy of the gene.

These factors affect the pattern of inheritance of the faulty gene (how it 'runs in the family').

A mutation in a single gene is described as 'recessive' or 'dominant'; this concept is explained in more detail in Genetics Fact Sheet 5.

The pattern of inheritance of the faulty gene also depends on whether it is located on one of the numbered chromosomes (*autosomes*) or on the X chromosome (*X-linked*). Patterns of inheritance of mutations in single genes are explained in Genetics Fact Sheets 8, 9 & 10.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 5, 8, 9, 10 11, 22, 34, 48, 50