Fact sheet **14**

EPIGENETICS

This fact sheet talks about epigenetics, which refers to the ways in which our genetic information is switched on or off in the cells of our body.

IN SUMMARY

- Epigenetics describes the way cells switch on (express) or switch off genetic information
- There are a number of epigenetic factors which play a role in the way genetic information is switched on
- Epigenetics does not change the genetic information (DNA code) but can affect the way this information is read by the cell.

CHROMOSOMES, GENES AND DNA

Our bodies are made up of billions of cells. Each cell contains a complete copy of our genetic information or DNA. Chromosomes are long strands of DNA found in the cells of the body. DNA contains genes that provide the coded information for our bodies to grow, develop and function. The genes send messages to the cell to make important chemical products such as proteins.

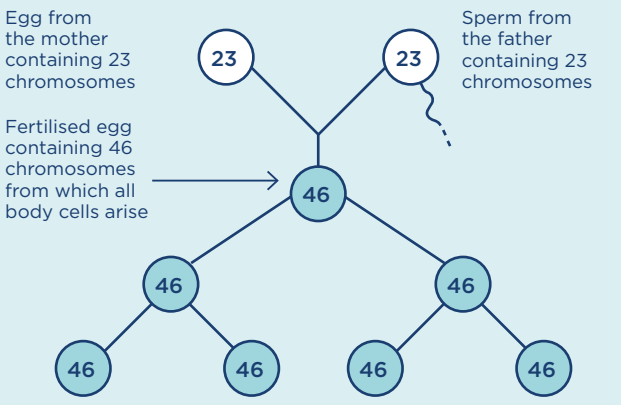
There are typically 46 chromosomes in each cell that come in 23 pairs. One of each pair or half a set of chromosomes are passed on to us from our mother (in the egg) and the other of each pair from our father (in the sperm). 22 of these chromosome pairs are numbered. These numbered pairs are known as the autosomes. 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.

When the egg and sperm join at conception, the baby will have 46 chromosomes in its cells, just like the parents (see *Figure 14.1*).

In a genetic testing laboratory, the chromosomes may be coloured (stained) with special dyes to produce unique banding patterns. These patterns allow the laboratory to check the size and structure of the chromosomes. A **karyotype** refers to the number and type of chromosomes in a person's cells.

Since the chromosomes come in pairs, there are also two copies of each of the genes. The exception to this rule applies to the genes carried on the sex chromosomes called X and Y. The genes in our DNA provide the instructions for proteins, which are the building blocks of the cells that make up our body. Although we all have variation in our genes, sometimes this can affect how our bodies grow and develop. Generally, DNA variations that have no impact on our health are called **benign variants** or polymorphisms. These variants tend to be more common in people. Less commonly, variations can change the gene so that it sends a different message. These changes may mean that the gene does not work properly or works in a different way that is harmful. A variation in a gene that causes a health or developmental condition is called a **pathogenic variant** or mutation.

Figure 14.1:
At conception, the sperm and egg combine to form the first cell of a baby



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EPIGENETICS

The term epigenetics comes from the words 'epi' meaning upon or over and 'genetics' meaning to do with our DNA. Epigenetics can change the way a cell reads the DNA message in a number of ways. One of these ways is by adding tags to the DNA bases or structures that DNA wraps around to change the activity of a gene. Sometimes these tags give messages to activate (switch on) the gene and make the protein, while others stop the protein from being created (switch off the gene).

Even though the DNA code ('spelling') is fairly stable, these DNA tags can change quite a lot over time. There are a number of different types of tags or ways in which the DNA messages are controlled.

Therefore some genes can be affected by something in addition to the DNA code itself. Epigenetic factors are the cause of some genetic conditions.

Two ways in which epigenetics can work are described below.

- **X-inactivation** is the epigenetic system that allows males and females to have balanced gene products for genes on the X chromosome, even though typically females have two X chromosomes and males have only one
- **Genetic imprinting** is the epigenetic system where tagging of the genetic information happens depending on whether it is inherited from the mother or the father.

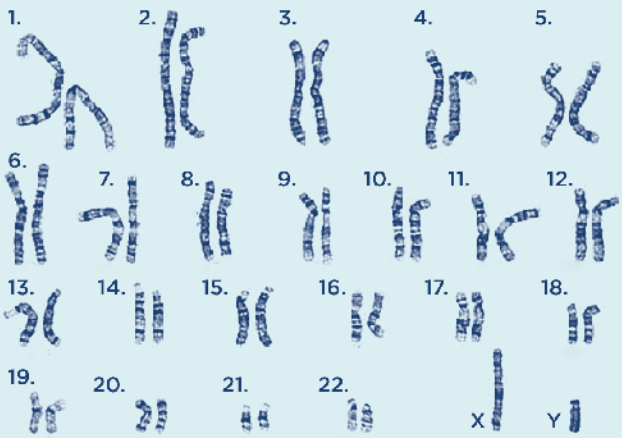
X-INACTIVATION

Unlike the Y chromosome, the X chromosome has many genes that are needed for healthy growth and development. Females have two copies of the X chromosome in their cells and therefore their cells contain two copies of the X chromosome genes.

Males have only one copy of the X chromosome in their cells, so they only have one copy of the X chromosome genes.

To bring back balance between the genetic information in males and females, the cells have a system so only one copy of most of the

Figure 14.2:
Chromosome picture (karyotype) from a male 46,XY.



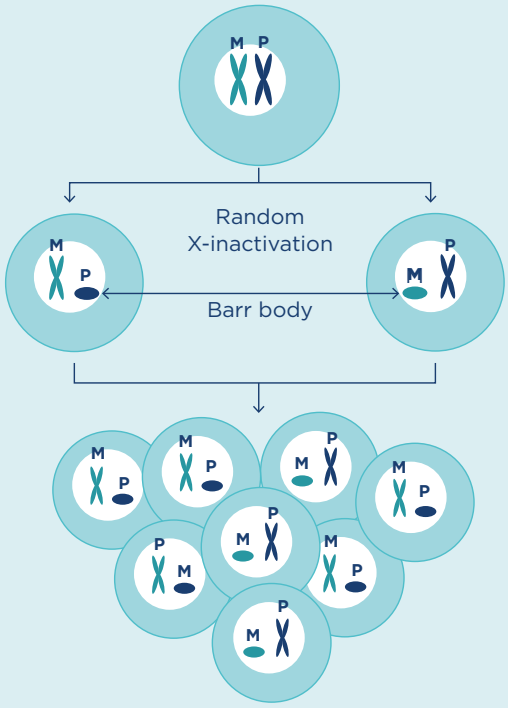
X chromosome genes in a female cell is **active** (switched on) and makes gene products. Most of the genes on the other partner X chromosome are **inactivated** or switched off. Only one copy of the X chromosome genes are needed for health and development.

This system of switching off one of the X chromosome copies is seen in all mammals, including humans, and is sometimes called **lyonisation**.

In each body cell (**somatic cell**) of a developing baby girl, one of the X chromosomes becomes very tightly wound so that most of its genes are not able to be read by the cells. Looking at typical female cells under a microscope (*Figure 14.3*) reveals a dark shadow in the cell called a Barr body, which is the inactivated X chromosome.

This system of inactivation in the body cells is usually **random** so that females' bodies have a mixture of cells with regard to the X chromosome that is switched on. Some cells will have the X chromosome switched off that came from their mother, while other cells will have the X chromosome from their father switched off. How this happens may vary from one female to the next.

Figure 14.3:
Mother's copy of the X chromosome represented by 'M' and father's (paternal) copy of the X chromosome represented by 'P'. Shortly after conception, the chromosome inherited from either the mother or the father is randomly inactivated (switched off), forming a tightly-wound structure known as a Barr body.



Mixture of cells with one of the other X chromosomes inactivated

X-inactivation affects most of the genes located on the X chromosome but not all. There are some genes located on the end of the short (p) arms of the X and Y chromosomes that are called **pseudo-autosomal genes**.

These genes are in the areas of the X and Y chromosomes that pair up during the production of sperm cells in men.

Some genes on the X chromosome have their 'partner' or pair on the Y chromosome. Therefore, in a male's body cells, two copies of these genes would be active in the cell: one on the X and one on the Y chromosome. For this to be balanced in a female, these special genes on the X chromosome are not switched off, so that there are two copies of these genes available for the cell to use.

In addition, a gene called *XIST* a 'master control' gene for X-inactivation is not switched off.

Is the X-inactivation process always random?

Females who are 'carriers' of a gene variant on one of their X chromosomes, which causes a genetic condition, will have some cells in their body in which the X chromosome with the gene variant is switched on and other cells where the working copy of the gene is switched off.

The usual random process of X-inactivation means that usually females would not show any symptoms since there would be enough cells with the working copy of the gene switched on.

Rarely, females show some of the signs and symptoms of the condition.

One reason for this is that the working copy of the X-chromosome is not switched on enough to protect this person from developing the condition. So X-inactivation may be **skewed** towards switching off the working copy of the gene on the X-chromosome.

In other rare cases, females have a structural change of one of their X chromosomes such as a deletion (missing piece) or rearrangement of the chromosome material (translocation). It may be that the altered X chromosome is switched off rather than the working copy. Perhaps cells with the working gene copy switched off do not survive as well.

Sometimes, females have a special type of chromosome rearrangement in their cells, where the X chromosome is attached to at least part of one of the numbered chromosomes (autosomes). In the cells of these women, the standard copy of the X chromosome may be switched off, rather than the rearranged (translocated) X chromosome copy.

If the translocated X chromosome was inactivated, not only would the process 'switch off' the X chromosome genes but also important genes from the autosome attached. These cells may therefore be less likely to survive.

GENETIC IMPRINTING

As we have pairs of chromosomes, there are pairs of every gene carried on the chromosomes numbered 1-22 in each cell of the body:

- One copy comes from the mother (the **maternal** copy of the gene)
- One copy comes from the father (the **paternal** copy of the gene)

As a general rule, the information contained in both the maternal copy of the gene and the paternal copy is used by the cells to make gene products. Therefore for numbered chromosomes, both gene copies are usually switched on in the body cells.

Sometimes though, activity of some of these genes on numbered chromosomes depends on whether the gene copy was passed down from the father or the mother.

This process controlling how a gene copy is switched on or off depending on whether it was passed to the baby through the egg or the sperm, is called **imprinting**.

Imprinting refers to the fact that some chromosomes, segments of chromosomes, or some genes, are tagged with a 'memory' of the parent from whom it came.

There are tests that can tell us which chromosome copy came from the mother and which copy was inherited from the father.

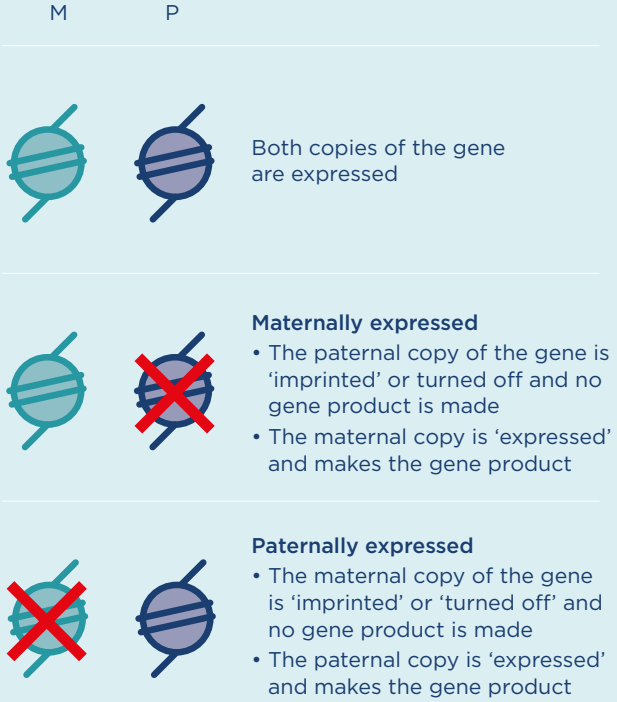
How does imprinting happen?

Genetic imprinting (or *genomic imprinting*) is the name given to this 'tagging' process.

As shown in *Figure 14.4*, if the gene copy is tagged, it will be turned off in that person and the cells will not make any gene product from that imprinted gene copy.

This process is not a variation in the genetic code since the gene sequence itself is unchanged.

Figure 14.4:
Maternal copy of the gene represented by 'M' and paternal copy of the gene represented by 'P'.
Usually both copies of a given gene on a numbered chromosome are active. Sometimes one copy, either maternal or paternal may be imprinted or 'switched off'.



- Even though both imprinting of a gene and a variant in a gene may affect how a protein is made (*Figure 14.4*), a variant is a more permanent change than an imprinting difference
- The imprinting change is reversible in the next generation as described below
- When a gene has a variant, if it can also be imprinted, the way the gene product is made is further impacted.

Example of Imprinting

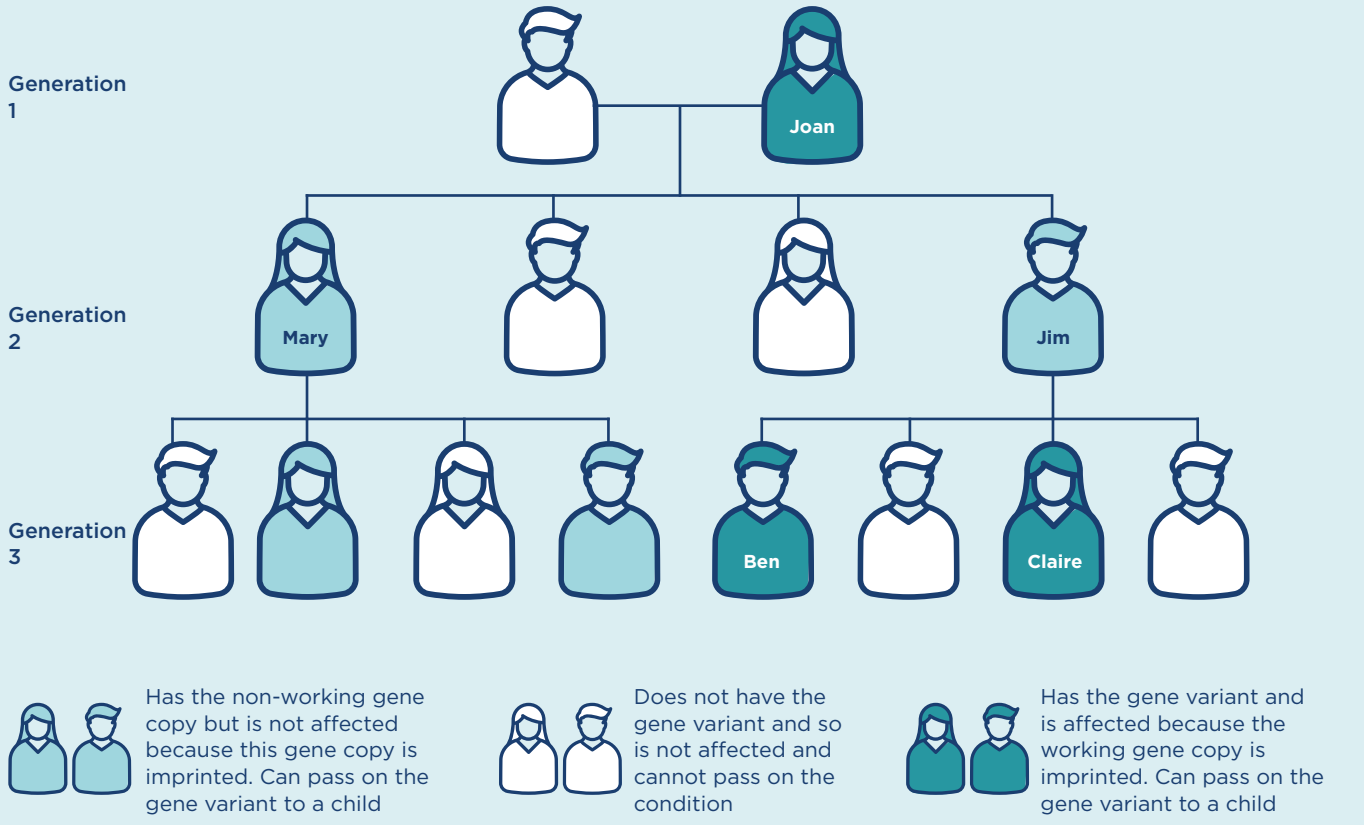
(a) A maternally imprinted gene is switched off

In *Figure 14.5* the gene copy inherited by a child from their mother (through the egg) that is causing the condition is always 'switched off' (imprinted). The gene copy remains active when passed to the baby through the sperm from their father.

Joan (in Generation 1) has a genetic condition caused by a gene variant on a numbered chromosome, she inherited from her father.

- Only the non-working message made from her father's gene variant is switched on in Joan's cells
- The working copy of the gene, inherited from her mother, is switched off as it passed to her through her mother's egg (maternally imprinted)
- Two of Joan's children, Mary and Jim in generation 2, inherited the gene variant from Joan. They also received a working copy of the gene from their father
- *But* Mary and Jim *do not* have the condition because this gene variant is 'switched off' (inactive) when inherited from their mother
- The gene copy that is switched on in Jim and Mary is the working copy that they inherited from their father
- Jim and Mary have in each of their cells, a non-working copy of the gene, that is switched off (inherited from their mother) and a working, active gene copy (inherited from their father). Therefore, Mary and Jim have a 50% chance of passing on the gene variant to each of their children.

Figure 14.5:
The non-working gene copy causing the condition is always 'switched off' (imprinted) when it passes to the baby through the egg. It remains active when passed to the baby through the sperm.



Half of Mary's egg cells will contain the working copy of the gene and half will contain the non-working copy of the gene.

- *But* when the variant is passed down to a child through the egg, it is switched off
- Therefore, none of Mary's children (generation 3), including those who inherit the gene variant, will have the genetic condition. This is because the gene is always switched off when passed from the mother.

Half of Jim's sperm cells will have the working copy of the gene and half will have the non-working copy.

- If the sperm has the gene variant, it stays switched on (not imprinted)
- Therefore, any of Jim's children who inherit the variant from him will have a non-working copy of the gene in their cells that remains switched on when passed from their father
- Jim's children will have the genetic condition because the gene variant is active. The working copy they inherit from their mother (Jim's partner) will be switched off.

This same pattern of inheritance, where the gene is switched off as it passes through the maternal line, but remains switched on when it is passed through the paternal line, will keep happening in each generation.

When does genetic imprinting happen?

Genetic imprinting happens early when eggs and sperm are first formed.

Some genes are imprinted so that they are switched off only if they are passed down through an egg cell; others will be switched off only if they are passed down through a sperm cell.

Imprinting is 'reset' in each generation when that person produces their own sperm or eggs.

Imprinting of Chromosomes: Uniparental Disomy

Uniparental disomy (UPD) happens when a person inherits both copies of a chromosome from one parent only. Therefore gene copies come from one parent only (**uniparental**) rather than the usual one copy of each gene from each parent (**biparental inheritance**).

Where the chromosome involved in the UPD is imprinted, there may be implications for that person. For instance, if there is UPD for chromosome 15, there are different possibilities:

- If both copies of chromosome 15 come from the mother (**maternal UPD**), a genetic condition called Prader Willi syndrome occurs
- If both copies of chromosome 15 come from the father (**paternal UPD**) a different genetic condition called Angelman syndrome occurs.

Features of these two different conditions include intellectual impairment and distinct facial features.

Different conditions result from the UPD being maternal or paternal, since the effect of imprinting causes different genes to be switched off in each case.