

This fact sheet describes epigenetics which refers to factors that can influence the way our genes are expressed in the cells of our body.

### In summary

- **Epigenetics is a phenomenon that affects the way cells express or shut down certain genetic information**
- **There are a number of epigenetic factors which can have a role in the way genetic information is expressed**
- **Epigenetics does not change the genetic information but can affect the way the information is read or interpreted by the cell.**

### DNA AND GENES

DNA can be thought of like an extremely long thin string made up of sections that code for proteins (our genes), and sections that do not code for proteins. Proteins do the work in our cells and these are very important for normal cell function and health.

Genes are strings of instructions arranged in a specific order like a recipe for a very complex cake. The ingredients in the cake are proteins and how they are added, how much and when is all important for the gene product (cake) to turn out correctly.

### EPIGENETICS

The term epigenetics comes from the words “epi-“ meaning upon or over and “genetics” meaning our genes. Epigenetics can change the way a cell reads the DNA message in a number of ways and one of these ways is by adding tags or notes to the DNA bases or structures that DNA wraps around to change the activity within a gene. Sometimes these tags give messages to activate the gene and create the protein, while others stop the protein from being created.

These tags are not permanent and 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.

This is a very simple way of explaining the reason why some genes can be affected by something in addition to the DNA code itself within a cell.

Epigenetic factors are the cause of some genetic conditions.

Two well understood epigenetic mechanisms are described below.

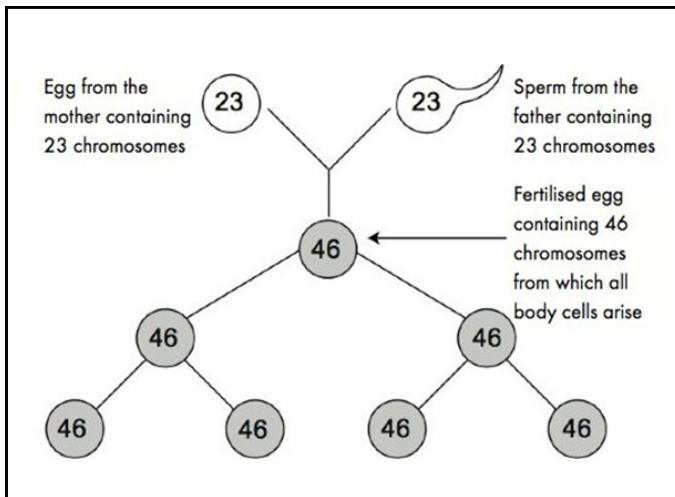
- **X-inactivation** is the epigenetic system that enables men and women to have equal expression of the genes carried on the X chromosome despite the fact that women have two X chromosome copies and men have only one
- **Genetic imprinting** is the epigenetic system where ‘stamping’ of the genetic information occurs according to whether it is inherited from the mother or the father.

### CHROMOSOMES IN THE BODY

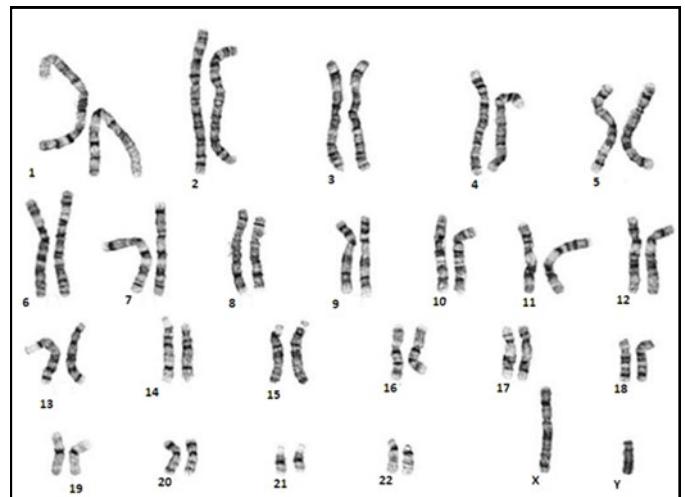
In each human cell, except the egg and sperm cells, there are 46 chromosomes. Chromosomes are found in pairs and each pair varies in size. Thus there are 23 pairs of chromosomes, one of each pair being inherited from each parent.

- There are 22 numbered chromosomes from the largest to the smallest: i.e. 1-22. These are called **autosomes**
- There are also two **sex chromosomes**, called X and Y.

In females, cells in the body have 46 chromosomes (44 autosomes plus two copies of the X chromosome). Eggs (female reproductive cells) are different as they only contain half of the chromosomes (23; made up of 22 numbered chromosomes and an X chromosome).



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



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

In males, cells in the body have 46 chromosomes (44 autosomes plus an X and a Y chromosome). Sperm (male reproductive cells) are different as they only contain half of the chromosomes (23 made up of 22 numbered chromosomes and an X chromosome or a Y chromosome).

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

In a genetic testing laboratory, the chromosomes may be coloured (stained) with special dyes to produce distinctive banding patterns. These patterns allow the laboratory to check the size and structure of the chromosomes. *Figure 14.2* shows a banded chromosome set from a male where each chromosome has been numbered from the largest (chromosome number 1) to the smallest (chromosome number 22) and arranged in pairs in order of size. We know these chromosomes are from a male because of the X and a Y.

### X-INACTIVATION

Unlike the Y chromosome, the X chromosome has many genes involved in important processes needed for healthy growth and development. Women have two copies of the X chromosome in their cells and therefore their cells contain two copies of the X chromosome genes.

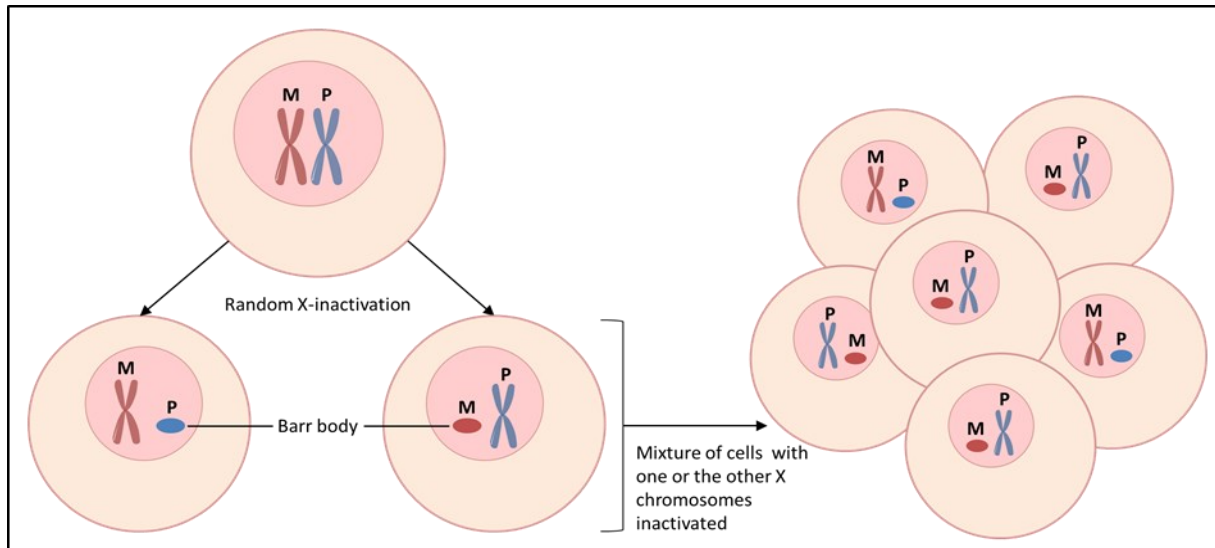
On the other hand, men have only one copy of the X chromosome in their cells so they only have one copy of the X chromosome genes.

In order to adjust this potential imbalance between the genetic information in men and women, the cells have a system to ensure that only one copy of most of the X chromosome genes in a female cell is **active**. Most of the genes on the other partner X chromosome are **inactivated** or switched off. This mechanism ensures that only the genes located on the **active** copy of the X chromosome are able to be used by the cell to direct the production of proteins.

As men grow and develop just like women it is obvious that only one copy of the X chromosome genes are necessary to direct normal growth and development.

Inactivation of one copy of the X chromosome in female cells ensures that both men and women have the same number of X chromosome genes instructing the body to grow, develop and function.

This system of switching off one of the X chromosome copies is seen in all mammals and is often called **lyonisation**, named after Mary Lyon who first described the system in 1962. It occurs very early in embryonic development in humans.



**Figure 14.3:** Maternal copy of the X chromosome represented by 'M' and paternal copy of the X chromosome represented by 'P'. Shortly after conception either the maternally inherited or paternally inherited X chromosome is randomly inactivated forming a super-condensed structure known as a Barr body.

In each body cell (*somatic cell*) of a developing baby girl, one of the X chromosomes becomes very shortened and condensed so that most of its genes are not able to be read by the cells. An examination of female cells under a microscope (*Figure 14.3*) reveals a dark shadow in the cell (called a Barr body, because they were discovered by Murray Barr) which is the inactivated X chromosome.

This system of inactivation in the body cells is usually **random** so that women's bodies have a mixture of cells in regard to the inactivated X chromosome. Some cells will have the X chromosome switched off that came from their mother, while other cells will have the paternal X chromosome inactivated. The relative proportion of cells with an active maternal or paternal X chromosome varies from female to female (even between identical twins) because the process is usually random.

X-inactivation only occurs in the somatic cells, since X chromosomes need to be active in the egg cells for their normal development.

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. For example, the gene called *ZFK* which codes for a protein that is possibly involved in the production of both egg and sperm cells.

Therefore, in male cells, two copies of these genes would be active in the cell: one on the X and one on the Y chromosome. In order for the same number of active genes to be operating in women, these special genes on the X chromosome are not switched off so that women also have two copies of these genes available for the cell to use.

In addition, a gene called *XIST* that is thought to control the inactivation process itself, is not switched off.

#### **Is the X-inactivation process always random?**

Women who are 'carriers' of a gene mutation which causes a genetic condition on one of their X chromosomes will have some cells in their body in which the X with the mutation is activated and other cells the working copy of the gene inactivated.

The usual random process of X-inactivation means that these women would not show any symptoms since there would be enough cells with the working copy of the gene to produce the necessary protein.

Rarely, some women have more cells in which the X chromosome carrying the mutation is active so that they show some of the symptoms of the condition. In these rare cases the X-inactivation has been skewed and research is still ongoing to understand this process.

In other rare cases, women have a structural change of one of their X chromosomes such as a deletion (missing piece) or rearrangement of the chromosome material. Usually it is this altered X chromosome that is inactivated rather than the working copy.

While this may appear to be a protective mechanism by the cell, it is more likely that the cells in which the working copy is inactivated do not survive because the deleted or changed X chromosome would be missing segments of important genes.

In additional other rare cases, women have a special type of chromosome rearrangement in their cells called a translocation where the X chromosome is attached to one of the numbered chromosomes. In the cells of these women, it is the working copy of the X chromosome that is usually inactivated, 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 those on the other chromosome that are attached to it. The cells in which the translocated chromosome was inactivated would be missing a large number of important genes located on the autosome and would be unlikely to survive.

### GENETIC IMPRINTING

As mentioned above, each human cell, except the egg and sperm cells, contain 46 chromosomes. Chromosomes are found in pairs and each pair varies in size. Thus there are 23 pairs of chromosomes, one of each pair being inherited from each parent.

Just as there are two copies of each chromosome, there are two copies 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)

Usually, the information contained in both the maternal copy of the gene and the paternal copy is used by the cells to make protein products because both the maternal and paternal genes are usually active or 'expressed' in the cells.

The expression, however, or activity of a small number of the many genes in the cells is dependent on whether the gene copy was passed down from the father or the mother.

This process, whereby the expression of a gene copy is altered depending upon whether it was passed to the baby through the egg or the sperm, is called **imprinting**.

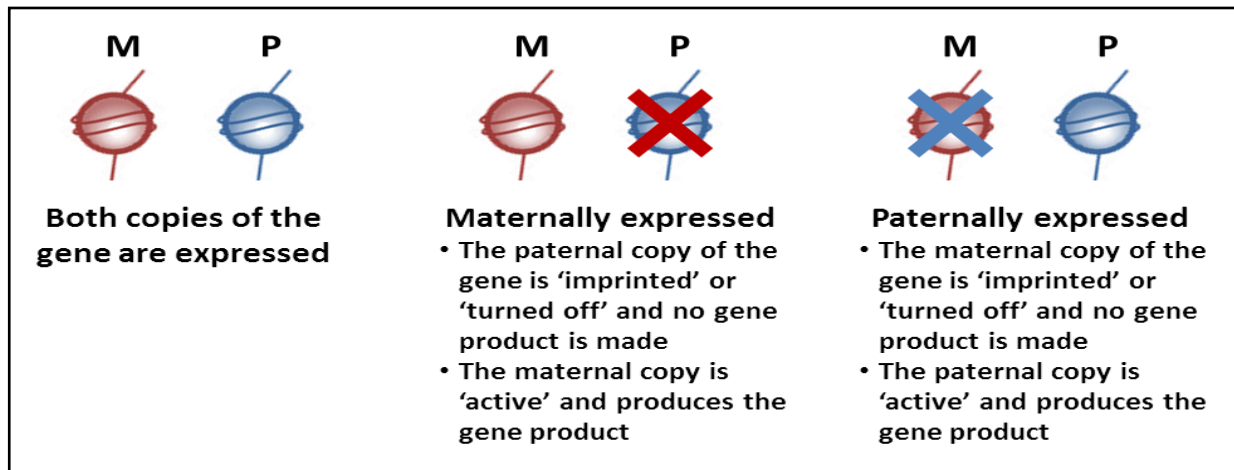
The term imprinting refers to the fact that some chromosomes, segments of chromosomes, or some genes, are stamped with a 'memory' of the parent from whom it came.

In the cells of a child it is possible to tell which chromosome copy came from the mother (maternal chromosome) and which copy was inherited from the father (paternal chromosome). This expression of the gene is called a 'parent of origin effect' and was first described by Helen Crouse in 1960.

### How does imprinting occur?

It is thought that there are a number of mechanisms whereby the gene may be 'stamped' so that the expression of the inherited genetic information is modified according to whether it is passed to a child through the egg or the sperm.

This modification determines whether the information contained in the gene copy is expressed or not. Genetic imprinting (or *genomic imprinting*) is the name given to this modification process.



**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 gene are active, in rarer cases one copy, either maternal or paternal may be imprinted or 'switched off'.

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

It is important to remember that this process is not a mutation or variation in the genetic code since the gene sequence itself is unchanged.

- Even though both imprinting of a gene and a mutation in a gene prevent the gene copy from making the appropriate gene product (*Figure 14.4*), a mutation is a more permanent change than an imprinting difference
- The imprinting modification process is reversible in the next generation as described below
- When a gene has a mutation, if it is also subject to imprinting, the expression of that gene is further impacted.

### Example of Imprinting

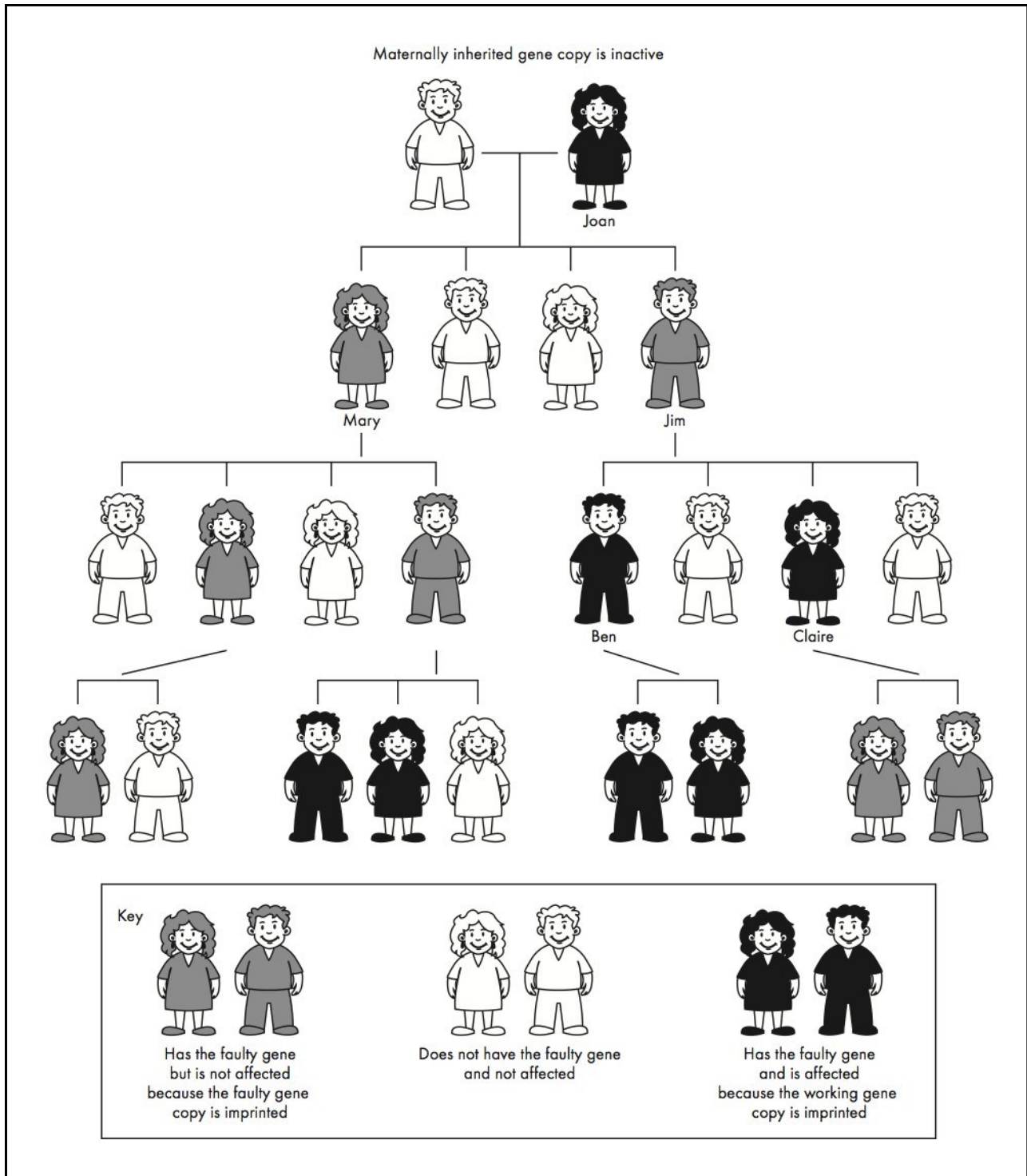
*(a) A maternally imprinted gene is switched off*

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 I) has a genetic condition caused by a gene mutation she inherited from her father.

- Only the faulty message translated from her father's gene mutation is expressed by 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
- Two of Joan's children, Mary and Jim in Generation II, inherited the gene mutation from Joan. They also received a working copy of the gene from their father
- Neither Mary or Jim have the condition because this gene mutation is 'switched off' (inactive) when inherited from the mother (passed down the maternal line)
- Thus the only copy of the gene which is active in Jim and Mary is the working copy which they inherited from their father: they are therefore unaffected by the condition.

Importantly, both Jim and Mary have, in each of their cells, a faulty, inactive copy of this gene mutation (inherited from their mother) and a working, active gene copy (inherited from their father). Therefore, Mary and Jim have a 50% chance of passing the gene mutation on to their children.



**Figure 14.5:** The faulty 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.

When **Mary's egg cells** develop, half of her cells will contain the working copy of the gene and half will contain the mutation.

- When the mutation is passed down to a child through the egg, however, it is switched off
- Therefore, none of Mary's children (Generation III), even those who inherit the mutation, will be affected by the condition. This is because the gene is always switched off when passed through the mother.

When **Jim's sperm cells** develop, half of his cells will contain the working copy of the gene and half will contain the mutation.

- If the mutation is contained in the sperm, it remains active i.e. it is not switched off
- Thus, any of Jim's children who inherit the mutation from him will have this active gene in their cells because the gene always remains active when passed through the father
- Jim's children will be affected by the condition because the gene mutation is the only active one they have. The working copy they received 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 active when it is passed through the paternal line, will occur in the next generation.

- Ben, Jim's affected son, can also have affected children if they receive the mutation from Ben
- On the other hand, Claire, Jim's affected daughter, will not have children with the condition as the gene copy will not be active when passed to her children.

The same situation can happen in reverse when considering imprinting of a paternal gene. The gene causing the condition is switched off when it is passed from the father, to his children, through the sperm and remains active when passed by the mother, to her children, in the egg.

### When does genetic imprinting occur?

Genetic imprinting occurs in the ovary or testis early in the formation of the eggs and sperm.

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

Imprinting will then occur again in the next generation when that person produces his or her own sperm or eggs.

### Imprinting of Chromosomes: Uniparental Disomy

Uniparental disomy (UPD) occurs when an individual receives both copies of a chromosome from one parent only. Therefore the child inherits some of their genes from one parent only (**uniparental**) rather than the usual situation where one copy of each gene is inherited from the father, and the other from the mother (**biparental inheritance**).

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

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

These two distinctly different conditions have features including intellectual impairment and characteristic 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.