X CHROMOSOME INACTIVATION – Epigenetics 1

FACT SHEET 14

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Important points

- Changes to the genetic code are not the only factors that influence the expression of health problems. For example, environmental factors interact with the information in the genes
- Another system of influence on the expression of genes is referred to as ***epigenetics*** that works in addition to the direct translation of the genetic information: a system that switches the genetic information on and off
- One example of an epigenetic system 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 (in addition to a Y chromosome). The system is called X chromosome inactivation
- This cellular system ensures that only one copy of most of the X chromosome genes in a female cell is 'active'. Most of the other genes on the other partner X chromosome copy 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
- In this system of randomly 'switching off' of **most** of one of the X chromosomes copies in each body cell (*somatic cell*) in the very early development of a 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. Genes in the areas of the X and Y chromosomes that enable pairing up during the production of sperm cells are not inactivated
- Some cells will have the X chromosome that came from their mother switched off (an inactive maternal X chromosome); other cells will have the paternal X chromosome inactivated

Epigenetics

The cells of the body contain the genes or set of instructions for the cell to make all the necessary products for our bodies to grow and work normally (see Genetics Fact Sheet 1). The information in the genes is in the form of a genetic code that the cells translate into products such as proteins.

If the information in a gene (ie. the sequence of letters in the DNA) is changed so that it does not work properly, the gene is described as being faulty (i.e. there is a gene *mutation* present). The result is that either a protein is produced that is faulty, produced in limited quantity or is not produced at all (see Genetics Fact Sheets 4 & 5).

It is, however, increasingly clear that translation of the genetic code is not the only way that our genes influence our growth, development and health and that changes in the genetic information are not the only factors that influence the expression of health problems. Genetics Fact Sheet 11 discusses the interaction of environmental factors with the information in the genes.

Another system of influence on the expression of genes is referred to as ***epigenetics*** that means 'on top of genetics'. In other words, it is a system in addition to the direct translation of the genetic information: a system that switches the genetic information on and off.

To date several epigenetic systems in humans have been described:

- ***'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 (see Fact Sheet 15)
- This Fact Sheet discusses the epigenetic system called ***X-inactivation*** 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 - in addition to a Y chromosome

The sex chromosomes

There are 46 chromosomes in our body cells. Of these, 23 came through our mother's egg and 23 came through our father's sperm.

When the egg and the sperm join at the time of conception, they form the first cell of the baby. This cell has 46 chromosomes, made up of 23 pairs, which is all the genetic material needed for a new person to start developing (*Figure 14.1*).

The chromosomes are numbered from the largest (chromosome number 1) to the smallest (chromosome number 22). *Figure 14.2* is a picture of chromosomes, stained with special dyes to produce the distinctive banding patterns, arranged in pairs and in order of size.

These numbered, paired chromosomes are called ***autosomes***. There are also two chromosomes that have been given the letters X and Y: these are ***the sex chromosomes***.

In **their body cells** (except their eggs or sperm), everyone has the same number of chromosomes - a total of 46. Women have 44 autosomes and two copies of the X chromosome (XX); men

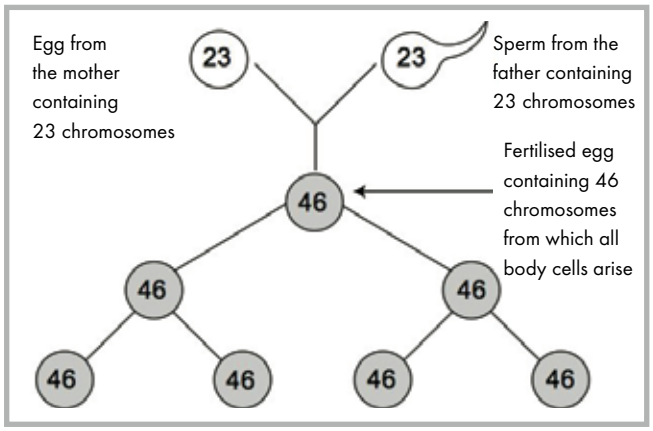

Figure 14.1: *At conception, the sperm and egg combine to form the first cell of a baby*

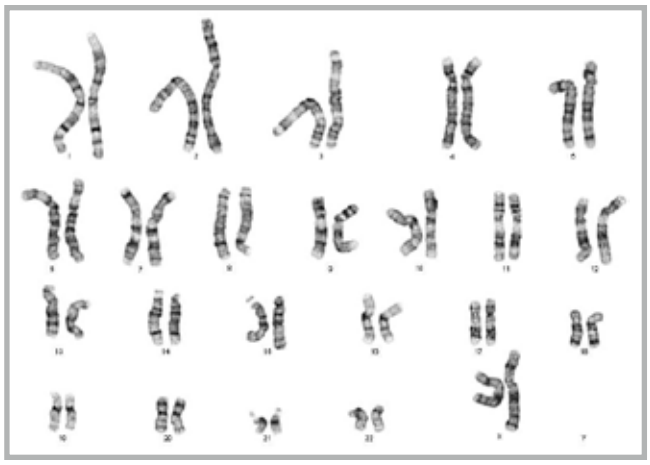

Figure 14.2: *Chromosome picture (karyotype) from a female (SEALS Genetics, Prince of Wales Hospital, Randwick)*

have 44 autosomes as well as an X and a Y chromosome (XY). The chromosomes pictured in *Figure 14.2* must be from a female as there are two copies of the X chromosome present. See Genetics Fact Sheet 1 for a picture of chromosomes from a male.

In their **egg cells**, women have 22 autosomes and an X chromosome; men have 22 autosomes and an X or Y chromosome in their **sperm cells**.

The genes on the X and Y chromosomes

As of May 2007, due to the continuing work initiated by the Human Genome Project (see Genetics Fact Sheet 24), 122 genes have been mapped to the ***Y chromosome.***

- Many of the Y chromosome genes contain the instructions to make the baby develop as a male rather than a female
- Without the presence of the Y chromosome genes, the baby will develop into a female
- In rare cases, a male baby is born with his cells containing 47 chromosomes: made up of 44 autosomes, two X chromosome copies and the Y chromosome (see Genetics Fact Sheet 31 – Klinefelter (XXY) syndrome)
- Despite the presence of the two copies of the X chromosomes in the cells, the baby still develops as a male because of the instructions issued by the Y chromosome genes

Unlike the Y chromosome, the ***X chromosome*** is 'gene rich' with 1021 genes mapped to it (May 2007). Many of the X chromosome genes are very important for growth and development; e.g. the genes that contain the instructions for a major protein in muscles (*dystrophin*), several proteins that control clotting in the blood and a number of genes involved in the development of intelligence. When these particular X chromosome genes are faulty, specific genetic conditions may result: haemophilia, Duchenne and Becker muscular dystrophy and fragile X syndrome (see Genetics Fact Sheets 40, 41 & 42 respectively).

- These conditions all follow a pattern of inheritance called X-linked recessive inheritance (see Genetics Fact Sheet 10)
- Women who have the faulty gene copy as well as a 'back up' working gene copy on the other partner X chromosome copy, means that they are usually unaffected by these conditions
- Men have no other X chromosome to provide 'back up' so will usually be affected due to the faulty gene being expressed in the cells

Ensuring men and women have the same number of 'active' X chromosome genes

Chromosomes can be thought of as strings of genes as described in Genetics Fact Sheet 1.

- As there are two copies of each autosome, there are two copies of each gene located on chromosomes numbered 1-22 in both men and women
- Similarly, women are born with 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 other genes on the other partner X chromosome copy 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 most of the X chromosome genes is 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.

The system of 'X-inactivation'

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

In each body cell (*somatic cell*) of the 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 body in the cell (called a Barr body) which is the inactivated X chromosome.

If a cell has more than two X chromosomes (such as in XXX syndrome), two Barr bodies may be seen. In boys with XXY syndrome, the system of X inactivation also occurs so that the boys with this syndrome also have only one active X chromosome, just like other boys.

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 (an inactive maternal X chromosome); other cells will have the

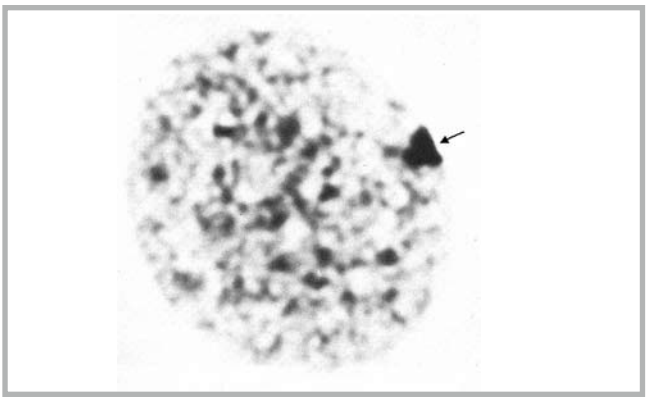

Figure 14.3: *A female cell showing a darkly stained 'Barr Body' which is the inactivated X chromosome (source: Gardner RJM & Sutherland GR (1996): Chromosome abnormalities and genetic counselling. Oxford Monographs on Medical Genetics No. 29. Oxford University Press, UK)*

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 both X chromosomes need to be active in the egg cells for their normal development.

Are all the genes on the inactivated X chromosome 'switched off'?

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.

Finally, other research has shown that 10%-15% of genes on other parts of the X chromosome that were thought to be 'silenced' by the inactivation process were switched on. So for these genes, women do express an increased amount of their products – an interesting situation that may contribute to some differences between men and women but the size of that contribution is still very much in question.

Is the X-inactivation process always random?

Women who are 'carriers' of the faulty genes on their X chromosomes involved in conditions such as haemophilia and Duchenne muscular dystrophy (see Genetics Fact Sheets 40 & 41), will have some cells in their body in which the faulty gene is activated and others inactivated the working copy of the gene will be activated. The usual random process of X-inactivation means that these women would not show any symptoms due to the faulty gene as 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 faulty gene is active ie. not switched off, so that these women do show some of the symptoms of these conditions due to the faulty genes. In these rare cases the X - inactivation has been '**skewed**'.

In other rare cases, women have a structural change of one of their X chromosomes (see Genetics Fact Sheet 6): their X chromosome may be missing a small part (deleted) or rearranged in some way. Usually it is this changed 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 (autosomes) - see Genetics Fact Sheet 7. 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 chromosome was inactivated, not only would the process 'switch off' the X chromosome genes but also those on the autosome that were 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.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 4, 5, 6, 7, 10, 11, 15, 24, 31, 40, 41, 42

Information in this Fact Sheet is sourced from:

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