This fact sheet talks about how genes affect our health when they follow a well understood pattern of genetic inheritance known as X-linked dominant inheritance.

**IN SUMMARY**

- Genes contain the instructions for growth and development. Some gene variations 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*.
- If a genetic condition occurs when a gene on the X chromosome has a variation, this is called *X-linked inheritance*.
- An X-linked dominant gene is a gene located on the X chromosome and may affect males and females differently.

**CHROMOSOMES, GENES AND DNA**

In all the cells of our body, our genes are found on chromosomes (long strings of genes). We have many thousands of genes that provide information for our body to grow, develop and stay healthy. The gene sends messages to the cell to make important chemical products such as proteins.

There are usually 46 chromosomes in each cell that are arranged into 23 pairs. One of each pair is passed on to us from our mother and the other from our father. 22 of these chromosome pairs are numbered. These numbered pairs are known as the autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Typically males have an X and a Y chromosome and females have two copies of the X chromosome.

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*.

If a DNA change occurs in only one copy of the pair of genes and this causes a health condition, it is called a *dominant variant*. If a health condition only occurs when both copies of the gene are changed, this is called a *recessive variant*.

An *autosomal* gene is a gene located on a numbered chromosome and usually affects males and females in the same way.

An *X-linked* gene is located on the X or Y chromosome and affects males and females differently.
A CLOSE LOOK AT X-LINKED INHERITANCE

This type of inheritance refers to the inheritance of a gene variant on the X chromosome. Males typically have one X chromosome and one Y chromosome whereas females typically have two copies of the X chromosome and no Y chromosome. Because of this, males will only have one copy of each X chromosome gene while females will have two (see Figure 10.1).

In females, although each body cell has two X chromosomes, only one is used for making the gene product and the other X chromosome is switched off.

**Figure 10.2:**
Where an X-linked dominant gene variant is shown as 'D' and the working gene copy by 'd', there are several possibilities a person could have and depending on whether they are male or female, the effect of the genetic makeup will differ.

A. 
- This typical female has the gene pair 'Dd' on the X chromosomes. This means that one copy of the gene is working (d) and producing the gene product in the right way, however the other copy (D) is not working
- When this person has a child, there is a 50% (1 in 2) chance that the working (d) copy of the gene is passed on to each of her children, and a 50% (1 in 2) chance that they will pass on the non-working gene copy (D)
- They will themselves have the genetic condition caused by the X-linked dominant variant because the (D) 'dominates' over the working copy of the gene, and so the gene product is not made properly by the cells.

B. 
- This represents a typical unaffected female who has two working copies (dd) of the gene on her X chromosomes
- When this person has a child, there is a 100% chance they will pass on the working copy of the gene if they have sons and daughters. So none of the children will have the non-working copy of the gene causing the particular condition.

C. 
- This represents a typical affected male with an X-linked dominant gene copy on his X chromosome. There is no working copy of the gene and therefore they will not make the gene product in the right way and will show symptoms of that particular condition
- When this person has a child, there is a 100% chance that they will pass on the gene variant on the gene copy that is not working (D), to each daughter. If this person has a son, they will not pass on the X chromosome, but rather the Y chromosome which means that all sons (100%) will not inherit the gene variant from him, and therefore will not have the condition.

D. 
- This represents a typical unaffected male who has a working copy of the gene on the X chromosome. Their body cells can therefore make the right gene product and will not show symptoms of that particular condition
- When this person has a child, there is a 100% chance that they will pass on the working copy of the gene if they have a daughter. If this person has a son, they will not pass on the X chromosome, but rather the Y chromosome, which means all their sons will not have inherited the gene variant causing the condition.
This process of switching off is known as **X-inactivation**. This usually happens randomly so that in some of the female’s cells, one particular X will be inactivated (switched off) and in another cell, that X will be active (switched on).

**WHAT DOES IT MEAN IF YOU HAVE AN X-LINKED DOMINANT GENE VARIANT?**

Variants on the X chromosome are most often recessive. This means that if there is a working copy of the same gene in each cell of a person, they will not usually show symptoms of the condition. In other words, the working copy of the gene is a backup for the other non-working copy of the gene.

When a gene variant is dominant, however, the body cells cannot work properly. The X-linked dominant variant on the non-working copy of the gene appears to override or dominate the working copy of the gene. It is very rare for a female to have a dominant gene variant on both copies of the X chromosome.

**HOW ARE X-LINKED DOMINANT GENE VARIANTS PASSED DOWN THROUGH THE FAMILY?**

**If the mother is affected by a condition caused by an X-linked dominant gene variant**

When the mother has a condition caused by an X-linked dominant gene variant (as in Figure 10.2A), there are different possibilities for what the child can receive from the parents (Figure 10.3).

For such a couple, this means that in every pregnancy there is a:

- 1 in 2 (50%) chance that both **sons** and **daughters** will inherit the **X-linked dominant gene variant** from the mother and have the condition. The gene product is not made in the right way by the cells
- 1 in 2 (50%) chance that children (both **sons** and **daughters**) will inherit the working copy of the gene (‘d’) from her and will not have the condition

**If the father is affected by a condition caused by an X-linked dominant gene variant**

When the father has a condition caused by an X-linked dominant gene variant (as in Figure 10.2C).

The father will pass on the X-linked dominant gene variant (on the X chromosome) to all his daughters and pass on his Y chromosome to all his sons. The unaffected mother will only give working copies of the gene to her children.

For such a couple, there are different possibilities the child can receive from the parents (Figure 10.4):

- None of their **sons** can inherit the X-linked dominant gene variant since the son only inherits the Y chromosome from the father. They will inherit the **working gene copy** from their mother. None of their sons will have the condition

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Fact sheet 10

X-LINKED DOMINANT INHERITANCE

• All of their daughters will inherit the working gene copy from their mother and the X-linked dominant gene variant from their father. All daughters will therefore have the condition.

Figure 10.4:
X-linked dominant inheritance where the father carries the X-linked dominant gene copy and has the condition. The non-working copy of the gene is represented by ‘D’, the working copy by ‘d’.

Non-carrier mother

Affected father with X-linked dominant gene variant

eggs

sperm

Girls

Boys

All girls affected

No boys affected

Non-carriers

WHAT GENETIC CONDITIONS ARE CAUSED BY AN X-LINKED DOMINANT GENE VARIANT?

There are very few conditions that have been shown to follow a pattern of X-linked dominant inheritance. Rett syndrome, which is a condition that causes physical and intellectual disability in females, is one example. Males with the variant sometimes survive but are affected more severely than females.

You can find more about the underlined topics by following the links in the online version of this document. Go to www.genetics.edu.au/FS10 for an online and downloadable copy.