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

**IN SUMMARY**

- Genes contain the instructions for growth and development. Some gene variations or 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 genetic condition happens when a gene on the X chromosome has a variation, this is called **X-linked inheritance**.

- An X-linked recessive gene is a gene located on the X chromosome and affects 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 happens 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 usually 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. Typically males have one X chromosome and one Y chromosome whereas females have two copies of the X chromosome and no Y chromosome (see Figure 9.1). Because of this, males will only have one copy of each X chromosome gene while females will have two.

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.

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 RECESSIVE 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.

For example, in Figure 9.2A, the female has two copies of the gene because there are two X chromosomes. One of the X chromosomes has a recessive variant and the other has a working copy of the gene.

This person is a genetic carrier and although only one of the gene copies is sending the right instructions to make the gene product, the cell can usually work with this.

In many X-linked recessive conditions, females who carry a gene variant will not have any symptoms of the condition (Figure 9.2Ai).

Some conditions, however, may affect females who are genetic carriers and this is thought to be due to the X inactivation process switching off the X with the working gene copy in more body cells (Figure 9.2Aii). So the working copy of the X-chromosome is not switched on enough to protect this person from developing the condition.

Males who have the recessive gene variant on their X chromosome do not have a second chromosome with a working copy of the gene.

Therefore, they will not be able to send the right message to the cells to make the gene product, and will have the condition (see Figure 9.2C).

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

If the mother is a carrier of an X-linked recessive gene variant

The chances of a mother who is a carrier of an X-linked recessive gene variant having a child with the condition are different for her sons and daughters.

In Figure 9.3, where the non-working X-linked recessive gene copy is represented by ‘r’ and the working copy by ‘R’, the mother is a carrier of an X-linked recessive gene health condition and the father has only a working copy of the gene. There are four possibilities in every pregnancy that the child can receive from the parents.

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

- 1 chance in 4, (25% chance) that a son will inherit the Y chromosome from their father and X-linked recessive non-working gene copy with the variant from the mother. In this case, the body cells cannot make gene product in the right way. This person will therefore have the condition.
- 1 in 4, (25%) chance that a son will inherit the Y chromosome from their father and the working copy of the X-linked gene from the mother. This person will therefore not have the condition.
If the father is affected by an X-linked recessive genetic condition

If the father is affected by an X-linked recessive genetic condition, the chance of passing on the non-working recessive gene copy is different for his sons and daughters.

As shown in Figure 9.4, there are two possibilities in every pregnancy that the child can receive from the parents. The father passes his Y chromosome to his sons and his X chromosome to his daughters.

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

- All sons will inherit the working X-linked gene copy from their mother and the Y chromosome from their father and will therefore not have the condition.
- All daughters will inherit a working copy of the X-linked gene from their mother and X-linked recessive gene variant from their father. They will be carriers of the variant and can pass this on to their children. They will usually not have the condition.

In summary, if pregnant with a son, there is a 50% (1 in 2) chance that the child will have the condition. If pregnant with a daughter, there is also a 50% (1 in 2) chance they will be a genetic carrier of the condition.

• 1 in 4, (25%) chance that a daughter will inherit both working copies of the X-linked genes: one copy from their father and one from the mother. A daughter will therefore be unaffected by the condition. In addition they will also NOT be a carrier of the X-linked recessive gene copy with the variant
• 1 in 4, (25%) chance that a daughter will inherit from their father the working copy of the X-linked gene and the X-linked recessive non-working gene copy with a variant from the mother. This person will be a genetic carrier of the condition like the mother and will usually be unaffected.

In summary, if pregnant with a son, there is a 50% (1 in 2) chance that the child will have the condition and if pregnant with a daughter, a 50% (1 in 2) chance they will be a genetic carrier of the condition.

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

The most common conditions that are caused by an X-linked recessive gene variant are haemophilia, Duchenne muscular dystrophy and fragile X syndrome.

Usually female genetic carriers of an X-linked recessive condition do not develop health concerns by being a genetic carrier.

Clues for why a female might be a genetic carrier of an X-linked recessive gene variant include having a family history of a condition that usually only affects males.

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/FS9 for an online and downloadable copy.