

This fact sheet describes 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 make the gene faulty so that the message is not read correctly or is not read at all by the cell**
- **A variation in a gene that makes it faulty is called a *mutation* or *pathogenic variant***
- **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 remain 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. 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. There may be small variations in our genes that can affect how our bodies grow and develop.

Generally, these variations do not have any impact on our health and are called neutral variants or polymorphisms. Some gene variations make the gene faulty so that the message is not read correctly or is not read at all by the cell. A variation in a gene that makes it faulty is called a **pathogenic variant** or **mutation**.

If a DNA variation occurs in only one of the pair of genes and this causes a health condition, it is called a **dominant mutation**.

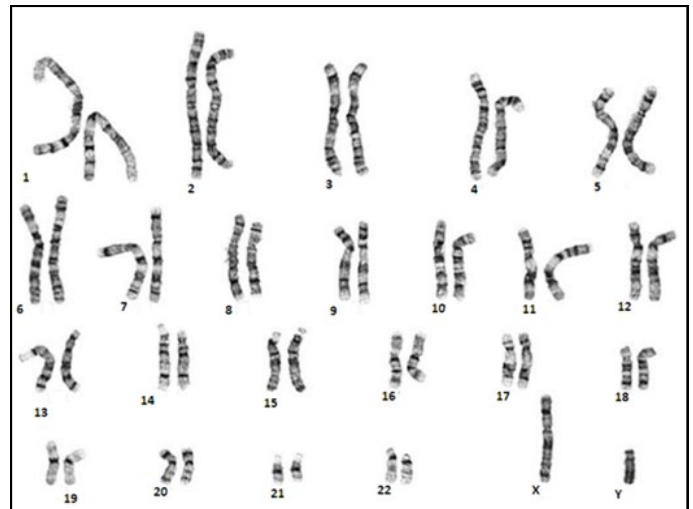


Figure 9.1: Chromosome picture (karyotype) from a male 46,XY.

If a health condition only occurs when both copies of the gene have a variation that makes them faulty, this is called a **recessive mutation**.

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 RECESSIVE INHERITANCE

This type of inheritance refers to the inheritance of a gene mutation on the X chromosome. 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*). Men will therefore only have one copy of each X chromosome gene whereas women will have two.





A		<ul style="list-style-type: none"> This female has the gene pair Rr on her X chromosomes. This means that one copy of the gene is working (R) and producing the correct gene product however the other copy (r) is not working. When this woman has a child, there is a 50% chance that she will pass on a working (R) gene to each of her children and a 50% chance that she will pass on the gene mutation which is not working (r). Her children will either not develop symptoms of the genetic condition (see i. below) or be affected (see ii. below) <ol style="list-style-type: none"> For most X-linked recessive conditions, genetic carrier females will not show symptoms themselves because for this gene, you only need one working copy and the X with the working copy is switched on in most or all of their cells. Some X-linked recessive conditions can show up in females who are genetic carriers. This is due to the X with the working copy of the gene being switched off or inactivated in many or all of the cells in the body.
B		<ul style="list-style-type: none"> This represents an unaffected female who has two working copies of the gene on her X chromosomes. When this woman has a child, there is a 100% chance that she will pass on the working copy of the gene to all her sons and daughters.
C		<ul style="list-style-type: none"> This represents an affected male who has an X-linked recessive gene on his X chromosome. There is no working copy of the gene and therefore he will not be making the correct gene product and will show symptoms of that particular condition. When this man has a child, there is a 100% chance he will pass on the gene mutation which is not working (r) if he has a daughter. If he has a son, he will not pass on the X chromosome, but rather the Y chromosome which means his sons will not have inherited the gene mutation from him.
D		<ul style="list-style-type: none"> This represents an unaffected male who has a working copy of the gene on his X chromosome. His body cells can therefore make the correct gene product and will not show symptoms of that particular condition. When this man has a child, there is a 100% chance he will pass on the working copy of the gene if he has a daughter. If he has a son, he will not pass on the X chromosome, but rather the Y chromosome which means his sons will not have inherited the gene mutation.

Figure 9.2: Where an X-linked recessive gene mutation is represented by 'r' and the working gene copy by 'R', There are several possible combinations a person could have and depending on whether they are male or female, the effect of the genetic combination will differ.

In women, despite the fact that 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 switching off is known as **X-inactivation** and is thought to occur randomly so that in some of the woman's cells, one particular X will be inactivated and in another cell, that X will be active while the other copy of the X is switched off or inactive.

WHAT DOES IT MEAN IF YOU HAVE AN X-LINKED RECESSIVE GENE MUTATION?

Mutations on the X chromosome are more commonly recessive. This means that if there is a normal working copy of the same gene in each cell of a person, they will not usually show symptoms of the condition.

For example, in *Figure 9.2A*, the female has two copies of the gene because she has two X chromosomes. One of her X chromosomes has a recessive mutation and the other has a working copy of the gene.

She is a genetic carrier and although only one of the gene copies is correctly sending the instructions to make the gene product, the cell can usually still work with this reduced amount.

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

Some conditions however, do affect women who are genetic carriers and this is thought to be due to the X inactivation process switching off the X with the working gene and preventing that woman from producing enough of the gene product (*Figure 9.2Aii*).

Men who have the recessive gene mutation 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 information to the cells to make the gene product and will be affected by the condition (see *Figure 9.2C*).

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

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

The chances of a woman who is a carrier of an X-linked recessive gene mutation having an affected child are different for her sons and daughters.

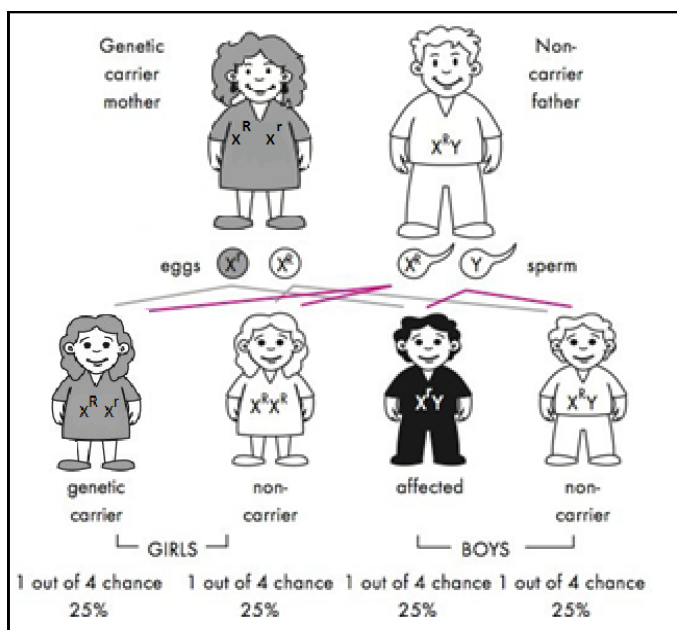


Figure 9.3: X-linked recessive inheritance where the mother is a carrier of the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'; the working copy by 'R'.

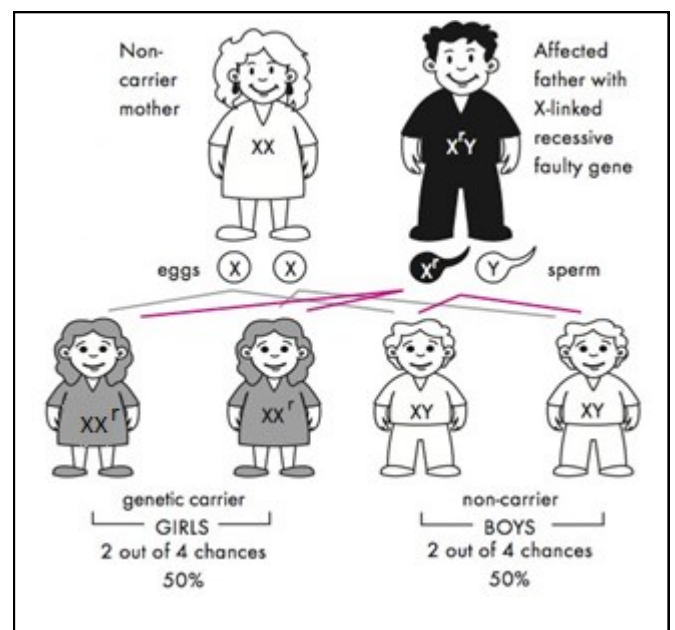


Figure 9.4: X-linked recessive inheritance where the father has the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'.

In *Figure 9.3*, where the X-linked recessive gene mutation is represented by 'r' and the working copy by 'R', the mother is a carrier of an X-linked recessive gene mutation and the father has only a working copy of the gene. There are four possible combinations in every pregnancy of the genetic information 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 his father and **X-linked recessive gene mutation** from his mother. In this case, no working gene or the right amount of the gene product will be able to be made by his cells. He will therefore be affected by the condition
- 1 chance in 4, (25% chance) that a **son** will inherit the Y chromosome from his father and **the working copy of the X-linked gene** from his mother. He will not be affected by the condition
- 1 chance in 4, (25% chance) that a **daughter** will inherit **both working copies of the X-linked genes**: one copy from her father and one from her mother. In this case she will not only be unaffected by the condition but she will also NOT be a carrier of the X-linked recessive gene mutation
- 1 chance in 4, (25% chance) that a **daughter** will inherit the **working copy of the X-linked gene** from her father and the **X-linked recessive gene mutation** from her mother. She will be a genetic carrier of the condition like her mother and will usually be unaffected.

In summary, if pregnant with a son, there is a 50% chance they will be affected by the condition and if pregnant with a daughter, a 50% chance they will be a genetic carrier of 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 recessive gene mutation is different for his sons and daughters.

As shown in *Figure 9.4*, there are four possible combinations in every pregnancy of the genetic information 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 mutation** from their father. They will be carriers of the X-linked recessive gene mutation and can pass the faulty gene on to their children. They will usually be unaffected by the condition.

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

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

Usually female genetic carriers of an X-linked recessive gene mutation do not show any symptoms of the condition and do not develop health concerns by being a genetic carrier.

Indications that a woman may be a genetic carrier of an X-linked recessive gene mutation include having a family history of a condition that usually only affects males.