X-linked Inheritance

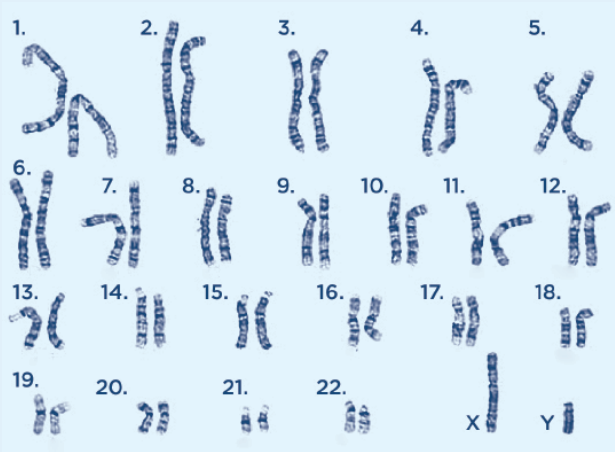
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This fact sheet talks about health conditions caused by genes on the X chromosome. Genes that are on the X chromosome are said to be 'X-linked'.

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**.
- People can have X and/or Y sex chromosomes. If a gene on the X chromosome has a variation causing a genetic condition, this is called **X-linked inheritance.**
- The impact of an X-linked condition is related to a person's sex chromosomes.

Figure 1:
Chromosome picture (karyotype) from a male (46,XY)



Chromosomes, Genes and DNA

Our bodies are made up of billions of cells, and in each cell is a copy of our genetic information, which is carried on DNA. This is generally packaged into 46 chromosomes, arranged into 23 pairs *(Figure 1)*. One pair is the sex chromosomes, X and Y. Most of the time, people of male sex have one X and one Y chromosome. Most people of female sex have two X chromosomes *(Figure 2)*.

Chromosomes contain genes, which provide instructions for our body to grow and function. Our genes send messages to the cells to produce a particular product such as a protein. This is called the gene product. We all have variation in our genes which makes us unique. Some gene variations, however, may mean that the gene does not work properly or works in a different way that is harmful.

Figure 2:
X and Y chromosomes and the body





People with XX chromosomes

People with XX sex chromosomes are typically born with traits that fit medical norms for a female body. It is common for people with XX chromosomes to identify as female.

People with XX chromosomes are referred to as 'female/XX people' throughout this factsheet

People with XY chromosomes

People with XY sex chromosomes are typically born with traits that fit medical norms for a male body. It is common for people with XY chromosomes to identify as male.

People with XY chromosomes are referred to as 'male/XY people' throughout this factsheet

- Some people (intersex people) are born with traits that do not fit medical expectations for a male or female body.
- Self-identified gender and preferred pronouns should always be respected.

A variation that causes a health or developmental condition is called a **pathogenic variant**.

Gene variants may be inherited (passed down) from a biological parent or happen for the first time in a person. Once a person has a gene variant it may be passed on to future generations. This is referred to as genetic inheritance.

The first 22 pairs of chromosomes are called **autosomes** and are numbered according to their size *(Figure 1)*. A pathogenic variant in an autosomal gene usually affects males/XY people and females/XX people in the same way. A pathogenic variant in an **X-linked** gene usually affects males/XY people and females/XX people differently *(Figure 3)*.

Figure 3:
Below, a non-working X-linked gene with a pathogenic variant is represented by 'X*' and the working gene copy by 'X'.
The impact of a non-working X-linked gene depends on the sex chromosomes of the person.

A.



Female/XX person with two working X

- A typical unaffected female/XX person who has two working copies of the gene on their X chromosomes. Their body cells make the gene product in the expected way, and they do not have the X-linked condition.

B.



Female/X*X person with non-working X-linked gene

- A typical female with X*X genes on their chromosomes. This means that one copy of the gene is working (X) and making the gene product in the expected way, and the other copy (X*) is not.
- Females/X*X people often have no symptoms or less severe symptoms of X-linked conditions, depending on the gene involved. This is because their working copy of the gene acts as a "backup" for the non-working copy of the gene.
- In some X-linked conditions, females/X*X people are referred to as "carriers". These types of conditions are sometimes described as X-linked recessive.
- In some X-linked conditions, females/X*X people can be very significantly affected. These X-linked conditions are sometimes described as X-linked dominant.

C.



Male/XY person with one working X

- A typical male/XY person who has a working copy of the gene on the X chromosome. Their body cells make the gene product in the expected way and they will not have the X-linked condition.

D.



Male/X*Y person with non-working X-linked gene

- A typical male who has a non-working gene on their one X chromosome (X*). They have no working copy of the gene. They will not be making the gene product in the expected way and will have the X-linked condition.

A close look at X-linked Inheritance

Males/XY people only have one copy of each X chromosome gene, which is used in all cells to make the gene product. Females/XX people have two copies of each X chromosome gene, but only one is used for making the gene product. The other X chromosome is "switched off".

This process of switching off is known as **X-inactivation**. This usually happens randomly. This means the same X chromosome will be inactivated (switched off) in some cells, and active (switched on) in others.

What does it mean if you have an X-linked gene variant?

Whether a person is affected by an X-linked condition or is a carrier depends on the gene involved and the sex chromosomes of the person. X-inactivation can also play a role.

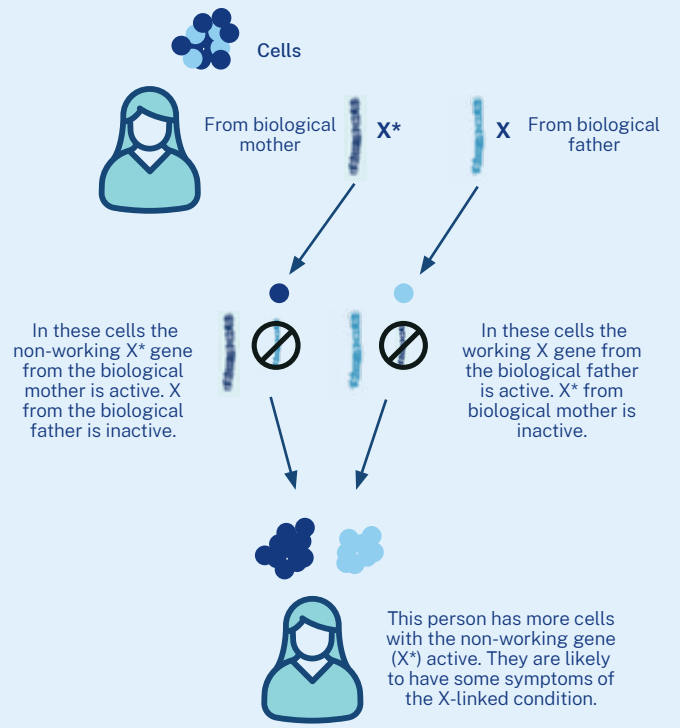
All male/X*Y people with a pathogenic variant in an X-linked gene will have the X-linked condition *(Figure 3D)*.

By contrast, in many X-linked conditions, a female/X*X person with a pathogenic variant would simply be a carrier and have minimal or no symptoms *(Figure 3B)*. X-linked conditions like this are sometimes described as X-linked recessive.

For some X-linked conditions, females/X*X people do have symptoms. There are two reasons why this could happen:

1. The working copy of the X chromosome is not active in enough cells to protect this person from developing the condition *(Figure 4)*. This can happen when more cells with the working copy of the gene have been switched off through X-inactivation than cells with the non-working gene.
2. Having one working copy of the X-linked gene is not enough to protect the person from the condition. X-linked conditions like this are sometimes described as X-linked dominant. There are a small number of X-linked conditions where this is seen, for example Rett syndrome - a rare genetic neurological condition. In these types of conditions, male/X*Y pregnancies with a pathogenic variant may not continue to full term. Male/X*Y babies that are born generally do not survive. Female/X*X people will have a significant health condition that impacts many aspects of their day-to-day life.

Figure 4:
X-inactivation where a female/XX person has inherited a non-working copy of an X-linked gene (X*) from their biological mother. The chromosome with the non-working X-linked gene (X*) is randomly active in more of their cells than the X chromosome inherited from the biological father (X).



How are X-linked gene variants passed down through families?

Typically, a baby is made from the egg of a female/XX person and the sperm of a male/XY person. Families are made up in many ways. A child's parents may include one, both, or neither of the two people that gave egg and sperm to make them. In this fact sheet, the person giving the egg is called the biological mother and the person giving the sperm is called the biological father.

If the biological mother is a carrier of an X-linked genetic condition

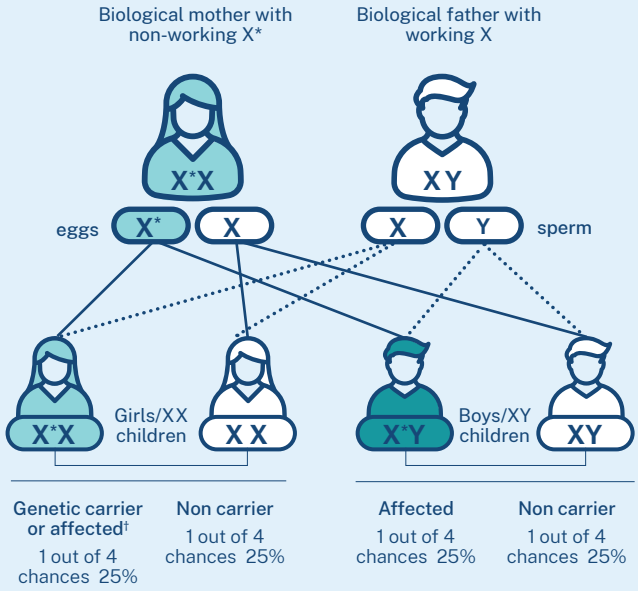
If the biological mother is a carrier of an X- linked genetic condition, their chance of having a child with the genetic condition depends on the sex chromosomes of that child.

As shown in *Figure 5*, if the biological mother is a carrier of an X-linked condition then in every pregnancy there is a:

- 1 in 4 (25%) chance that a **daughter/XX child** will inherit **both working copies of the X-linked genes**. They will be unaffected by the condition and will not be a carrier.
- 1 in 4 (25%) chance that a **daughter/X*X child** will inherit the **working copy of the X-linked gene** from the biological father and the **non-working gene copy (X*)** from the biological mother. This person will be affected or a genetic carrier of the condition, depending on the gene involved and X-inactivation.
- 1 in 4 (25%) chance that a **son/XY child** will inherit the Y chromosome from the biological father and **the working copy of the X-linked gene (X)** from the biological mother. This person will not have the condition.
- 1 in 4 (25%) chance that a **son/X*Y child** will inherit the Y chromosome from the biological father and the **X-linked non-working gene copy (X*)** from the biological mother. In this case, the body cells cannot make gene product in the expected way. This person will have the genetic condition.

In summary, if a female/X*X person with a non-working X* is pregnant with a son/XY child, there is a 50% (1 in 2) chance the child will have the X-linked condition. If a female/X*X person is pregnant with a daughter/XX child, there is a 50% (1 in 2) chance they will have the X-linked condition or be a carrier.

Figure 5:
X-linked inheritance where the biological mother has a non-working copy of the X-linked gene. The non-working copy of the X-linked gene is represented by 'X*'; the working copy by 'X'.



†Depending on gene involved and X-inactivation

If the biological father is affected by an X-linked genetic condition

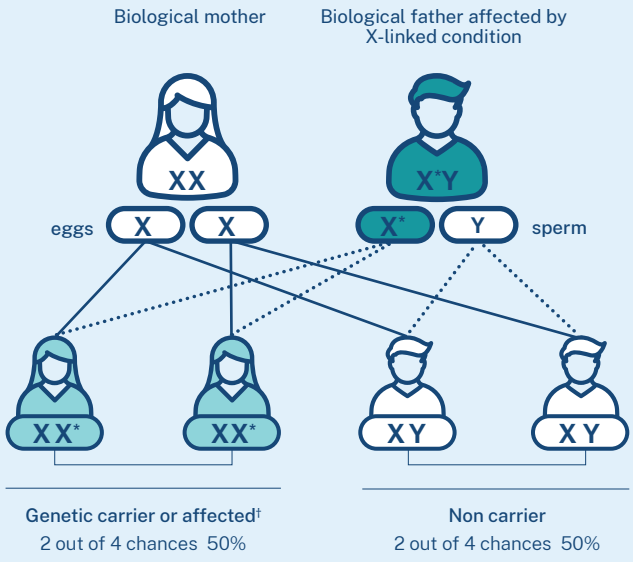
If the biological father is affected by an X-linked genetic condition, their chance of having a child with the condition depends on the sex chromosomes of that child.

As shown in *Figure 6*, the biological father passes a Y chromosome to their sons/XY children and an X chromosome to their daughters/XX children. In every pregnancy:

- All **daughters/XX children** will inherit a **working copy of the X-linked gene (X)** from the biological mother and **non-working gene copy (X*)** from the biological father. They will either be carriers of the X-inked condition or affected by the condition, depending on the gene involved and X-inactivation. They can pass the condition on to their children.
- All **sons/XY children** will inherit the **working X-linked gene copy (X)** from their biological mother and the Y chromosome from their biological father and will therefore not have the condition.

In summary, if a male/X*Y person affected by an X-linked condition conceives a daughter/XX child, they will be a carrier of the condition.
If a male/X*Y person conceives a son/XY child, they will not be affected or a carrier.

Figure 6:
X-linked inheritance where the biological father has an X-linked condition. The non-working X-linked gene copy is represented by 'X*'.



†Depending on gene involved and X-inactivation

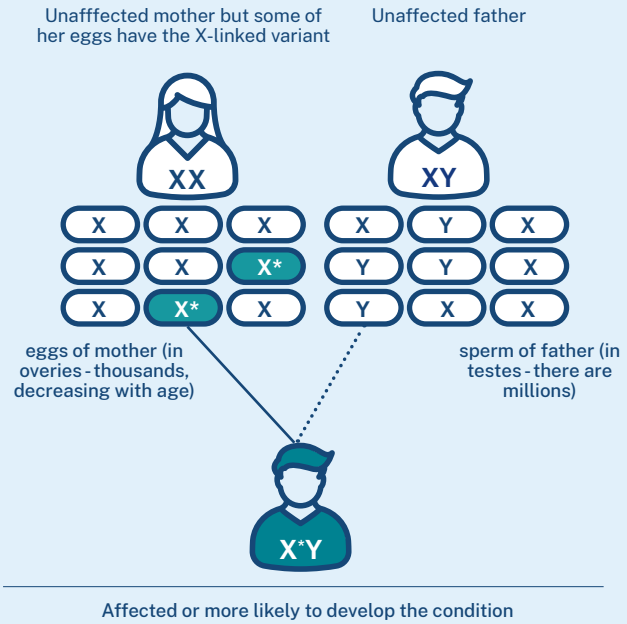
If neither parent has the X-linked gene variant but they have a child with the X-linked condition. This is called *de novo* inheritance.

A *de novo* (meaning 'new') variant occurs when the biological parent has the X-linked variant in their egg or sperm cells only. The biological parent will not be affected by the X-linked condition. However, a child made with the egg or sperm that has the X-linked variant will have the X-linked condition (*Figure 7*). The X-linked condition is therefore 'new' in that child.

As shown in *Figure 7*, the biological mother (XX) has some egg cells with an X-linked variant (X*). The biological mother does not have the X-linked condition and will have no signs or symptoms of the condition. In every pregnancy:

- There is generally a low chance of having a child with the X-linked variant (often approximately 1%). However, if the biological parent has a significant proportion of egg or sperm with the variant, this chance may be up to 50%. This phenomenon is called germline mosaicism.
- In some X-linked conditions germline mosaicism occurs more often than expected. This means that chance of having another pregnancy affected by the *de novo* X-linked condition may be increased. Your doctor or genetic counsellor may be able to provide specific advice on this.

Figure 7:
De novo inheritance of an X-linked condition. The variant is *de novo* (meaning new – occurring for the first time) in the child. Both parents are unaffected – they have the working gene copy, but either the mother or the father has some eggs or sperm with the variant. The non-working X-linked gene copy is represented by 'X*'; the working copy by 'X'.



This information is not a substitute for professional medical advice. Always consult a qualified health professional for personal advice about genetic risk assessment, diagnosis and treatment. Knowledge and research into genetics and genetic conditions can change rapidly. While this information was considered current at the time of publication, knowledge and understanding may have changed since.

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