

Important points

- Genes located on the X chromosome are called X-linked genes. There are very few genes located on the Y chromosome. Women have two X chromosomes; men have an X and a Y
- Some changes in genes stop the gene from working properly: the gene is said to be faulty (mutated). The gene change can be either 'dominant' or 'recessive'
- A woman who has a 'recessive' gene change in one of her X-linked gene copies and the other copy has the right information, is a carrier of the recessive faulty gene and will generally not be affected by the condition. Males have no 'back-up' working copy and so will generally be affected by the condition if they have the X-linked faulty gene
- A woman who has a 'dominant' change in one of her X-linked gene copies and the other copy has the right information, is a carrier of the dominant faulty gene but will generally be affected
- The expression of genes on the X chromosome is also influenced by **epigenetics** which involves 'switching off' most of one of the X chromosomes in women. This process ensures that women and men have generally the same number of X chromosome genes working in the cell
- X-linked inheritance refers to the pattern of inheritance of a condition caused by a faulty gene on the X. The faulty gene may be recessive or dominant
- Conditions that follow a pattern of **X-linked recessive inheritance** include haemophilia, Duchenne and Becker types of muscular dystrophy and fragile X syndrome
- The chance that a child will inherit an X-linked recessive condition in every pregnancy is different for sons and daughters and depends on whether the mother or father has the faulty gene:
 - When the mother is a carrier of an X-linked recessive faulty gene there is 1 chance in 2 (50%) that a **son** will be affected by the condition and a 1 chance in 2 that a **daughter** will be a carrier like the mother
 - When the father is affected by a condition due to an X-linked recessive faulty gene, **none** of his **sons** will be affected but **all** of his **daughters** will be carriers of the X-linked recessive faulty gene, although they will generally be unaffected by the condition
- Information regarding the appropriateness and availability of testing to determine if a woman is a carrier of an X-linked recessive faulty gene and testing in pregnancy where available and appropriate, can be obtained from the local genetic counselling service
- There are very few conditions that have been shown to follow a pattern of X-linked dominant inheritance. Rett syndrome is one example

Our genes, located on our chromosomes in our cells, provide the information for the growth, development and function of our bodies. When the information in a gene is changed, there is a different message sent to the cells. A change to the genetic code that causes the gene not to work properly is called a **mutation**: the gene is described as faulty (see Genetics Fact Sheet 1).

A faulty (mutated) gene may directly cause a genetic condition (see Genetics Fact Sheets 2, 4 & 5). Having a faulty gene however, may also be beneficial as described in Genetics Fact Sheets 5 & 35.

Inheritance patterns in families of conditions due to faulty genes

The inheritance pattern depends on whether the

- Faulty gene is located on one of the chromosomes numbered 1-22 called an *autosome* or on the X chromosome that is one of the *sex chromosomes* (see Genetics Fact Sheet 1)
- Change to the genetic code that makes the gene faulty is 'recessive' or 'dominant' (see Genetics Fact Sheets 4 & 5)

The four most common patterns of inheritance of genetic conditions due to a change in a single gene in families are therefore described as:

- Autosomal recessive
- Autosomal dominant
- X-linked recessive
- X-linked dominant

This Fact Sheet addresses X-linked recessive and X-linked dominant inheritance. See Genetics Fact Sheets 8 & 9 for information about the other traditional patterns of inheritance.

The inheritance of X-linked recessive faulty genes

Changes in genes on the X chromosome are more commonly 'recessive'. The pattern of inheritance of a condition due to a recessive faulty gene that is located on the X chromosome is called X-linked recessive inheritance.

The effect of an X-linked recessive change in a gene that is part of the X chromosome is different in men and women.

Men who have the faulty gene copy on their X chromosome do not have a partner chromosome with a working copy of the gene and will not be able to send the right information to the cells to make the gene product. Men will therefore be affected by the

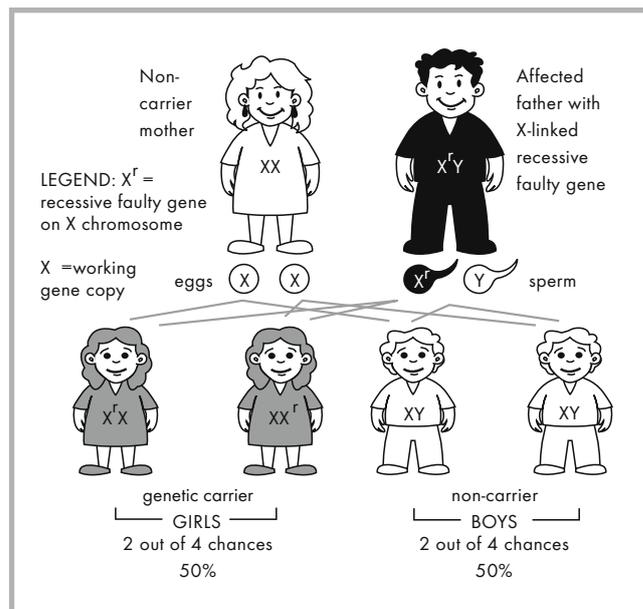
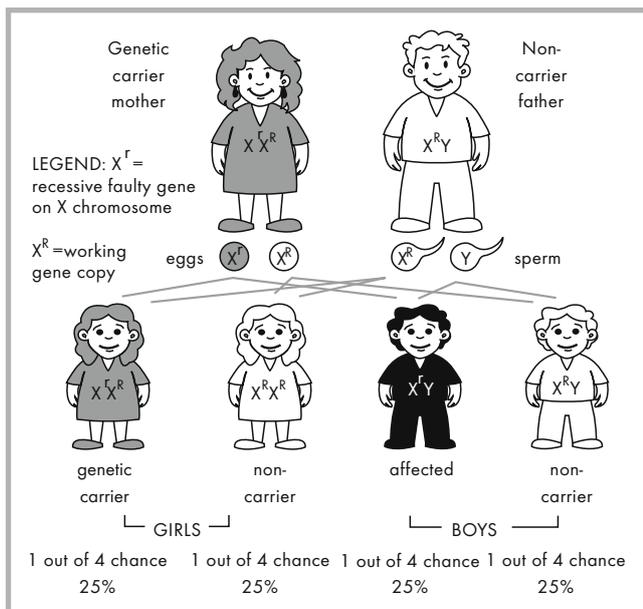


Figure 10.1: X-linked recessive inheritance where the mother is a carrier of the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'; the working copy by 'R'.

Figure 10.2: 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'.

condition due to the X-linked recessive faulty gene being expressed in the cells, even when the gene mutation is recessive.

If the body can still work normally with the available gene product, a **woman** will generally have no health problems as a result of the X-linked faulty gene copy that she is carrying. The change making the gene copy faulty is thus hidden or 'recessive' to the unchanged information in the working copy of the gene.

In some cases, however, women who are carrying a faulty X-linked gene will show the effects. This can be because the normal random process of 'switching off' one of the X chromosomes has been skewed strongly towards switching off the X chromosome carrying the working copy of the gene (see Genetics Fact Sheet 14). As a result, more cells in the woman's body would contain an active X chromosome with the faulty gene copy. This would lead to less of the working gene product being available and the woman will show the effects of the faulty gene, though usually less severely than in men.

What happens if the mother is an unaffected carrier of the faulty X-linked recessive gene?

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

In *Figure 10.1*, where the recessive faulty gene copy is represented by 'r' and the working copy by 'R', the mother is a carrier of an X-linked recessive faulty gene copy and the father has only working copies of the gene, there are four possible combinations in every pregnancy of the genetic information that a child can receive from the parents.

This means that **in every pregnancy** there is

- 1 chance in 4, or 25% chance, that a **son** will inherit the Y chromosome from his father and **the faulty copy of the X-linked gene** from his mother. In this case, no working product or the right amount of the gene product will be able

to be made by his cells. He will generally be affected by the condition

- 1 chance in 4, or 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, or 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 faulty gene
- 1 chance in 4, or 25% chance, that a **daughter** will inherit from her father the **working copy of the X-linked gene** and **the faulty copy** from her mother. She will be a genetic carrier like her mother and will generally be unaffected

What if the father is affected by an X-linked recessive faulty gene?

If the father is affected by an X-linked recessive faulty gene, the chance for passing on the faulty gene is also different for his sons and daughters.

As shown in *Figure 10.2*, as a father passes his Y chromosome to his sons and his X chromosome to his daughters, none of their sons will have the condition and their daughters will also be generally unaffected.

This means that **in every pregnancy**

- His **sons** will inherit the working X-linked faulty gene copy from their mother and will therefore not have the condition
- His **daughters** will inherit from their mother **the working copy of the X-linked gene** and **the faulty copy** from their father. They will be carriers of the X-linked recessive faulty gene and can pass the faulty gene on to their children, although they will generally be unaffected by the condition

Is there always a history of the X-linked recessive condition in the family?

In some cases, there will be men affected by a condition over several generations of a family. For example, there is a history of haemophilia (Genetics Fact Sheet 40) affecting men in the British Royal family.

In some cases, a boy will be affected with a condition due to an X-linked recessive faulty gene but there is no family history of other male members being affected. The change making the X-linked gene faulty in the affected boy may, for unknown reasons, have occurred for the first time (a 'spontaneous' gene change) in a single egg cell, a single sperm cell, or during or shortly after conception.

The condition is described as being due to a new or 'spontaneous' mutation that makes the gene faulty. His mother is not a carrier of the faulty gene and for his siblings to be affected by the same condition would require a change to occur in the same X-linked gene in another egg. The chance of this happening is very low. The affected male could, however, pass on the faulty X-linked gene to his children as described in *Figure 10.2*.

In other cases where there is no family history, the mother is a carrier of the faulty recessive gene on her X chromosome. The change making the X-linked gene faulty in the woman may, for unknown reasons, have occurred

- In either the egg or sperm from which she was conceived
- At the time of her conception
- In the first cell divisions following fertilisation of the egg in early development

Again, the gene change is new or spontaneous and she is the first in her family to carry the faulty gene and pass it on to her children. As she will generally be unaffected, she may never know she is a genetic carrier until she has an affected child.

On the other hand, the change in the gene could have occurred in this way in a previous generation and have been passed down through the family but, by chance, no male family members inherited the faulty gene, or only females may have been conceived.

What types of conditions follow a pattern of X-linked recessive inheritance in families?

Haemophilia, Duchenne and Becker types of muscular dystrophy and fragile X syndrome all follow a pattern of X-linked recessive inheritance (see Genetics Fact Sheets 40, 41 & 42).

Can carriers of X-linked recessive faulty genes be detected?

Following the birth of the first affected boy in the family, genetic testing (see Genetics Fact Sheet 21) may be used to establish whether a woman is a carrier of the X-linked recessive faulty gene or not. This may also provide information for other family members and for planning in her future pregnancies.

In some cases, the gene product is analysed; in others, the gene itself is tested to see if the faulty gene is present.

It is not possible to check every gene on the X chromosome to see if a woman is a carrier of a gene that is faulty.

What can be done if a woman is a carrier of an X-linked recessive faulty gene?

If a woman is a genetic carrier of an X-linked recessive condition, she can find out information about the condition, her risk for having an affected child and discuss her reproductive options with a genetic counsellor (see Genetics Fact Sheet 3).

Testing in pregnancy to determine the presence of the faulty gene may be possible. For more information about prenatal testing options see Genetics Fact Sheet 17C.

Testing of the embryo in association with assisted reproductive technologies (ART) such as preimplantation genetic diagnosis (PGD) may also be possible (see Genetics Fact Sheet 18).

A discussion with a genetic counsellor will assist in enabling a couple to make an informed decision with the most up-to-date information.

The inheritance of X-linked dominant faulty genes

If the body cannot work normally with less than the usual amount of working gene product, a woman may be affected by the X-linked faulty gene that she is carrying. In these cases, the change making the gene copy faulty appears to override or 'dominate' the unchanged information in the working copy of the gene: it is described as an X-linked dominant faulty gene. It is very rare for a woman to have a dominant faulty gene copy on both copies of her X chromosome.

In *Figure 10.3*, where the X-linked dominant faulty gene copy is represented by 'D' and the working copy by 'd', the mother is affected by a condition due to carrying an X-linked dominant faulty gene copy and the father has only working copies of the X-linked gene. There are four possible combinations of the genetic information that a child can inherit from his/her parents. Unlike

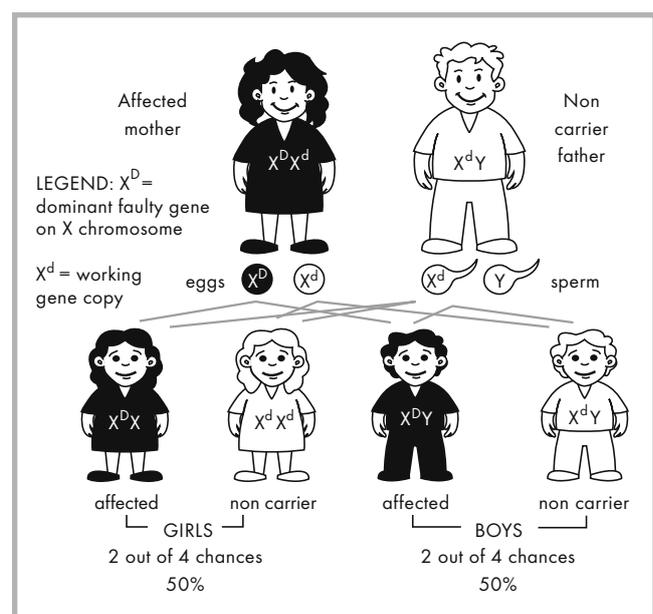


Figure 10.3: X-linked dominant inheritance where the mother carries the faulty X-linked dominant gene and is affected. The faulty copy of the X-linked gene is represented by 'D', the working copy by 'd'.

with X-linked recessive inheritance, there is no difference in risks for their sons and daughters.

When the mother is an affected X-linked dominant faulty gene carrier, **in every pregnancy**, there is

- 1 chance in 2, or 50% chance, that both her sons and daughters will inherit **the faulty gene copy** from her and be affected by the condition. No working gene product or the right amount of the gene product will be able to be made by the cells

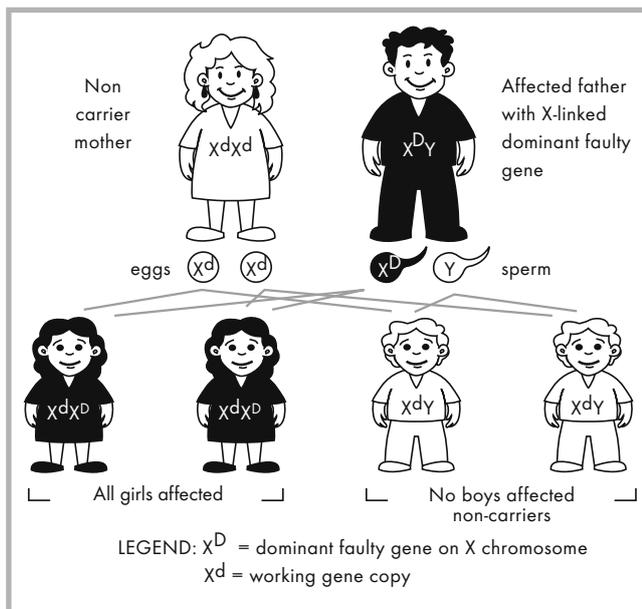


Figure 10.4: X-linked dominant inheritance where the father carries the faulty X-linked dominant gene and is affected. The faulty copy of the X-linked gene is represented by 'D', the working copy by 'd'.

- 1 chance in 2, or 50% that her children (both sons and daughters) will inherit the working copy of the gene from her ('d') and not be affected by the condition

This pattern of inheritance is superficially similar to that of autosomal dominant inheritance (see Genetics Fact Sheet 9).

When the father is affected by a condition due to an X-linked dominant faulty gene (Figure 10.4), the unaffected mother will only give working copies of the gene to her children but the father will pass his X chromosome to his daughters.

This means that **in every pregnancy**:

- None of his **sons** can inherit the faulty gene since the son only inherits from his father the Y chromosome that does not have the faulty gene copy. They will inherit the **working copy** from their mother. None of his sons will have the condition
- All of his **daughters** will inherit from their mother the **working gene copy and the faulty gene copy** from him. All of his daughters will have the condition

What types of conditions follow a pattern of X-linked dominant inheritance in families?

There are very few conditions that have been shown to follow a pattern of X-linked dominant inheritance. Rett syndrome is one example.

The local genetic counselling service can provide information regarding the appropriateness and availability of genetic carrier testing for X-linked dominant conditions (see Genetics Fact Sheet 3)

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 4, 5, 8, 9, 14, 17C, 18, 21, 35, 40, 41, 42

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