

Important points

- Women have two X chromosomes; men have an X and a Y
- Genes located on the X chromosome are called X-linked genes. There are very few genes located on the Y chromosome.
- Some variations in genes stop the gene from working properly: the gene is said to be faulty (mutated). The gene variation can be either 'dominant' or 'recessive'
- A woman who has a 'recessive' gene variation in one of her X-linked gene copies and the other copy is working as it should, is a carrier of the recessive faulty gene. She 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 is working as it should, is a carrier of the dominant faulty gene. She will generally be affected by the condition
- 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 each cell of a woman. 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 chromosome. The faulty gene may be recessive or dominant
- Conditions that follow a pattern of **X-linked recessive inheritance** include haemophilia and Duchenne and Becker types of muscular dystrophy
- 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% chance) that a **son** will be affected by the condition and a 1 chance in 2 that a **daughter** will be a usually unaffected genetic 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 can be obtained from the local genetic counselling service.
- Information regarding the appropriateness and availability of testing in pregnancy or testing of an embryo for an X-linked condition 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 variation 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 or predispose a person to develop it (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*; (See Genetics Fact Sheet 1) or Faulty gene is located on the X chromosome that is one of the sex *chromosomes* (see Genetics Fact Sheet 1)
- Variation in 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

Variations 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 gene variation 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. So they will not be able to send the right information to the cells to make the gene product. Men will be affected by the condition due to the X-linked recessive faulty gene being expressed in the cells, even when the gene variation (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 carrying the X-linked faulty gene copy. The variation making the gene copy faulty is thus hidden or 'recessive' to the usual 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).

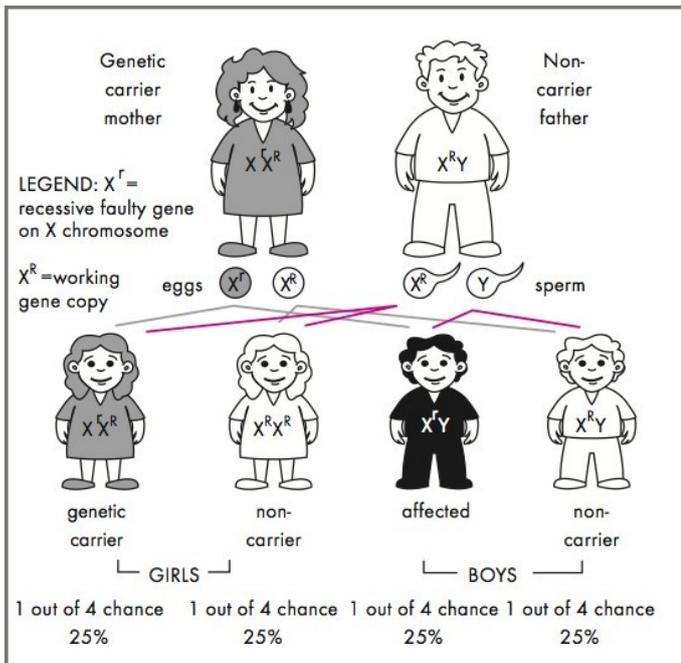


Figure 10.1: X-linked recessive inheritance where the mother is a carrier of the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'; the working copy by 'R'.

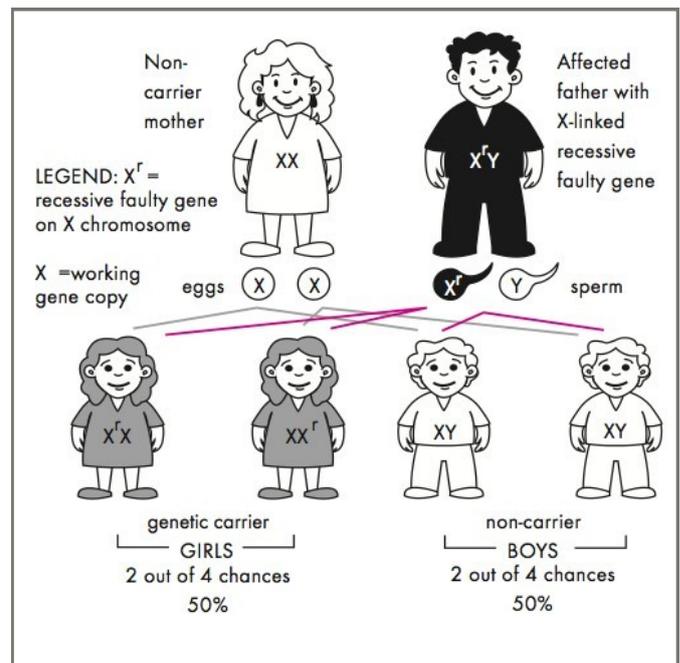


Figure 10.2: X-linked recessive inheritance where the father has the faulty copy of the X-linked gene. The X-linked recessive faulty gene copy is represented by 'r'.

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 the child can receive from the parents.

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 **the faulty copy of the X-linked gene** from his mother. In this case, no working gene 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, (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 faulty gene

- 1 chance in 4, (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 of the condition like her mother and will usually 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. Their daughters will also be usually unaffected. There are four possible combinations in every pregnancy of the genetic information that the child can receive from the parents

This means that **in every pregnancy**

- All their **sons** will inherit the working X-linked faulty gene copy from their mother and will therefore not have the condition
- All of their **daughters** will inherit the **working copy of the X-linked gene** from their mother **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. They will usually 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 variation 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, it 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 variation 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 variation 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 usually be unaffected, she may never know she is a genetic carrier until she has an affected child.

On the other hand, the variation 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 and Duchenne and Becker types of muscular dystrophy all follow a pattern of X-linked recessive inheritance (see Genetics Fact Sheets 40 & 41).

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 currently not feasible 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.

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

Information in this Fact Sheet is sourced from:

Harper P. (2010). *Practical Genetic Counseling (7th Edition)*. London: Arnold

Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) [online]. Available from: <http://www.ncbi.nlm.nih.gov/omim/> [Accessed June 2012]

Read A and Donnai D. (2010). *New Clinical Genetics (2nd Edition)*. Bloxham, Oxfordshire: Scion Publishing Ltd

Trent R. (1997). *Molecular medicine*. 2nd ed. New York. Churchill Livingstone Ltd

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Author/s: A/Prof Kristine Barlow-Stewart

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