

## How does X-inactivation affect me or my child ?

The effects of X-inactivation depend on whether an X chromosome carries a clinically significant genetic change. For almost all pathogenic variants of X chromosome genes identified to date (2019), all boys and men who inherit such a variant, would be expected to be affected by the genetic change. The possible number and severity of symptoms for girls and women with the same variant however can vary considerably depending on their own **unique pattern of X-inactivation**. Some girls and women may show no, or mild, symptoms while others may be more severely affected.

A girl or woman with an X chromosome variant who does not appear to show any symptoms can be described as a **carrier**. She may have skewed X-inactivation that favours the inactivation of the X chromosome carrying the variant. If she passes her variant on to her son, he will be affected. If the variant is passed on to a daughter, the child's symptoms will depend on her own unique pattern of X-inactivation, she could be a carrier herself, or have mild, moderate or severe symptoms.

**X chromosome aneuploidy:** Some people, male and female, have **one or more additional X chromosomes**. Research has shown that when this happens, all X chromosomes apart from one are inactivated. It is thought that significantly skewed X-inactivation may contribute to the symptoms experienced by people with additional X chromosomes. The number and type of genes that remain active on the inactivated X chromosomes may also have an affect.

**X chromosome translocation:** For some people, part of an X chromosome has broken off and joined an autosome (chromosomes 1-22). This is known as a **chromosome X:autosomal translocation** and symptoms can vary depending on whether the translocation is **balanced** (when no genetic material has been lost and/or duplicated) or **unbalanced** (when some genetic material has been lost and/or duplicated) as well as whether the **X-inactivation centre (XIC)** is silencing the autosome, and how much X chromosome is lost or is no longer being silenced.

For example, some girls and women with an **unbalanced X:autosomal translocation** can have a very large duplication of autosomal DNA but because it is located on the same chromosome as the **XIC**, the additional genes are silenced and symptoms can be much milder than would be expected in someone with the duplication alone. Similarly, some females with **balanced X:autosomal translocations** can be affected, although no genetic material has been lost or gained, since the **XIC** is silencing genes on the autosome.

A number of translocation information guides are freely available on Unique's website [www.rarechromo.org](http://www.rarechromo.org).

## X-inactivation test

The most common test used to investigate X-inactivation patterns is known as **methylation** (the addition of chemical groups) analysis. DNA is extracted from a blood sample and the methylation status of a gene or genes on the X chromosome is analysed. Gene methylation typically represses (slows down or stops) gene activity so can be used as an indication of which X chromosome has been inactivated.

X-inactivation tests are usually performed on the genetic material located in blood samples. Since X-inactivation varies between tissues, a non-skewed inactivation result in blood does not necessarily mean there is not a significantly skewed X-inactivation in other organs such as the brain, where X-linked genes are highly expressed. Inactivation ratios of two X chromosomes between 50:50 and 79:21 are considered as indicating random X-inactivation, ratios between 80:20 and 100:0 indicate skewed X-inactivation.

## Inform Network Support



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Understanding Chromosome & Gene Disorders

# X-inactivation

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## What are chromosomes ?

Our bodies are made up of many different types of cells, most of which contain our chromosomes. Chromosomes are made from DNA and contain genes. They usually come in pairs, with one member of each chromosome pair being inherited from each parent. Most cells have 23 pairs of chromosomes (a total of 46). Egg and sperm cells, however, have a single copy of each chromosome pair, so that when these cells join together at conception, the chromosomes pair up to make a total of 46. We usually have 22 chromosomes (called [autosomes](#)), numbered 1-22 roughly according to decreasing size, and two sex chromosomes, that determine the characteristics associated with biological sex. Males commonly have one X chromosome and one Y chromosome (XY), and females usually have two X chromosomes (XX).

Chromosomes can't be seen with the naked eye but if cells are prepared in a specific way, the chromosomes can be stained and viewed under a microscope. This image shows the chromosomes present in a typical male cell.



Chromosomes pairs 1-22, X and Y (male)

## What is X-inactivation ?

X-inactivation is a process that occurs naturally, usually inactivating all but one X chromosome in each cell of our body. The chromosome is 'silenced' by being wrapped up and packaged into a dense structure that only allows a few select genes to remain active. X-inactivation, is described as an [epigenetic](#) change, this means it is not a change within the DNA sequence.

## Why are X chromosomes inactivated ?

It is thought that our cells should only have a single active X chromosome. This is normally the case in boys and men since they usually only have one X chromosome in each cell. Girls and women however usually have two X chromosomes, so one is 'automatically' inactivated. It is thought that this occurs naturally to stop too many X chromosome genes from being active. This means that most people, regardless of gender, will have similar activity from genes located on the X chromosome.

## Which X chromosome is inactivated ?

The initial choice of which X chromosome is inactivated is thought to occur during very early embryonic development. The process is commonly believed to be random.

Each cell is thought to independently inactivate one copy of the X chromosome. In girls and women, this can be the copy that was passed on from the father or the one passed on by the mother. Boys and men usually have a single X chromosome passed on by their mother; it is not inactivated.

Once an X chromosome is inactivated it is presumed to remain inactive, and when that cell divides to make more cells as we grow and develop, any cell that is produced from that cell will also have the same X chromosome inactivated.

This means that new cells that originate from a particular cell are said to have [skewed X-inactivation](#). Some body parts may have [mosaic X-inactivation](#), this means that in a typical XX female, some cells will have the maternal X chromosome inactivated, and some will have the paternal X chromosome inactivated.

Which X chromosome is inactivated would not ordinarily be of any concern unless one of the X chromosomes carries a mutation, also known as a variant, that can affect health, growth and development (such variants are called [pathogenic](#)).

## Is X-inactivation random ?

Although X-inactivation is commonly believed to be random, this is not always thought to be the case. If it were a random event, you could expect half of girls and women who have inherited a pathogenic X chromosome variant to be affected. However, for the majority (but not all) pathogenic X chromosome variants identified to date (2019), fewer females are identified with symptoms of similar severity to those of boys who have a variant of the same gene.

There are a number of simple (and more complex) theories behind non-random X-inactivation. It is possible that X chromosomes with certain variations carry a physical characteristic that makes them more likely to be preferentially inactivated. This would result in [skewed X-inactivation](#) of the chromosome with the variant. Alternatively, it's possible that cells containing a specific X chromosome variant may not replicate well (may not make copies of themselves well as we grow) so more cells with the unaffected X chromosome would be used to form our bodies.

## How does X-inactivation work ?

There is a 'control centre' located on each X chromosome that carries the information necessary for X inactivation. This is called the [X-inactivation centre \(XIC\)](#). If XIC is missing (deleted), the chromosome will not be inactivated. If XIC is moved ([translocated](#)) to a different chromosome, all or part of that chromosome will be inactivated instead.

XIC contains four important genes involved in X-inactivation. These genes do not code for proteins, but for a product similar to DNA known as RNA. The genes are known as [Xist](#), [Tsix](#), [Jpx](#) and [Ftx](#). The [Xist](#) gene is the most important, it produces Xist RNA that 'coats' the inactive X chromosome. The inactive X chromosome is also modified in many other different ways at the molecular level to maintain gene silencing.

## Are all genes inactivated on the 'inactive' X ?

Not all genes on the 'inactive' X chromosome are actually inactivated. Many genes escape inactivation; it has been estimated that up to one quarter of genes on the inactive X chromosome can escape inactivation. It is also possible that a different number of genes escape inactivation in the same organ in different people, and that the number of genes that escape inactivation in different tissues or organs can vary.

Some genes that are not inactivated may have the same activity level as the same gene on the active X chromosome but others may have a lower activity level.

Many of the genes which escape inactivation are actually also present on the Y chromosome. These 'matching' regions of chromosome X and Y are called [pseudoautosomal regions \(PAR\)](#). This is because these genes are present as two copies in males and females, just as other genes are in autosomal chromosomes (1-22). Other genes that can escape inactivation are scattered across the whole chromosome.

