How will this affect me or my child?

Effects of chromosome and gene anomalies vary greatly between individuals; even members of the same family with the same genetic change can have different symptoms. Effects are dependent on what and how much genetic material is altered as well as the unique genetic background of each individual and other environmental factors.

Genetic anomalies on the X chromosome are often referred to as X-linked. Some X-linked genetic changes are known to affect intellectual abilities and/or cause physical and functional changes to our bodies. Such changes are thought to mostly and/or more severely affect males (XY) since they do not usually have a second functional X chromosome to compensate for any altered or loss of gene function. It is, in most cases identified so far, more common for females with an X-linked disorder to show no symptoms, or have milder symptoms compared to males. This is why some X-linked disorders are unknowingly passed on from an unaffected 'carrier' mother to an affected son. However, this is not always the case and there is increasing evidence that females who carry X-linked genetic changes can be affected by them in a range of different ways and severities. If, and how much, a female might be affected is generally thought to depend on which X chromosome is inactivated during the natural process of X inactivation as well as which genes escape inactivation. Which X chromosome is inactivated can vary between different cells and during different stages of development.

There are a few X-linked conditions where females are primarily affected. This can be either because boys with these genetic variants sadly do not usually survive (e.g. MECP2, CDKL5, DDX3X, SMC1A, STAG2 or NAA10), or because the boys are not affected (e.g. PCDH19) or less severely affected (e.g. EFNB1). In some cases, somatic mosaicism is involved (this is when only some of the cells in or our bodies carry the genetic change) and boys can be affected (e.g. PCDH19).

It is now also apparent that different changes to the same gene can cause different disorders. For some genes, whether males and/or females are affected may depend on the exact gene sequence change.

Why did this happen and can it happen again?

X chromosome deletions, duplications and gene variants can be inherited from an unaffected or affected parent, or happen as a new event (*de novo*).

Genetic changes can occur during the formation of eggs or sperm or during the complicated replication process that is needed to produce new cells as we grow and develop. It is important to know that nothing could have been done to prevent a change from happening. They are natural events that no lifestyle, dietary or environmental factors are known to cause. There is nothing that anyone did before or during pregnancy to cause the change.

If a father carries the genetic change, he has a 50% chance of passing it on to a daughter, but is not expected to pass it on to a son (fathers pass on a Y chromosome to boys). A mother would have a 50% chance of passing on the genetic change to either a boy or a girl. If the change is classified as *de novo*, there is still a small chance (<1%) of passing it on if it is present in egg or sperm cells but not other cells of the body (this is known as germline mosaicism).

Inform Network Support

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Version 1 (AP)

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Company Number 5460413

Understanding Chromosome & Gene Disorders

Chromosome X Deletions, Duplications & Single gene disorders

Learning disability and developmental delay

rarechromo.org

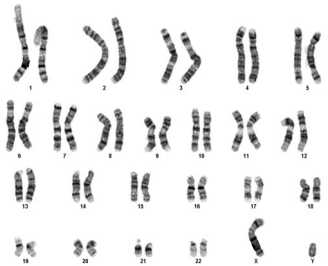
What is the X chromosome?

Our bodies are made up of many different types of cells, most of which contain our chromosomes.

Chromosomes come in pairs; one member of each pair is usually inherited from each parent. We have 23 pairs of chromosomes (making a total of 46). Eggs and sperm, however, have a single copy of each chromosome, so only have 23 chromosomes.

22 of our chromosome pairs are called autosomes, numbered 1-22 roughly according to decreasing size. We also have a pair of sex chromosomes that determine the characteristics associated with biological sex. Males usually have one X 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. The image to the right shows the chromosomes present in a typical male (XY) cell.



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

Chromosomes are made from incredibly long and highly compacted pieces of a complex structure called DNA. DNA can be described as a sequence (or code) of four letters (known as bases): G, A, T and C. Parts of these sequences code for genes - the 'instructions' that our bodies use for many functions including the control of growth and development. We are thought to have roughly 20,000 genes, about 850 of which are found on the X chromosome.

Since females usually have two X chromosomes and males usually have one, the effects of having a genetic change on an X chromosome varies considerably between males and females. There is also the added complication that one X chromosome in a female is almost completely 'switched off'. This is known as X inactivation, *Unique* publishes a separate guide to X inactivation freely available at www.rarechromo.org.

What are deletions and microdeletions?

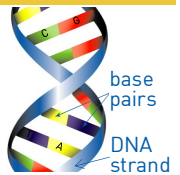
A chromosomal deletion is the loss of a piece of genetic material from a chromosome. Deletions vary in size; those that are too small to be seen under the microscope are called microdeletions. *Unique* publishes a separate general guide to deletions and microdeletions.

What are duplications and microduplications?

A chromosomal duplication is the presence of an extra copy of a piece of genetic material from a chromosome. Duplications vary in size; those that are too small to be seen under the microscope are called microduplications. *Unique* publishes a separate general guide to duplications and microduplications.

What are gene variants?

A gene variant is a change to a gene sequence (meaning a change to one or more of the bases G, A, T or C). *Unique* publishes a separate general guide to single gene disorders.

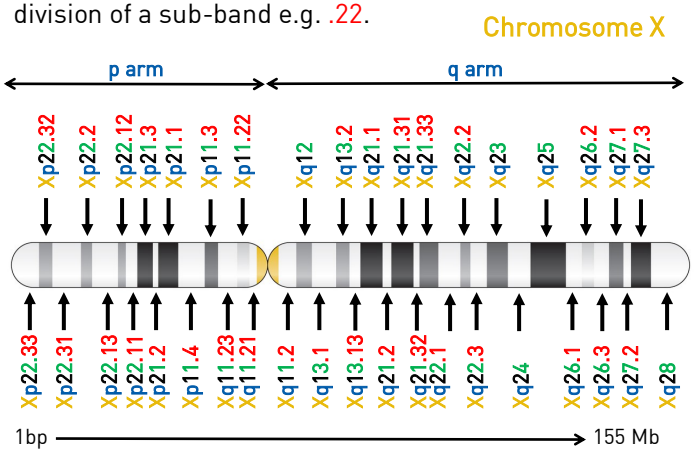


Genetic changes are described as pathogenic, meaning 'disease causing', if they affect health and development. When it's difficult to establish if a genetic change is associated with observed symptoms, it is classified as having uncertain pathogenicity [for single gene disorders the terminology is 'variant of uncertain significance' (VUS or VOUS)]. Some genetic changes are classified as likely pathogenic when they are strongly believed to cause symptoms. Further research and diagnoses are required to understand more about these changes. There are also many genetic changes that are thought to have no ill effect, these are known as benign.

The X chromosome

The X chromosome consists of two 'arms' - a short 'p' arm, and a longer 'q' arm. Each arm can be identified as a series of bands. The bands on each arm are numbered starting where the two arms meet (called the centromere and numbered 10) and finishing at the arm extremities.

The location of genes and changes to the X chromosome are often described according to which 'arm' they are on and which 'band' they are in. Descriptions start with X followed by the arm letter, p or q, then the number of the region e.g. 1, followed by the band number e.g. 1, then any smaller sub-bands such as .2 or an even smaller division of a sub-band e.g. .22.



More precise locations (as well as the size of deletions and duplications) are described according to their base pair (bp) coordinates. The start of the p arm being base pair number 1 and the end of the q arm being the last base to be counted. Chromosome X consists of roughly 155 million base pairs (155 Mb). Gene variants are described according their base pair position within a gene.

Genetic test results

An example result of a chromosome microarray (CMA) test, that can identify deletions and duplications, is shown here for a micro-duplication within band Xp11.22 between base pair (bp) numbers 53374149 and 53656331: arr[hg38]Xp11.22(53374149-53656331)x3. Hg38 signifies which genome assembly was used (this is important since base pair positions change in different assemblies). x3 signifies three copies of the sequence were found (one copy would be expected for a male and two for a female).

An example result of a DNA sequencing test (e.g. WES or WGS), that can identify gene variants, is shown here for the PCDH19 gene: p.Asp558His (D558H) (GAC→CAC): c.1672 G→C in exon 1 of the PCDH19 gene (NM_001184880.1). p.Asp558His (D558H) signifies the protein change; GAC→CAC signifies the gene sequence change; c.1672 signifies the base pair position of the change within the gene sequence; exon 1 signifies which part of the gene has been altered; NM denotes the reference sequence used.