X chromosome

The X chromosome is one of the two sex chromosomes in humans (the other is the Y chromosome). The sex chromosomes form one of the 23 pairs of human chromosomes in each cell. The X chromosome spans about 155 million DNA building blocks (base pairs) and represents approximately 5 percent of the total DNA in cells.

Each person normally has one pair of sex chromosomes in each cell. Females have two X chromosomes, while males have one X and one Y chromosome. Early in embryonic development in females, one of the two X chromosomes is randomly and permanently inactivated in cells other than egg cells. This phenomenon is called X-inactivation or lyonization. X-inactivation ensures that females, like males, have one functional copy of the X chromosome in each body cell. Because X-inactivation is random, in normal females the X chromosome inherited from the mother is active in some cells, and the X chromosome inherited from the father is active in other cells.

Some genes on the X chromosome escape X-inactivation. Many of these genes are located at the ends of each arm of the X chromosome in areas known as the pseudoautosomal regions. Although many genes are unique to the X chromosome, genes in the pseudoautosomal regions are present on both sex chromosomes. As a result, men and women each have two functional copies of these genes. Many genes in the pseudoautosomal regions are essential for normal development.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. The X chromosome likely contains 800 to 900 genes that provide instructions for making proteins. These proteins perform a variety of different roles in the body.

Health Conditions Related to Chromosomal Changes

The following chromosomal conditions are associated with changes in the structure or number of copies of X chromosome.

46,XX testicular disorder of sex development

In most individuals with 46,XX testicular disorder of sex development, the condition results from an abnormal exchange of genetic material between chromosomes (translocation). This exchange occurs as a random event during the formation of sperm cells in the affected person's father. The translocation affects the gene responsible for development of a fetus into a male (the *SRY* gene). The *SRY* gene, which is normally found on the Y chromosome, is misplaced in this disorder, almost

always onto an X chromosome. A fetus with an X chromosome that carries the *SRY* gene will develop as a male despite not having a Y chromosome.

48,XXYY syndrome

48,XXYY syndrome is caused by the presence of an extra X chromosome and an extra Y chromosome in a male's cells. Extra genetic material from the X chromosome interferes with male sexual development, preventing the testes from functioning normally and reducing the levels of testosterone in adolescent and adult males. Extra copies of genes from the pseudoautosomal regions of the extra X and Y chromosome contribute to the signs and symptoms of 48,XXYY syndrome; however, the specific genes have not been identified.

intestinal pseudo-obstruction

Intestinal pseudo-obstruction, a condition characterized by impairment of the muscle contractions that move food through the digestive tract (peristalsis), can be caused by genetic changes within the X chromosome.

Some individuals with intestinal pseudo-obstruction have mutations, duplications, or deletions of genetic material in the X chromosome that affect the *FLNA* gene. Researchers believe that these genetic changes may impair the function of the filamin A protein, causing abnormalities in the cytoskeleton of nerve cells (neurons) in the gastrointestinal tract. These abnormalities result in impaired peristalsis, which causes abdominal pain and the other gastrointestinal symptoms of intestinal pseudo-obstruction.

Deletions or duplications of genetic material that affect the *FLNA* gene can also include adjacent genes on the X chromosome. Changes in adjacent genes may account for some of the other signs and symptoms, such as neurological abnormalities and unusual facial features, that occur in some affected individuals.

Klinefelter syndrome

Klinefelter syndrome is caused by the presence of one or more extra copies of the X chromosome in a male's cells. Extra genetic material from the X chromosome interferes with male sexual development, preventing the testes from functioning normally and reducing the levels of testosterone (a hormone that directs male sexual development). A shortage of testosterone can lead to delayed or incomplete puberty, genital abnormalities, breast enlargement (gynecomastia), reduced facial and body hair, and an inability to have biological children (infertility). Children with Klinefelter syndrome may also have learning disabilities, delayed speech and language development, and a shy and unassuming personality.

Typically, people with Klinefelter syndrome have one extra copy of the X chromosome in each cell, for a total of two X chromosomes and one Y chromosome (47,XXY). Less commonly, affected individuals may have two or three extra X

chromosomes (48,XXXY or 49,XXXXY). As the number of extra sex chromosomes increases, so does the risk of learning problems, intellectual disability, birth defects, and other health issues.

Some people with features of Klinefelter syndrome have the extra X chromosome in only some of their cells; in these individuals, the condition is described as mosaic Klinefelter syndrome (46,XY/47,XXY). Individuals with mosaic Klinefelter syndrome may have milder signs and symptoms, depending on how many cells have an additional X chromosome.

microphthalmia with linear skin defects syndrome

A deletion of genetic material in a region of the X chromosome called Xp22 causes microphthalmia with linear skin defects syndrome. This region includes a gene called *HCCS*, which carries instructions for producing an enzyme called holocytochrome c-type synthase. This enzyme helps produce a molecule called cytochrome c. Cytochrome c is involved in a process called oxidative phosphorylation, by which mitochondria generate adenosine triphosphate (ATP), the cell's main energy source. It also plays a role in the self-destruction of cells (apoptosis).

A deletion of genetic material that includes the *HCCS* gene prevents the production of the holocytochrome c-type synthase enzyme. In females (who have two X chromosomes), some cells produce a normal amount of the enzyme and other cells produce none. The resulting overall reduction in the amount of this enzyme leads to the signs and symptoms of microphthalmia with linear skin defects syndrome.

In males (who have only one X chromosome), a deletion that includes the *HCCS* gene results in a total loss of the holocytochrome c-type synthase enzyme. A lack of this enzyme appears to be lethal very early in development, so almost no males are born with microphthalmia with linear skin defects syndrome. A few affected individuals with male appearance but who have two X chromosomes have been identified.

A reduced amount of the holocytochrome c-type synthase enzyme can damage cells by impairing their ability to generate energy. In addition, without the holocytochrome c-type synthase enzyme, the damaged cells may not be able to undergo apoptosis. These cells may instead die in a process called necrosis that causes inflammation and damages neighboring cells. During early development this spreading cell damage may lead to the eye and skin abnormalities characteristic of microphthalmia with linear skin defects syndrome.

triple X syndrome

Triple X syndrome (also called 47,XXX or trisomy X) results from an extra copy of the X chromosome in each of a female's cells. Females with triple X syndrome have three X chromosomes, for a total of 47 chromosomes per cell. An extra copy of the X

chromosome is associated with tall stature, learning problems, and other features in some girls and women.

Some females with triple X syndrome have an extra X chromosome in only some of their cells. This phenomenon is called 46,XX/47,XXX mosaicism.

Females with more than one extra copy of the X chromosome (48,XXXX or 49,XXXXX) have been identified, but these chromosomal changes are rare. As the number of extra sex chromosomes increases, so does the risk of learning problems, intellectual disability, birth defects, and other health issues.

Turner syndrome

Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth, leading to short stature, ovarian malfunction, and the other features of Turner syndrome.

About half of individuals with Turner syndrome have monosomy X (45,X), which means each cell in an individual's body has only one copy of the X chromosome instead of the usual two sex chromosomes. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely absent.

Some women with Turner syndrome have a chromosomal change in only some of their cells, which is known as mosaicism. Some cells have the usual two sex chromosomes (either two X chromosomes or one X chromosome and one Y chromosome), and other cells have only one copy of the X chromosome. Women with Turner syndrome caused by X chromosome mosaicism (45,X/46,XX or 45,X/46,XY) are said to have mosaic Turner syndrome.

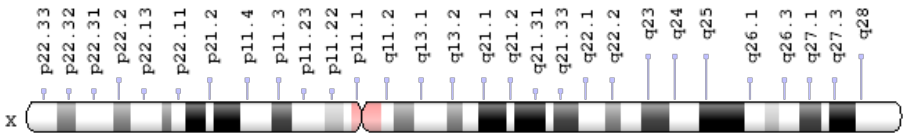
Researchers have not determined which genes on the X chromosome are responsible for most of the features of Turner syndrome. They have, however, identified one gene called *SHOX* that is important for bone development and growth. The *SHOX* gene is located in the pseudoautosomal regions of the sex chromosomes. Missing one copy of this gene likely causes short stature and skeletal abnormalities in women with Turner syndrome.

other chromosomal conditions

Chromosomal conditions involving the sex chromosomes often affect sex determination (whether a person has the sexual characteristics of a male or a female), sexual development, and the ability to have children (fertility). The signs and symptoms of these conditions vary widely and range from mild to severe. They can be caused by missing or extra copies of the sex chromosomes or by structural changes in the chromosomes.

Chromosome Diagram

Geneticists use diagrams called idiograms as a standard representation for chromosomes. Idiograms show a chromosome's relative size and its banding pattern, which is the characteristic pattern of dark and light bands that appears when a chromosome is stained with a chemical solution and then viewed under a microscope. These bands are used to describe the location of genes on each chromosome.



Credit: Genome Decoration Page/NCBI

Additional Information & Resources

MedlinePlus

- Encyclopedia: Chromosome
  https://medlineplus.gov/ency/article/002327.htm

Additional NIH Resources

- National Human Genome Research Institute: Chromosome Abnormalities
  https://www.genome.gov/11508982/
- National Human Genome Research Institute: Studies Expand Understanding of X Chromosome (March 2005)
  https://www.genome.gov/13514331/

GeneReviews

- Microphthalmia with Linear Skin Defects Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK7041
- Nonsyndromic 46,XX Testicular Disorders of Sex Development
  https://www.ncbi.nlm.nih.gov/books/NBK1416

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Chromosomes,+Human,+X%5BMAJR%5D%29+AND+%28X+Chromosome%5BTI%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

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