X chromosome

Description

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 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 usually has one pair of sex chromosomes in each cell. Females typically have two X chromosomes, while males typically have one X and one Y chromosome. Early in the embryonic development of people with two X chromosomes, one of the 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 people with two X chromosomes have only one functional copy of the X chromosome in each cell. Because X-inactivation is random, normally, the X chromosome inherited from one parent is active in some cells, and the X chromosome inherited from the other parent 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, males and females each have two functional copies of these genes. Many genes in the pseudoautosomal regions are essential for normal development.

Identifying the 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 900 to 1,400 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 difference of sex development

46,XX testicular difference of sex development is a condition in which individuals with

two X chromosomes in each cell, the pattern generally found in females, have a typically male appearance. In most individuals with 46,XX testicular difference of sex development, the condition is caused by 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 the development of a fetus into a male (the *SRY* gene). The *SRY* gene, which is normally found on the Y chromosome, is misplaced in people with this condition and is almost always located on an X chromosome. A fetus with an X chromosome that carries the *SRY* gene will develop sex characteristics that are typical for males despite not having a Y chromosome.

48,XXXY syndrome

48,XXXY syndrome is a chromosomal condition that causes intellectual disabilities, developmental delays, physical differences, and an inability to have biological children (infertility). Individuals with 48,XXXY syndrome have the usual single Y chromosome plus three copies of the X chromosome, for a total of 48 chromosomes in each cell.

Having extra copies of multiple genes on the X chromosome affects many aspects of development, including sexual development before birth and at puberty. Researchers are working to determine which genes contribute to the specific developmental and physical differences that occur in people with 48,XXXY syndrome.

48,XXXY syndrome is sometimes described as a variation of another sex chromosome disorder called Klinefelter syndrome (described below). However, the features of 48, XXXY syndrome tend to be more severe than those of Klinefelter syndrome, and they affect more parts of the body. As doctors and researchers have learned more about the differences between these sex chromosome disorders, they have started to consider them separate conditions.

48,XXYY syndrome

48,XXYY syndrome is a chromosomal condition that causes infertility, developmental and behavioral disorders, and other health problems. This condition is caused by the presence of an extra X chromosome and an extra Y chromosome in cells. Extra genetic material from the X chromosome interferes with sexual development, though affected individuals are typically assigned male at birth. Affected individuals often have small testes that do not function normally and lead to a reduction in the levels of testosterone (a hormone that directs male sexual development). Extra copies of genes from the pseudoautosomal regions of the extra X and Y chromosomes likely contribute to the signs and symptoms of 48,XXYY syndrome.

49,XXXXY syndrome

49,XXXXY syndrome is a chromosomal condition that causes intellectual disabilities, developmental delays (especially in speech and language), changes in sex characteristics and other physical features, and infertility. Individuals with 49,XXXXY syndrome have the usual single Y chromosome plus four copies of the X chromosome,

for a total of 49 chromosomes in each cell.

Having extra copies of multiple genes on the X chromosome affects many aspects of development, including sexual development before birth and at puberty. Researchers are working to determine which genes contribute to the specific developmental and physical differences that occur in people with 49,XXXXY syndrome.

49,XXXXY syndrome is sometimes described as a variation of Klinefelter syndrome (described below). However, the features of 49,XXXXY syndrome tend to be more severe than those of Klinefelter syndrome, and they affect more parts of the body. As doctors and researchers have learned more about the differences between these sex chromosome disorders, they have started to consider them separate conditions.

Intestinal pseudo-obstruction

Intestinal pseudo-obstruction can be caused by genetic changes in the X chromosome. This condition impairs the coordinated waves of muscle contractions that move food through the digestive tract (peristalsis).

Some individuals with intestinal pseudo-obstruction have duplications or deletions of genetic material on the X chromosome that affect the *FLNA* gene. The protein produced from this gene, filamin A, helps form the branching network of filaments called the cytoskeleton, which gives structure to cells and allows them to change shape and move.

Researchers believe that the changes in the X chromosome that affect the *FLNA* gene impair the function of the filamin A protein. Studies suggest that impaired filamin A function affects the shape of cells in the smooth muscles of the gastrointestinal tract during development before birth, causing abnormalities in the layering of these muscles. Smooth muscles line the internal organs; they contract and relax without being consciously controlled. In the digestive tract, abnormal layering of these muscles may interfere with peristalsis.

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 individuals with intestinal pseudo-obstruction.

Klinefelter syndrome

Klinefelter syndrome is a chromosomal condition that can affect physical and intellectual development. It is caused by an extra copy of the X chromosome. Individuals with Klinefelter syndrome have a single Y chromosome plus two copies of the X chromosome, for a total of 47 chromosomes in each cell (47,XXY).

Having an extra copy of genes on the X chromosome affects many aspects of development, including sexual development before birth and at puberty. Researchers are working to determine which genes contribute to the specific developmental and physical differences that can occur in people with Klinefelter syndrome.

Some people with features of Klinefelter syndrome have an extra X chromosome in only some of their cells; other cells have one X and one Y chromosome. In these individuals, the condition is described as mosaic Klinefelter syndrome (46,XY/47,XXY). People with mosaic Klinefelter syndrome may have milder signs and symptoms than those with the extra X chromosome in all of their cells, depending on what proportion of cells have the additional 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 condition is characterized by small or poorly developed eyes (microphthalmia) and unusual linear skin markings on the head and neck.

The Xp22 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, which allows mitochondria to generate adenosine triphosphate (ATP), the cell's main energy source. It also plays a role in controlled cell death (apoptosis).

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

In people who have only one X chromosome (typical of males), 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 babies with only one X chromosome are born with microphthalmia with linear skin defects syndrome. In a few cases, individuals with microphthalmia with linear skin defects syndrome have two X chromosomes but have sex characteristics that are typical for males.

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 that are characteristic of microphthalmia with linear skin defects syndrome.

Trisomy X

Trisomy X (also called triple X syndrome or 47,XXX) is caused by an extra copy of the X chromosome in each cell. People with trisomy X have three X chromosomes, for a total of 47 chromosomes in each cell. An extra copy of the X chromosome can be associated

with tall stature, developmental delays, learning problems, and other features.

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

People 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 disabilities, birth defects, and other health issues.

Turner syndrome

Turner syndrome occurs when one normal X chromosome is present in 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 other features.

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 people with Turner syndrome have a chromosomal change in only some of their cells. 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. Individuals 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. Having only one copy of this gene likely causes short stature and skeletal abnormalities seen in individuals with Turner syndrome.

X-linked acrogigantism

Duplication of a small amount of genetic material on the X chromosome causes X-linked acrogigantism (X-LAG), which is characterized by abnormally fast growth that begins in infancy or early childhood. Affected individuals may have the condition as a result of an enlargement (hyperplasia) of the pituitary gland or the development of a noncancerous tumor in the gland (called a pituitary adenoma). The pituitary is a small gland at the base of the brain that produces hormones that control many important body functions, including growth hormone, which helps direct growth of the body. The abnormal gland releases more growth hormone than normal, causing rapid growth in individuals with X-LAG.

The duplication, often referred to as an Xq26.3 microduplication, occurs on the long (q) arm of the X chromosome at a location designated q26.3. It can include several genes,

but only duplication of the *GPR101* gene is necessary to cause X-LAG. The *GPR101* gene provides instructions for making a protein whose function is unknown, although it is thought to be involved in the growth of cells in the pituitary gland or in the release of growth hormone from the gland.

Duplication of the *GPR101* gene leads to an excess of GPR101 protein. It is unclear how extra GPR101 protein results in the development of a pituitary adenoma or hyperplasia or in the release of excess growth hormone.

Other chromosomal conditions

Other chromosomal conditions involving the X chromosome can also affect sexual development and 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 X chromosome or by structural changes in the chromosome.

Additional Information & Resources

Additional NIH Resources

- National Human Genome Research Institute: Chromosome Abnormalities (https://www.genome.gov/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?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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