X Chromosome

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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.

chromosomes & mtDNA

1. Introduction

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.

2. Health Conditions Related to Chromosomal Changes

2.1. 46,XX testicular disorder of sex development

46,XX testicular disorder of sex development is a condition in which individuals with two X chromosomes in each cell, the pattern normally found in females, have a male appearance. 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.

2.2. 48,XXXY syndrome

48,XXXY syndrome is a chromosomal condition in boys and men that causes intellectual disability, developmental delays, physical differences, and an inability to father biological children (infertility). This condition results from having two extra X chromosomes in each cell. Boys and men 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 with 48,XXXY syndrome.

48,XXXY syndrome is sometimes described as a variant of Klinefelter syndrome (described below). However, the features of 48,XXXY syndrome tend to be more severe than those of Klinefelter syndrome and 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 as separate conditions.

2.3. 48,XXYY syndrome

48,XXYY syndrome is a chromosomal condition that causes infertility, developmental and behavioral disorders, and other health problems in affected boys and men. This condition 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 (a hormone that directs male sexual development) in adolescent and adult males. Extra copies of genes from the pseudoautosomal regions of the extra X and Y chromosomes contribute to the signs and symptoms of 48,XXYY syndrome; however, the specific genes have not been identified.

2.4. 49,XXXXY syndrome

49,XXXXY syndrome is a chromosomal condition in boys and men that causes intellectual disability, developmental delays (especially in speech and language), physical differences, and infertility. This condition results from having three extra X chromosomes in each cell. Boys and men 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 with 49,XXXXY syndrome.

49,XXXXY syndrome is sometimes described as a variant of Klinefelter syndrome (described below). However, the features of 49,XXXXY syndrome tend to be more severe than those of Klinefelter syndrome and 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 as separate conditions.

2.5. Intestinal pseudo-obstruction

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

Some individuals with intestinal pseudo-obstruction have mutations, 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 affected individuals.

2.6. Klinefelter syndrome

Klinefelter syndrome is a chromosomal condition in boys and men that can affect physical and intellectual development. It is caused by an extra copy of the X chromosome. Boys and men with Klinefelter syndrome have the usual 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 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). Boys and men 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.

Several conditions resulting from the presence of more than one extra sex chromosome in each cell are sometimes described as variants of Klinefelter syndrome. These conditions include 48,XXXY syndrome and 49,XXXXY syndrome (both described above). The features of these disorders tend to be more severe than those of Klinefelter syndrome and 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 as separate conditions.

2.7. 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, 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 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.

2.8. 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 can be associated with tall stature, developmental delays, 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.

2.9. 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 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.

2.10. 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 beginning in infancy or early childhood. Affected individuals may have the condition as a result of enlargement (hyperplasia) of the pituitary gland or 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 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.

2.11. 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 biological 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.

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