46,XX testicular difference of sex development

Description

46,XX testicular difference of sex development is a condition in which individuals with two X chromosomes in each cell, the pattern typically found in females, have a male appearance. People with this condition have male external genitalia. They generally have small testes and may also have other features such as undescended testes (cryptorchidism) or the urethra opening on the underside of the penis (hypospadias). A small number of affected people have external genitalia that do not look clearly male or clearly female. Affected children are typically raised as males and develop a male gender identity.

At puberty, most affected individuals require treatment with the male sex hormone testosterone to induce development of male secondary sex characteristics such as facial hair and deepening of the voice (masculinization). Hormone treatment can also help prevent breast enlargement (gynecomastia). Adults with this condition are usually shorter than average for males and are unable to have children (infertile).

Frequency

Approximately 1 in 20,000 individuals with a male appearance have 46,XX testicular difference of sex development.

Causes

People normally have 46 chromosomes in each cell. Two of the 46 chromosomes, known as X and Y, are called sex chromosomes because they help determine whether a person will develop male-typical or female-typical sex characteristics. Females usually have two X chromosomes (46,XX), and males usually have one X chromosome and one Y chromosome (46,XY).

The SRY gene, normally located on the Y chromosome, provides instructions for making the sex-determining region Y protein. The sex-determining region Y protein causes a fetus to develop as a male.

In about 80 percent of individuals with 46,XX testicular difference 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 causes the
SRY gene to be misplaced, almost always onto an X chromosome. If a fetus is conceived from a sperm cell with an X chromosome bearing the SRY gene, it will develop as a male despite not having a Y chromosome. This form of the condition is called SRY-positive 46,XX testicular difference of sex development.

About 20 percent of people with 46,XX testicular difference of sex development do not have the SRY gene. This form of the condition is called SRY-negative 46,XX testicular difference of sex development. The cause of the condition in these individuals is often unknown, although changes affecting other genes involved in the development of sex characteristics have been identified in a small number of people with the condition. Individuals with SRY-negative 46,XX testicular difference of sex development are more likely to have genitalia that do not clearly look male or female than are people with the SRY-positive form.

Learn more about the genes and chromosomes associated with 46,XX testicular difference of sex development

- NR5A1
- SOX9
- SRY
- WT1
- x chromosome
- y chromosome

Additional Information from NCBI Gene:
- SOX3

Inheritance

SRY-positive 46,XX testicular difference of sex development is almost never inherited. This condition results from the translocation of a Y chromosome segment containing the SRY gene during the formation of sperm (spermatogenesis). Affected people typically have no history of the condition in their family and cannot pass on the condition because they are infertile.

In rare cases, the SRY gene may be misplaced onto a chromosome other than the X chromosome. This translocation may be carried by an unaffected father and passed on to a child with two X chromosomes, resulting in 46,XX testicular difference of sex development. In another very rare situation, a male may carry the SRY gene on both the X and Y chromosome; a child who inherits his X chromosome will develop male sex characteristics despite having no Y chromosome.

The inheritance pattern of SRY-negative 46,XX testicular difference of sex development is variable. In affected people with a known genetic cause, the condition often follows an
autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. In some cases, the genetic variant (also known as a mutation) is inherited from an unaffected parent. Usually, the variant is inherited from an unaffected father. Sometimes, the variant is inherited from an unaffected mother. When some people with the variant do not develop features of the condition, it is said to have reduced (or incomplete) penetrance.

Other cases of SRY-negative 46,XX testicular difference of sex development result from new (de novo) variants in the gene that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development. These cases occur in people with no history of the condition in their family.

The inheritance pattern of SRY-negative 46,XX testicular difference of sex development without an identified genetic cause is unknown. A few families with unaffected parents have had more than one child with the condition, suggesting the possibility of autosomal recessive inheritance. Autosomal recessive means both copies of a gene in each cell have variants. The parents of an individual with an autosomal recessive condition each carry one copy of the altered gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- 46,XX testicular disorder of sex development
- 46,XX testicular DSD
- nonsyndromic 46,XX testicular disorder/difference of sex development
- XX male syndrome

Additional Information & Resources

Genetic Testing Information


Genetic and Rare Diseases Information Center

- 46,XX testicular disorder of sex development (https://rarediseases.info.nih.gov/diseases/399/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM
• 46,XX SEX REVERSAL 1; SRXX1 (https://omim.org/entry/400045)

Scientific Articles on PubMed

• PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28xx+male+syndrome%5BTIAB %5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600 +days%22%5Bdp%5D)

References


Last updated September 28, 2022