

## Swyer syndrome

### Description

Swyer syndrome is a condition that affects sex development. Sex development usually follows a particular path based on an individual's chromosomes; however, in Swyer syndrome, sex development is not typical for the affected individual's chromosomal pattern.

Chromosomes contain the genetic instructions for how the body develops and functions. People usually 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 or female reproductive structures. Girls and women typically have two X chromosomes (46,XX karyotype), while boys and men typically have one X chromosome and one Y chromosome (46,XY karyotype). In Swyer syndrome, individuals have one X chromosome and one Y chromosome in each cell, which is the pattern typically found in boys and men; however, they have female reproductive structures.

People with Swyer syndrome have female external genitalia and some female internal reproductive structures. These individuals usually have a uterus and fallopian tubes, but their gonads (ovaries or testes) are not functional. Instead, the gonads are small and underdeveloped and contain little gonadal tissue. These structures are called streak gonads. The streak gonadal tissue is at risk of developing cancer that is often hard-to-detect, so it is usually removed surgically. Swyer syndrome is also called 46,XY complete gonadal dysgenesis; the medical term "dysgenesis" means "abnormal development."

Because they appear female on the outside, babies with Swyer syndrome are usually raised as girls and develop a female gender identity, which is a person's sense of their gender (girl, boy, a combination, or neither). Swyer syndrome may be identified before birth, at birth, or later when a child does not go through puberty as usual. Because they do not have functional ovaries that produce hormones, affected individuals often begin hormone replacement therapy during early adolescence to start puberty, causing the breasts and uterus to grow, and eventually leading to menstruation. Hormone replacement therapy is also important for bone health and helps reduce the risk of low bone density (osteopenia) and fragile bones (osteoporosis). Women with Swyer syndrome do not produce eggs (ova), but if they have a uterus, they may be able to become pregnant with a donated egg or embryo.

## Frequency

Swyer syndrome occurs in approximately 1 in 80,000 people.

## Causes

In many individuals with Swyer syndrome, the cause is unknown. However, variants (also known as mutations) in one of several genes have been found to cause the condition in some affected individuals.

Variants in the *SRY* gene have been found in approximately 15 percent of individuals with Swyer syndrome. The *SRY* gene, located on the Y chromosome, provides instructions for making a protein called sex-determining region Y. This protein attaches (binds) to specific regions of DNA and helps control the activity of particular genes. The sex-determining region Y protein starts processes that are involved in male-typical sex development. These processes cause a fetus to develop male gonads (testes) and genitals and prevent the development of female internal reproductive structures (uterus, fallopian tubes, and upper part of the vagina) and genitals. *SRY* gene variants that cause Swyer syndrome prevent production of the sex-determining region Y protein or result in the production of a nonfunctioning protein. Without functional sex-determining region Y protein, a fetus will not develop testes but will develop female-typical internal and external reproductive structures, despite having an X and a Y chromosome.

Swyer syndrome can also be caused by variants in the *MAP3K1* gene; research indicates that variants in this gene may account for up to 18 percent of cases. The *MAP3K1* gene provides instructions for making a protein that helps control various processes in the body, including processes of determining sex characteristics before birth. The variants in the *MAP3K1* gene that cause Swyer syndrome decrease signaling that leads to male-typical sex development and increase signaling that leads to female-typical sex development. These changes in signaling prevent the development of testes and allow the development of female reproductive structures.

Variants in the *DHH* and *NR5A1* genes have also been identified in a small percentage of people with Swyer syndrome. The *DHH* gene provides instructions for making a protein that is important for early development of tissues in many parts of the body. The *NR5A1* gene provides instructions for producing a protein called steroidogenic factor 1 (SF1). This protein helps control the activity of several genes related to sex development and the production of sex hormones. Variants in the *DHH* and *NR5A1* genes disrupt the process of sex development, preventing affected individuals with a 46,XY karyotype from developing testes and causing them to develop female reproductive structures.

Changes affecting other genes have also been identified in a few people with Swyer syndrome. Nongenetic factors, such as hormonal medications taken by the mother during pregnancy, have very rarely been associated with this condition.

[Learn more about the genes associated with Swyer syndrome](#)

- *DHH*

- MAP3K1
- NR0B1
- NR5A1
- SOX9
- SRY

#### **Additional Information from NCBI Gene:**

- CBX2
- DHX37
- DMRT1
- FTHL17
- ZFPM2

### **Inheritance**

Most cases of Swyer syndrome are not inherited; they occur in people with no history of the condition in their family. These cases often result from new (de novo) variants in a gene that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development. Noninherited cases can rarely result from nongenetic causes.

*SRY*-related Swyer syndrome is usually caused by a new variant that is not inherited from either parent. However, some individuals with Swyer syndrome inherit an altered *SRY* gene from an unaffected father who is mosaic for the variant. Mosaic means that an individual has the variant in some cells (which can include some reproductive cells) but not in others. Because he has some cells that do not have the genetic variant, he does not have the condition and is able to have children; however, he can pass the variant to his offspring. In rare cases, a father may carry the variant in every cell of the body but also has other genetic variations that prevent him from being affected by the condition. Because the *SRY* gene is on the Y chromosome, Swyer syndrome caused by *SRY* gene variants is described as having a Y-linked inheritance pattern.

When Swyer syndrome is associated with an *MAP3K1* or *NR5A1* gene variant, the condition is also often caused by a new variant that is not inherited. In the rare inherited cases, the variant may be inherited from either parent, because these genes are not on the Y chromosome; however, only children with an XY chromosome pattern are affected (the condition is said to be sex-limited). In inherited cases, the condition has an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the condition. However, the parent with the genetic variant typically does not have signs and symptoms.

Swyer syndrome caused by variants in the *DHH* gene is inherited in a sex-limited autosomal recessive pattern, which means both copies of the gene in each cell have variants, and only individuals with an XY chromosome pattern are affected. The parents

of an individual with an autosomal recessive condition each have one copy of the altered gene, and they typically do not have signs and symptoms of the condition.

### **Other Names for This Condition**

- 46,XY CGD
- 46,XY complete gonadal dysgenesis
- 46,XY sex reversal
- Gonadal dysgenesis, 46,XY
- Pure gonadal dysgenesis 46,XY
- XY pure gonadal dysgenesis

### **Additional Information & Resources**

#### Genetic Testing Information

- Genetic Testing Registry: 46,XY disorder of sex development and 46,XY complete gonadal dysgenesis (<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN043561/>)
- Genetic Testing Registry: Pure gonadal dysgenesis 46,XY (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2936694/>)

#### Genetic and Rare Diseases Information Center

- 46,XY complete gonadal dysgenesis (<https://rarediseases.info.nih.gov/diseases/5068/index>)

#### Patient Support and Advocacy Resources

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

#### Catalog of Genes and Diseases from OMIM

- 46,XY SEX REVERSAL 4; SRXY4 (<https://omim.org/entry/154230>)
- 46,XY SEX REVERSAL 1; SRXY1 (<https://omim.org/entry/400044>)
- 46,XY SEX REVERSAL 2; SRXY2 (<https://omim.org/entry/300018>)
- 46,XY SEX REVERSAL 7; SRXY7 (<https://omim.org/entry/233420>)
- 46,XY SEX REVERSAL 3; SRXY3 (<https://omim.org/entry/612965>)
- 46,XY SEX REVERSAL 9; SRXY9 (<https://omim.org/entry/616067>)
- 46,XY SEX REVERSAL 5; SRXY5 (<https://omim.org/entry/613080>)
- 46,XY SEX REVERSAL 6; SRXY6 (<https://omim.org/entry/613762>)

## Scientific Articles on PubMed

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

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