



## Swyer syndrome

Swyer syndrome is a condition that affects sexual development. Sexual development is usually determined by an individual's chromosomes; however, in Swyer syndrome, sexual development does not match the affected individual's chromosomal makeup.

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 sex characteristics. Girls and women typically have two X chromosomes (46,XX karyotype), while boys and men usually have one X chromosome and one Y chromosome (46,XY karyotype). In Swyer syndrome, individuals with one X chromosome and one Y chromosome in each cell, the pattern typically found in boys and men, have female reproductive structures.

People with Swyer syndrome have typical female external genitalia. The uterus and fallopian tubes are normally-formed, but the gonads (ovaries or testes) are not functional; affected individuals have undeveloped clumps of tissue called streak gonads. Because of the lack of development of the gonads, Swyer syndrome is also called 46,XY complete gonadal dysgenesis. The residual gonadal tissue often becomes cancerous, so it is usually removed surgically early in life.

People with Swyer syndrome are typically raised as girls and have a female gender identity. Because they do not have functional ovaries, affected individuals usually begin hormone replacement therapy during adolescence to induce menstruation and development of female secondary sex characteristics such as breast enlargement and uterine growth. Hormone replacement therapy also helps reduce the risk of reduced bone density (osteopenia and osteoporosis). Women with this disorder do not produce eggs (ova), but they may be able to become pregnant with a donated egg or embryo.

Swyer syndrome usually affects only sexual development; such cases are called isolated Swyer syndrome. However, depending on the genetic cause, Swyer syndrome may also occur along with health conditions such as nerve problems (neuropathy) or as part of a syndrome such as campomelic dysplasia, which causes severe skeletal abnormalities.

### Frequency

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

### Causes

Mutations in the *SRY* gene have been identified in approximately 15 percent of individuals with Swyer syndrome. The *SRY* gene, located on the Y chromosome, provides instructions for making the sex-determining region Y protein. This protein is

a transcription factor, which means it 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 sexual development. These processes cause a fetus to develop male gonads (testes) and prevent the development of female reproductive structures (uterus and fallopian tubes). *SRY* gene mutations that cause Swyer syndrome prevent production of the sex-determining region Y protein or result in the production of a nonfunctioning protein. A fetus whose cells do not produce functional sex-determining region Y protein will not develop testes but will develop a uterus and fallopian tubes, despite having a typically male karyotype.

Swyer syndrome can also be caused by mutations in the *MAP3K1* gene; research indicates that mutations in this gene may account for up to 18 percent of cases. The *MAP3K1* gene provides instructions for making a protein that helps regulate signaling pathways that control various processes in the body. These include the processes of determining sexual characteristics before birth. The mutations in this gene that cause Swyer syndrome decrease signaling that leads to male sexual differentiation and enhance signaling that leads to female sexual differentiation, preventing the development of testes and allowing the development of a uterus and fallopian tubes.

Mutations in the *DHH* and *NR5A1* genes have also been identified in small numbers 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 another transcription factor called the steroidogenic factor 1 (SF1). This protein helps control the activity of several genes related to the production of sex hormones and sexual differentiation. Mutations in the *DHH* and *NR5A1* genes affect the process of sexual differentiation, preventing affected individuals with a typically male karyotype from developing testes and causing them to develop a uterus and fallopian tubes.

Changes affecting other genes have also been identified in a small number of people with Swyer syndrome. Nongenetic factors, such as hormonal medications taken by the mother during pregnancy, have also been associated with this condition. However, in most individuals with Swyer syndrome, the cause is unknown.

## **Inheritance Pattern**

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

*SRY*-related Swyer syndrome is usually caused by a new mutation. However, some individuals with Swyer syndrome inherit an altered *SRY* gene from an unaffected father who is mosaic for the mutation. Mosaic means that an individual has the mutation in some cells (including some reproductive cells) but not in others. In rare cases, a father may carry the mutation 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 mutations is described as having a Y-linked inheritance pattern.

When Swyer syndrome is associated with an *MAP3K1* or *NR5A1* gene mutation, the condition is also usually caused by a new mutation. In the rare inherited cases, the mutation may be inherited from either parent, since these genes are not on the Y chromosome. In these 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.

Swyer syndrome caused by mutations in the *DHH* gene is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition are carriers of one copy of the altered gene. Female carriers of a *DHH* gene mutation generally have typical sex development. Male carriers of a *DHH* gene mutation may also be unaffected, or they may have genital differences such as the urethra opening on the underside of the penis (hypospadias).

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

- 46,XY CGD
- 46,XY complete gonadal dysgenesis
- 46,XY sex reversal
- gonadal dysgenesis, 46,XY
- gonadal dysgenesis, XY female type
- pure gonadal dysgenesis 46,XY
- XY pure gonadal dysgenesis

### **Diagnosis & Management**

#### Genetic Testing Information

- What is genetic testing?  
[/primer/testing/genetic-testing](#)
- 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/>

### Other Diagnosis and Management Resources

- GeneReview: Nonsyndromic Disorders of Testicular Development  
<https://www.ncbi.nlm.nih.gov/books/NBK1547>
- MedlinePlus Encyclopedia: Intersex  
<https://medlineplus.gov/ency/article/001669.htm>
- University College London Hospitals: Disorders of Sexual Development  
<http://www.uclh.nhs.uk/OurServices/ServiceA-Z/WH/GYNAE/DSD/Pages/Home.aspx>

### **Additional Information & Resources**

#### Health Information from MedlinePlus

- Encyclopedia: Intersex  
<https://medlineplus.gov/ency/article/001669.htm>
- Health Topic: Endocrine Diseases  
<https://medlineplus.gov/endocrinediseases.html>
- Health Topic: Infertility  
<https://medlineplus.gov/infertility.html>

#### Genetic and Rare Diseases Information Center

- Swyer syndrome  
<https://rarediseases.info.nih.gov/diseases/5068/swyer-syndrome>

#### Educational Resources

- MalaCards: 46 xy gonadal dysgenesis  
[https://www.malacards.org/card/46\\_xy\\_gonadal\\_dysgenesis](https://www.malacards.org/card/46_xy_gonadal_dysgenesis)
- March of Dimes: Genital and Urinary Tract Defects  
<https://www.marchofdimes.org/baby/genital-and-urinary-tract-defects.aspx>
- Orphanet: 46,XY complete gonadal dysgenesis  
[https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=242](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=242)

#### Patient Support and Advocacy Resources

- Accord Alliance  
<http://www.accordalliance.org/>
- AIS-DSD Support Group  
<http://aisdsd.org/>
- National Organization for Rare Disorders  
<https://rarediseases.org/rare-diseases/swyer-syndrome/>
- RESOLVE: The National Infertility Association  
<https://resolve.org/>

### Clinical Information from GeneReviews

- Nonsyndromic Disorders of Testicular Development  
<https://www.ncbi.nlm.nih.gov/books/NBK1547>

### Scientific Articles on PubMed

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

### Catalog of Genes and Diseases from OMIM

- 46,XY SEX REVERSAL 1  
<http://omim.org/entry/400044>
- 46,XY SEX REVERSAL 2  
<http://omim.org/entry/300018>
- 46,XY SEX REVERSAL 3  
<http://omim.org/entry/612965>
- 46,XY SEX REVERSAL 4  
<http://omim.org/entry/154230>
- 46,XY SEX REVERSAL 5  
<http://omim.org/entry/613080>
- 46,XY SEX REVERSAL 6  
<http://omim.org/entry/613762>
- 46,XY SEX REVERSAL 7  
<http://omim.org/entry/233420>
- 46,XY SEX REVERSAL 9  
<http://omim.org/entry/616067>

### Medical Genetics Database from MedGen

- 46,XY disorder of sex development and 46,XY complete gonadal dysgenesis  
<https://www.ncbi.nlm.nih.gov/medgen/448007>
- Pure gonadal dysgenesis 46,XY  
<https://www.ncbi.nlm.nih.gov/medgen/445380>

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