



5-alpha reductase deficiency

5-alpha reductase deficiency is a condition that affects male sexual development before birth and during puberty. People with this condition are genetically male, with one X and one Y chromosome in each cell, and they have male gonads (testes). Their bodies, however, do not produce enough of a hormone called dihydrotestosterone (DHT). DHT has a critical role in male sexual development, and a shortage of this hormone disrupts the formation of the external sex organs before birth.

Many people with 5-alpha reductase deficiency are born with external genitalia that appear female. In other cases, the external genitalia do not look clearly male or clearly female (sometimes called ambiguous genitalia). Still other affected infants have genitalia that appear predominantly male, often with an unusually small penis (micropenis) and the urethra opening on the underside of the penis (hypospadias).

During puberty, an increase in the levels of male sex hormones leads to the development of some secondary sex characteristics, such as increased muscle mass, deepening of the voice, development of pubic hair, and a growth spurt. The penis and scrotum (the sac of skin that holds the testes) grow larger. Unlike many men, people with 5-alpha reductase deficiency do not develop much facial or body hair. Most affected individuals are unable to have biological children without assisted reproduction.

Children with 5-alpha reductase deficiency are often raised as girls. Some of these individuals adopt a male gender role in adolescence or early adulthood, while others adopt a female gender role.

Frequency

5-alpha reductase deficiency is a rare condition; the exact incidence is unknown. Large families with affected members have been found in several countries, including the Dominican Republic, Papua New Guinea, Turkey, and Egypt.

Genetic Changes

Mutations in the *SRD5A2* gene cause 5-alpha reductase deficiency. The *SRD5A2* gene provides instructions for making an enzyme called steroid 5-alpha reductase 2. This enzyme is involved in processing androgens, which are hormones that direct male sexual development. Specifically, the enzyme is responsible for a chemical reaction that converts the hormone testosterone to DHT. DHT is essential for the normal development of male sex characteristics before birth, particularly the formation of the external genitalia.

Mutations in the *SRD5A2* gene prevent steroid 5-alpha reductase 2 from effectively converting testosterone to DHT in the developing reproductive tissues. These hormonal

factors underlie the changes in sexual development seen in infants with 5-alpha reductase deficiency.

During puberty, the testes produce more testosterone. Researchers believe that people with 5-alpha reductase deficiency develop secondary male sex characteristics in response to higher levels of this hormone. Some affected people also retain a small amount of 5-alpha reductase 2 activity, which may produce DHT and contribute to the development of secondary sex characteristics during puberty.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the *SRD5A2* gene in each cell have a mutation. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they do not show signs and symptoms of the condition.

Although people who are genetically female (with two X chromosomes in each cell) may inherit mutations in both copies of the *SRD5A2* gene, their sexual development is not affected. The development of female sex characteristics does not require DHT, so a lack of steroid 5-alpha reductase 2 activity does not cause physical changes in these individuals. Only people who have mutations in both copies of the *SRD5A2* gene and are genetically male (with one X and one Y chromosome in each cell) have the characteristic signs of 5-alpha reductase deficiency.

Other Names for This Condition

- familial incomplete male pseudohermaphroditism, type 2
- male pseudohermaphroditism due to 5-alpha-reductase deficiency
- PPSH
- pseudovaginal perineoscrotal hypospadias
- steroid 5-alpha-reductase deficiency

Diagnosis & Management

Formal Treatment/Management Guidelines

- Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology.. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16882788>

Genetic Testing

- Genetic Testing Registry: 3-Oxo-5 alpha-steroid delta 4-dehydrogenase deficiency <https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268297/>

Other Diagnosis and Management Resources

- MedlinePlus Encyclopedia: Ambiguous Genitalia
<https://medlineplus.gov/ency/article/003269.htm>
- MedlinePlus Encyclopedia: Intersex
<https://medlineplus.gov/ency/article/001669.htm>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Ambiguous Genitalia
<https://medlineplus.gov/ency/article/003269.htm>
- Encyclopedia: Intersex
<https://medlineplus.gov/ency/article/001669.htm>
- Health Topic: Endocrine Diseases
<https://medlineplus.gov/endocrinediseases.html>

Genetic and Rare Diseases Information Center

- 5-alpha reductase deficiency
<https://rarediseases.info.nih.gov/diseases/5680/5-alpha-reductase-deficiency>

Educational Resources

- American Psychological Association: Answers to Your Questions About Individuals With Intersex Conditions
<http://www.apa.org/topics/lgbt/intersex.pdf>
- Disease InfoSearch: Pseudovaginal perineoscrotal hypospadias
<http://www.diseaseinfosearch.org/Pseudovaginal+perineoscrotal+hypospadias/6052>

- MalaCards: 5-alpha reductase deficiency
http://www.malacards.org/card/5_alpha_reductase_deficiency
- My46 Trait Profile
<https://www.my46.org/trait-document?trait=5-alpha%20reductase%20deficiency&type=profile>
- Orphanet: 46,XY disorder of sex development due to 5-alpha-reductase 2 deficiency
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=753

Patient Support and Advocacy Resources

- Accord Alliance
<http://www.accordalliance.org/>
- AIS-DSD Support Group
<http://aisdsd.org/>
- InterACT Advocates for Intersex Youth
<https://interactadvocates.org/>
- Resolve: The National Infertility Association
<https://resolve.org/>
- Resource List from the University of Kansas Medical Center: Ambiguous Genitalia
<http://www.kumc.edu/gec/support/ambig.html>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%285-alpha+reductase+deficiency%5BTIAB%5D%29+OR+%28ppsh%5BTIAB%5D%29+OR+%28pseudovaginal+perineoscrotal+hypospadias%5BTIAB%5D%29+OR+%28steroid+5-alpha-reductase+deficiency%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- PSEUDO-VAGINAL PERINEOSCROTAL HYPOSPADIAS
<http://omim.org/entry/264600>

MedGen

- 5-Alpha-Reductase Deficiency
<https://www.ncbi.nlm.nih.gov/medgen/777160>

Sources for This Summary

- Bahceci M, Ersay AR, Tuzcu A, Hiort O, Richter-Unruh A, Gokalp D. A novel missense mutation of 5-alpha reductase type 2 gene (SRD5A2) leads to severe male pseudohermaphroditism in a Turkish family. *Urology*. 2005 Aug;66(2):407-10.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16098368>
- Baldinotti F, Majore S, Fogli A, Marrocco G, Ghirri P, Vuerich M, Tumini S, Boscherini B, Vetri M, Scommegna S, Rinaldi R, Simi P, Grammatico P. Molecular characterization of 6 unrelated Italian patients with 5alpha-reductase type 2 deficiency. *J Androl*. 2008 Jan-Feb;29(1):20-8. Epub 2007 Jul 3.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17609295>
- Cohen-Kettenis PT. Gender change in 46,XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16010463>
- Hackel C, Oliveira LE, Ferraz LF, Tonini MM, Silva DN, Toralles MB, Stuchi-Perez EG, Guerra-Junior G. New mutations, hotspots, and founder effects in Brazilian patients with steroid 5alpha-reductase deficiency type 2. *J Mol Med (Berl)*. 2005 Jul;83(7):569-76. Epub 2005 Mar 16.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/15770495>
- Okeigwe I, Kuohung W. 5-Alpha reductase deficiency: a 40-year retrospective review. *Curr Opin Endocrinol Diabetes Obes*. 2014 Dec;21(6):483-7. doi: 10.1097/MED.000000000000116. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25321150>
- Sultan C, Lumbroso S, Paris F, Jeandel C, Terouanne B, Belon C, Audran F, Poujol N, Georget V, Gobinet J, Jalaguier S, Auzou G, Nicolas JC. Disorders of androgen action. *Semin Reprod Med*. 2002 Aug;20(3):217-28. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12428202>

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/5-alpha-reductase-deficiency>

Reviewed: April 2017

Published: April 17, 2018

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services