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Nonsyndromic Disorders of Testicular Development Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding the genetic causes of nonsyndromic disorders of testicular development, inform genetic counseling of at-risk family members, and review management options. The following are the goals of this overview.

Goal 1

To describe the clinical characteristics of nonsyndromic disorders of testicular development.

Goal 2

To review the genetic causes of nonsyndromic disorders of testicular development and conditions that may be in the differential diagnosis.

Goal 3

To provide an evaluation strategy to identify the genetic cause of nonsyndromic disorders of testicular development (when possible).

Goal 4

To inform management regarding sex of rearing, medical/surgical intervention (when appropriate), hormone therapy, and psychosocial aspects of care.

Goal 5

To inform genetic risk assessment in family members of a proband.

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GeneReview Scope

Nonsyndromic Disorders of Testicular Development: Included Phenotypes

- 46,XY disorder of sex development (DSD)
- 46,XY complete gonadal dysgenesis (CGD)

For synonyms and outdated names see Nomenclature.

1. Clinical Characteristics of Nonsyndromic Disorders of Testicular Development

Nonsyndromic disorders of testicular development are a group of disorders characterized by:

- Normal general physical examination **AND** absence of clinical findings involving other organ systems (i.e., nonsyndromic);
- Clinical and gonadal findings of a 46,XY disorder of sex development (DSD) or 46,XY complete gonadal dysgenesis (CGD);
- A normal 46,XY karyotype by conventional staining (see Evaluation Strategy).

Clinical Manifestations of Nonsyndromic 46,XY DSD

External genitalia can range over the following spectrum:

- Ambiguous with mild-to-severe penoscrotal hypospadias with or without chordee
- Microphallus
- Abnormalities of scrotal formation
- Normal-appearing female

Müllerian structures can range over the following spectrum upon ultrasound examination, MRI, and/or laparoscopy:

- Absent
- Fully developed uterus and fallopian tubes

Gonadal findings, as determined by a combination of physical examination, imaging, and hormonal testing (and on occasion histologic examination; see **Note**), can range over the following spectrum:

- Normal testis
- Ovotestis
- Dysgenetic testis (decreased size and number of seminiferous tubules, reduced number or absence of germ cells, peritubular fibrosis, and hyperplasia of Leydig cells)
- Streak gonad

Note: Results may be inaccurate because of biopsy sampling error; gonadal biopsy may harm the future growth and development of the gonad.

Clinical Manifestations of Nonsyndromic 46,XY CGD

Clinical manifestations of nonsyndromic 46,XY CGD include:

- **External genitalia.** Normal female
- **Müllerian structures.** Uterus and fallopian tubes present
- **Gonadal findings.** Streak gonads or dysgenetic testes

Nomenclature

The nomenclature for disorders of sex development (DSD) was revised in 2006 to reflect the genetic causes and pathogenesis of these conditions [Houk et al 2006].

- The term "differences of sex development" is often used to replace "disorders of sex development," although "disorders of sex development" is still appropriate to use among medical providers.
- The term "disorders of sex development" has replaced the term "intersex."
- The term "46,XY DSD" has replaced the following terms:
 - Male pseudohermaphrodite
 - Undervirilization of an XY male
 - Undermasculinization of an XY male
 - Mixed gonadal dysgenesis
 - Partial gonadal dysgenesis
- The term "46,XY CGD" has replaced the terms "46,XY sex reversal" and "46,XY female."
- The term "46,XY ovotesticular DSD" has replaced "46,XY true hermaphrodite."

2. Causes of Nonsyndromic Disorders of Testicular Development

Many genetic causes of nonsyndromic disorders of testicular development are not known. Approximately 60% of affected individuals will have an underlying genetic etiology identified through molecular genetic testing (Table 1) [Gomes et al 2022].

Table 1. Molecular Genetics of Nonsyndromic Disorders of Testicular Development

Gene ¹ / Pathogenic Mechanism	Proportion of Nonsyndromic DSD Attributed to Variants in Gene		MOI
	46,XY DSD	46,XY CGD	
<i>DHH</i>	Rare ²	Rare ²	AR
<i>DMRT1</i> ³	Rare ⁴	Rare ⁴	AD
<i>DHX37</i>	20% ⁵	10%-15% ⁵	AD
<i>MAP3K1</i>	10%-18% ⁶	10%-18% ⁶	AD
<i>NR5A1</i>	10%-15% ⁷	10% of <i>NR5A1</i> variants ⁷	AD
<i>SOX8</i>	Rare ⁸	Rare ⁸	AD
<i>SOX9</i> regulatory regions	Rare ⁹	Rare ⁹	AD
<i>SRY</i>	Rare ¹⁰	10%-15% ¹⁰	YL

Table 1. continued from previous page.

Gene ¹ / Pathogenic Mechanism	Proportion of Nonsyndromic DSD Attributed to Variants in Gene		MOI
	46,XY DSD	46,XY CGD	
Hemizygous duplication at Xp21 ^{11, 12}	Rare ¹³	Rare ¹³	XL

AD = autosomal dominant; AR = autosomal recessive; CGD = complete gonadal dysgenesis; DSD = differences/disorders of sex development; MOI = mode of inheritance; XL = X-linked; YL = Y-linked

1. Genes are listed in alphabetic order.

2. Biallelic pathogenic variants in *DHH* have been confirmed by functional studies to cause 46,XY DSD and 46,XY CGD. However, heterozygous pathogenic *DHH* variants are unlikely to cause DSD [Ayers et al 2019]. Some individuals with biallelic pathogenic *DHH* variants have 46,XY DSD and develop peripheral neuropathy presenting between ages 20 and 30 years (OMIM 607080) [Sato et al 2017, Baldinotti et al 2018].

3. Pathogenic variants may include heterozygous complete or partial deletions of *DMRT1* or pathogenic *DMRT1* sequence variants.

4. Deletions of 9p24 are a recurrent cause of 46,XY DSD and 46,XY CGD. While most reports are of individuals who have larger deletions of this chromosome region leading to syndromic features (see Table 3), rare individuals with a nonsyndromic 46,XY disorder of testicular development and a small complete or partial deletion encompassing *DMRT1* or a pathogenic variant in *DMRT1* have been reported [Zarkower & Murphy 2022].

5. *DHX37* pathogenic variants may explain 20% of cases of testicular regression syndrome [Elzaat et al 2022, Gomes et al 2022].

6. Ostrer [2014], Granados et al [2017], Chamberlin et al [2019]

7. *NR5A1* pathogenic variants have been associated with a wide range of phenotypes including isolated 46,XY partial and complete gonadal dysgenesis, 46,XY undervirilization, vanishing testes, and male infertility. 46,XX individuals can have premature ovarian insufficiency, and some have been reported to have testicular or ovotesticular DSD. Adrenal insufficiency is a rare finding [Fabbri-Scallet et al 2020].

8. Disruption of the *SOX8* locus has been reported to cause 46,XY CGD and 46,XY DSD [Portnoi et al 2018].

9. Deletion of *SOX9* upstream enhancers has been reported to cause 46,XY CGD [Croft et al 2018]. Pathogenic variants in *SOX9* cause campomelic dysplasia (see Table 3).

10. Hemizygous pathogenic variants in *SRY* primarily cause a 46,XY CGD phenotype [Buonocore et al 2019]. Rare reports of milder 46,XY DSD phenotypes in the setting of mosaicism for an *SRY* pathogenic variant have been published [Isidor et al 2009, Roberts et al 2018].

11. Genes involved in the duplications include *MAGEB*, *NROB1*, *CXorf21*, *GK*, and a portion of *MAP3K7IP3*. However, *NROB1* (*DAX1*) is presumed to be the gene responsible for the phenotype, although this has not been definitively proven [Barbaro et al 2012, García-Acero et al 2019].

12. Hemizygous deletions and pathogenic variants in *NROB1* are known to cause a different phenotype (X-linked adrenal hypoplasia congenita).

13. Barbaro et al [2007], Barbaro et al [2012], García-Acero et al [2019], Nishi et al [2022]

Disorders to consider in the differential diagnosis for apparent nonsyndromic disorders of testicular development are listed in Table 2.

Table 2. Additional Nonsyndromic DSD Conditions to Consider in the Differential Diagnosis of Ambiguous Genitalia and/or Sex Chromosome-Phenotype Discordance

Gene(s)	Disorder	MOI ¹	Distinguishing Features ²
Hormone biosynthetic defects			
<i>AKR1C2</i> <i>AKR1C4</i>	Aldo-keto reductase deficiency (OMIM 614279)	AR	Alternative pathway for DHT synthesis in fetal testis; XY persons phenotypically female or have ambiguous genitalia
<i>CYP11A1</i>	P450scc (formerly cholesterol desmolase) deficiency (OMIM 613743)	AR	Severe adrenal insufficiency w/salt wasting, ↑ ACTH & plasma renin, ↓ or absent adrenal steroids; XY persons phenotypically female.
<i>CYP17A1</i>	17-alpha-hydroxylase deficiency / 17,20-lyase deficiency (OMIM 202110)	AR	Hypertension, hypokalemic alkalosis, ↑ ACTH, LH & FSH; 46,XY persons have absent or incomplete virilization of external genitalia.
<i>HSD17B3</i>	17-beta-hydroxysteroid dehydrogenase deficiency (OMIM 264300)	AR	Interferes w/conversion of androstenedione to testosterone; 46,XY persons have absent or incomplete virilization of external genitalia but may virilize at puberty.

Table 2. continued from previous page.

Gene(s)	Disorder	MOI ¹	Distinguishing Features ²
<i>HSD3B2</i>	3-beta-hydroxysteroid dehydrogenase deficiency (OMIM 201810)	AR	Acute adrenal insufficiency w/↑ pregnenolone, 17-hydroxypregnenolone, & DHEA; 46,XY persons have severe hypospadias w/micropenis.
<i>POR</i>	Cytochrome P450 oxidoreductase deficiency	AR	Combined deficiency of p450c17 & p450c21 causing accumulation of steroid metabolites; incomplete virilization in 46,XY persons & ambiguous genitalia in 46,XX persons
<i>SRD5A2</i>	5-alpha-reductase deficiency (OMIM 264600)	AR	Interferes w/conversion of testosterone to dihydrotestosterone causing possible virilization at puberty; 46,XY persons may have ambiguous genitalia w/hypospadias & blind vaginal pouch or appear phenotypically female.
<i>STAR</i>	Lipoid adrenal hyperplasia (OMIM 201710)	AR	Severe adrenal insufficiency w/salt wasting, ↑ ACTH & plasma renin, ↓ or absent adrenal steroids; 46,XY persons phenotypically female
LH receptor defects			
<i>LHCGR</i>	Leydig cell hypoplasia (OMIM 238320)	AR	Leydig cell hypoplasia or agenesis, low T levels, ↑ LH/FSH, ↓ response to hCG stimulation testing
LH deficiency			
<i>ANOS1 (KAL1)</i>	Kallmann syndrome (See Isolated GnRH Deficiency .)	XL	See Isolated Gonadotropin-Releasing Hormone Deficiency . 46,XY persons typically have micropenis w/normally formed scrotum.
Androgen receptor defects			
<i>AR</i>	Androgen insensitivity syndrome	XL	Lack of virilization due to impaired androgen binding to androgen receptor or transactivation; incl complete & partial defects; normal or ↑ T levels
Other			
<i>CBX2</i>	<i>CBX2</i> -related complete gonadal dysgenesis (OMIM 613080)	AR	1 case reported ³ of phenotypic female w/46,XY karyotype, uterus, & histologically normal ovarian tissue

ACTH = adrenocorticotropic hormone; DHT = dihydrotestosterone; FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; MOI = mode of inheritance; T = testosterone

1. Typical MOI; exceptions occur.

2. The majority of the conditions in Table 2 can be differentiated from 46,XY CGD by the absence of müllerian structures.

3. The phenotype was proposed to be caused by biallelic pathogenic variants in *CBX2* [Biaison-Lauber et al 2009].

Syndromic conditions to consider in the differential diagnosis of ambiguous genitalia and/or sex chromosome/phenotype discordance are listed in Table 3.

Table 3. Syndromic DSD Conditions to Consider in the Differential Diagnosis of Ambiguous Genitalia and/or Sex Chromosome-Phenotype Discordance

Gene(s)	Disorder	MOI ¹	Clinical Features
<i>ARX</i>	X-linked lissencephaly w/ambiguous genitalia (OMIM 300215)	XL	Lissencephaly w/severe ID; genitalia of XY persons range from ambiguous to phenotypically female.
<i>ATRX</i>	Alpha-thalassemia X-linked ID syndrome	XL	Distinctive craniofacial features, genital anomalies, hypotonia, severe ID, mild-to-moderate anemia secondary to alpha-thalassemia
<i>DHCR7</i>	Smith-Lemli-Opitz syndrome	AR	Pre- & postnatal growth restriction, microcephaly, moderate-to-severe ID, distinctive facial features, cleft palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, syndactyly of toes 2-3; caused by deficiency of enzyme 7-dehydrocholesterol

Table 3. continued from previous page.

Gene(s)	Disorder	MOI ¹	Clinical Features
<i>DMRT1</i>	9p24 deletions ^{2, 3} (OMIM 154230)	AD	Trigonocephaly, dysmorphic features (widely spaced eyes, arched eyebrows, low-set ears, long philtrum, thin vermilion of upper lip), congenital heart defects, underdeveloped external genitalia in males, ID
<i>GATA4</i>	<i>GATA4</i> -related disorders (OMIM 615542)	AD	Testicular anomalies & congenital heart defects
<i>MYRF</i>	MYRF-related cardiac urogenital syndrome	AD	Congenital diaphragmatic hernia, cardiac defects, encephalopathy, & urogenital anomalies incl ambiguous genitalia, hypospadias, cryptorchidism ⁴
<i>PAX6</i> <i>WT1</i> ⁵	11p13 deletion (See PAX6-Related Aniridia & WT1 Disorder.)	AD	Wilms tumor-aniridia-genital anomalies-retardation (ID) (WAGR) syndrome
<i>POR</i>	Antley-Bixler syndrome w/disordered steroidogenesis (See Cytochrome P450 Oxidoreductase Deficiency.)	AR	Craniosynostosis, hydrocephalus, distinctive facies, choanal stenosis or atresia, low-set dysplastic ears w/stenotic external auditory canals, skeletal anomalies, renal anomalies, ↓ cognitive function, DD
<i>PPP2R3C</i>	Gonadal dysgenesis, dysmorphic facies, retinal dystrophy, & myopathy (OMIM 618419)	AR	Complete gonadal dysgenesis, facial dysmorphism, myopathy, retinal dystrophy, infertility
<i>SOX9</i>	Campomelic dysplasia	AD	Distinctive facies, Pierre Robin sequence w/cleft palate, shortening & bowing of long bones, clubfeet, laryngotracheomalacia w/ respiratory compromise
<i>WT1</i>	<i>WT1</i> -related disorders (See Wilms Tumor Predisposition & WT1 Disorder.)	AD	Fraiser syndrome: focal & segmental glomerulosclerosis of the kidney & 46,XY CGD Denys-Drash syndrome: mesangial sclerosis of kidney, Wilms tumor, & 46,XY DSD

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Typical MOI; exceptions occur

2. Deletions of 9p24 vary in size, including large, cytogenetically visible deletions or smaller deletions. None of these 9p24 deletions (including those that lead to apparently nonsyndromic 46,XY disorders of testicular development) is recurrent. See also Table 1.

3. *DMRT1*, located at 9p24, is considered the likely causative gene for the 46,XY DSD phenotype in those with a 9p24 deletion, although this has not been definitively proven [Quinonez et al 2013]. See also Table 1.

4. Eye anomalies, including high hyperopia and nanophthalmos, have also been described in individuals with pathogenic variants in *MYRF* [Garnai et al 2019, Hagedorn et al 2020], some of whom appear to have isolated eye anomalies without the other features of cardiac urogenital syndrome.

5. WAGR syndrome is associated with contiguous gene deletions including *PAX6* and *WT1*.

3. Evaluation Strategies to Identify the Genetic Cause of Nonsyndromic Disorders of Testicular Development

The initial evaluation of an individual suspected of having a nonsyndromic disorder of sex development is to determine the chromosome complement.

Chromosome Analysis

One genetic testing strategy is to perform a karyotype using conventional staining methods of a sufficient number of cells to detect mosaicism for sex chromosome aneuploidy (i.e., 45,X / 46,XY) **and** fluorescence in situ hybridization (FISH) for the presence of *SRY*.

Another genetic testing strategy is to perform a chromosomal microarray (CMA), as this will determine the sex chromosome complement, evaluate for the presence or absence of *SRY*, and screen for deletion/duplication

syndromes in which individuals may have genital anomalies within the DSD spectrum (see Tables 1, 2, and 3). If the karyotype is already known, CMA may still be pursued, particularly for individuals in whom a syndromic diagnosis is being considered.

Note: (1) If the individual has a 46,XY chromosome complement but is *SRY* negative, the cause of the individual's nonsyndromic disorder of testicular development has been determined. (2) If CMA detects a deletion of *SRY*, a limited karyotype can be considered to determine if the deletion was caused by a translocation or a complex rearrangement of genetic material.

Molecular Genetic Testing

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which genes are likely involved, whereas genomic testing does not. Individuals with distinctive hormonal, gonadal, and/or imaging findings described in Clinical Characteristics may be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other disorders of sex development are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic, laboratory, and imaging findings suggest the diagnosis of nonsyndromic disorders of testicular development, molecular genetic testing approaches can include use of a **multigene panel**.

A disorders of sex development multigene panel that includes some or all of the genes listed in Table 1 and other genes of interest (see Tables 2 and 3) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by 46,XY DSD, comprehensive genomic testing may be considered. **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

4. Management

Treatment of Manifestations

A consensus statement on the management of disorders of sex development (DSD) was developed under the sponsorship of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric

Endocrinology [Lee et al 2006]. Further consensus guidelines for the care of children with DSD were developed by León et al [2019] ([full text](#); purchase or subscription required) and Wisniewski et al [2019] ([full text](#)).

Evaluation and long-term management should be provided at a center with an interdisciplinary care team (including clinical geneticists, endocrinologists, surgeons, and mental health professionals) experienced in the diagnosis and management of DSD conditions.

The general concepts of care include the following.

Sex assignment

- All individuals should receive a sex of rearing.
- Sex assignment in newborns with ambiguous genitalia should not be decided prior to an evaluation by experts.
- The choice of sex of rearing for individuals with 46,XY DSD is based on the underlying diagnosis, expert opinion, and parental beliefs [Houk et al 2006].

Surgical decisions should be made after detailed discussion with the family about risks, benefits, and limitations of any proposed surgery. Many surgeries are not medically necessary and thus consideration should be given to delaying surgery in order to allow the affected individual to participate in the decision-making process.

- Surgical intervention in minors with DSD is controversial, particularly in those being reared female. Surgical intervention should focus on functionality; whenever possible, removal of tissue and irreversible procedures should be avoided.
- When **male** sex of rearing is chosen, surgical options may include hypospadias repair, orchiopexy, scrotoplasty, and phalloplasty. Removal of müllerian remnants may be considered.
- When **female** sex of rearing is chosen, surgical options may include clitoroplasty, vaginoplasty, and urogenital sinus mobilization. Vaginal dilation is also used for creation/expansion of the vagina.

Note: (1) No controlled clinical trials of the efficacy of different surgical techniques have been conducted. The long-term data regarding the quality of life and sexual function among those assigned male and female sex vary. (2) There is no consensus on the appropriate timing of the surgical procedures listed.

Management of gonads

- Streak gonads and dysgenetic gonads are at increased risk for the development of gonadoblastoma and should be surgically removed if nonfunctional.
 - In a 46,XY individual, absence of virilization and presence of müllerian structures implies that gonads are nonfunctional and were not making appropriate hormones, such as testosterone and anti-müllerian hormone, during fetal life and are unlikely to do so during postnatal life.
 - Nonfunctional gonads typically do not make hormones that can be detected in infancy and childhood, such as anti-müllerian hormone and inhibin B.
 - A human chorionic gonadotropin stimulation test will not detect an increase in testosterone level; this test is not always necessary, particularly if there is other evidence that a gonad is nonfunctional.
 - A greatly elevated follicle-stimulating hormone and/or luteinizing hormone in infancy is usually associated with nonfunctional gonads.

Note: Hormonal evaluation cannot distinguish between one versus two functioning gonads.

- If a dysgenetic gonad is located in the inguinal canal, it may be placed into the scrotum if results indicate some testicular function. However, this gonad will need to undergo surveillance for gonadoblastoma. There are no current guidelines on surveillance; one option would be yearly ultrasound of the gonad.

- Removal of gonads that are not consistent with the assigned sex of rearing is controversial.
 - Depending on the specific diagnosis, potentially functional gonads may be retained with appropriate surveillance for tumor development.
 - Routine surveillance for the development of contrasexual puberty is warranted in those whose sex of rearing is discordant with gonadal sex.

If contrasexual puberty occurs, hormonal suppression with replacement of the desired sex hormone can be used to avoid gonadectomy until the individual is of age of consent.
 - In some states, removal of potentially functional gonads in a minor requires a court order.

Hormone therapy. Sex steroid therapy is important for the development of secondary sexual characteristics and for normal adolescent bone mass accrual.

- If an individual is given a **male** sex assignment:
 - A short course of testosterone therapy may be used in infancy for treatment of micropenis (stretched penile length that is 2.5 SD below the mean for age).
 - Testosterone therapy is typically required to initiate and sustain puberty.
- If an individual is given a **female** sex assignment:
 - Estrogen therapy is used to initiate breast development and puberty.
 - If the affected individual has a uterus, progesterone will be added once puberty has progressed in order to promote menstrual cycles.
- 46,XY individuals with a heterozygous pathogenic variant in *NR5A1* may need to be managed for adrenal insufficiency.

Psychosocial aspects of care. As noted in Lee et al [2006], "The initial contact with the parents of a child with a DSD is important, because first impressions from these encounters often persist. . . . Ample time and opportunity should be made for continued discussion with review of information previously provided."

- Open communication with affected individuals and families, including their active participation in the decision-making process, is critical.
- Providers need to address the concerns of the affected individual and family respectfully and in strict confidence.
- Assigned sex of rearing may not be congruent with gender identity, which is determined by the individual over time.

Fertility

- Most individuals with a nonsyndromic DSD are infertile due to dysgenetic or streak gonads. Some pathogenic variants in *NR5A1* are associated with normal testicular development in individuals with a 46,XY chromosome complement, which may allow for fertility, although assisted reproductive technology may be required.
- Women with 46,XY DSD or 46,XY CGD with müllerian structures may become pregnant through oocyte donation.

Surveillance

Regular follow up with an interdisciplinary DSD team including endocrinology, medical genetics, obstetrics/gynecology, psychology, and urology is indicated.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

5. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nonsyndromic disorders of testicular development can be inherited in a sex-limited autosomal recessive, sex-limited autosomal dominant, Y-linked, or X-linked manner depending on the causative genetic alteration.

- Sex-limited autosomal recessive inheritance: mutation of *DHH*
- Sex-limited autosomal dominant inheritance: intragenic mutation of *DMRT1*, *DHX37*, *MAP3K1*, or *NR5A1*; complete or partial deletion of *DMRT1*
- Y-linked inheritance: mutation of *SRY*
- X-linked inheritance: duplication at Xp21

Sex-Limited Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual with a *DHH*-related nonsyndromic disorder of testicular development are presumed to be heterozygous for a *DHH* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DHH* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
 - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are usually asymptomatic.

Sibs of a proband

- If both parents are known to be heterozygous for a *DHH* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants, a 50% chance of inheriting one pathogenic variant, and a 25% chance of inheriting neither of the familial pathogenic variants.
- XY sibs who inherit biallelic pathogenic variants will have clinical features.
- Heterozygotes (carriers) are usually asymptomatic.

Offspring of a proband

- Individuals with sex-limited autosomal recessive 46,XY nonsyndromic disorder of testicular development are frequently unable to reproduce.
- If assisted reproductive technology enables an individual with a sex-limited autosomal recessive nonsyndromic disorder of testicular development to have children, all offspring will be heterozygous for a pathogenic variant in *DHH* and will therefore be carriers and usually asymptomatic.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DHH* pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the *DHH* pathogenic variants in the family.

Sex-Limited Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- An individual with a sex-limited autosomal dominant disorder of testicular development caused by a *DMRT1*, *DHX37*, *MAP3K1*, or *NR5A1* pathogenic variant or a *DMRT1* deletion may have inherited the genetic alteration from their mother or mildly affected father.
- Some individuals with a sex-limited autosomal dominant disorder of testicular development have a *de novo* genetic alteration.
- Testing of the parents for the genetic alteration identified in the proband is recommended to allow reliable recurrence risk counseling.
- If the genetic alteration identified in the proband is not identified in either parent and parental identity testing has confirmed biological relatedness, the following possibilities should be considered:
 - The proband has a *de novo* genetic alteration.
 - The proband inherited a pathogenic variant from a parent with mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with a sex-limited autosomal dominant nonsyndromic disorder of testicular development may appear to be negative because of a milder phenotypic presentation in a parent or the appearance of reduced penetrance due to the sex-limited expression of the genetic variant. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents and the sex chromosome complement of the sib:

- If a parent of the proband has the genetic alteration identified in the proband, the risk to sibs of inheriting the genetic alteration is 50%.
 - 46,XY sibs who inherit the genetic alteration will have clinical features.
 - In general, individuals with a 46,XX chromosome complement and a heterozygous *DMRT1*, *DHX37*, *MAP3K1*, or *NR5A1* pathogenic variant or a heterozygous *DMRT1* deletion do not show clinical findings; however, some females with a heterozygous pathogenic variant in *NR5A1* develop primary ovarian insufficiency [Fabbri-Scallet et al 2020].
- If the genetic alteration identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of a proband

- Individuals with a sex-limited autosomal dominant nonsyndromic disorder of testicular development are frequently unable to reproduce. Some pathogenic variants in *NR5A1* may allow for male fertility but assisted reproductive technologies may be needed.
- If assisted reproductive technology enables individuals with a sex-limited autosomal dominant nonsyndromic disorder of testicular development to have children, each child would have a 50% chance of inheriting the genetic alteration. 46,XY offspring would show clinical features. 46,XX offspring would generally be unaffected, although some 46,XX individuals with a heterozygous *NR5A1* pathogenic variant could be at risk for primary ovarian insufficiency.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the genetic alteration identified in the proband, family members of the heterozygous parent may be at risk.

Y-Linked Inheritance – Risk to Family Members

Parents of a proband

- Most individuals with an *SRY*-related nonsyndromic disorder of testicular development have a *de novo* pathogenic variant.
- Rarely, individuals with an *SRY*-related nonsyndromic disorder of testicular development have a paternally inherited *SRY* pathogenic variant. In these families, the father has EITHER:
 - Somatic (and presumably germline) mosaicism for an *SRY* pathogenic variant [Isidor et al 2009];
 - OR
 - Reduced penetrance of an *SRY* pathogenic variant [Isidor et al 2009].
- The frequency of paternal mosaicism and *SRY* pathogenic variants with reduced penetrance is not known.
- The mother of an individual with an *SRY*-related nonsyndromic disorder of testicular development does not require evaluation/testing.

Sibs of a proband. The risk to XY sibs depends on the genetic status of the father (XX sibs are not at risk):

- Because probands with an *SRY*-related nonsyndromic disorder of testicular development usually have a *de novo* pathogenic variant, the risk to XY sibs of a proband is presumed to be low.
- If the father of the proband has germline mosaicism or an *SRY* pathogenic variant with reduced penetrance, he may transmit an *SRY* pathogenic variant to XY sibs of the proband.

Offspring of a proband

- Individuals with an *SRY* pathogenic variant are unlikely to reproduce.
- If assisted reproductive technologies can enable individuals with an *SRY* pathogenic variant to have children, such individuals will pass the pathogenic variant to all of their XY offspring and none of their XX offspring.

Other family members. The risk to other family members depends on the genetic status of the proband's father.

X-Linked Inheritance – Risk to Family Members

Parents of a proband

- In a family with more than one individual with an Xp21 duplication-related nonsyndromic disorder of testicular development, the mother of an affected individual is an obligate heterozygote (carrier) of the

duplication. Note: If a woman has more than one affected child and no other affected relatives and if the duplication cannot be detected in her DNA, she most likely has germline mosaicism.

- If only one family member is affected (i.e., a simplex case), the mother may be a heterozygote (carrier), the proband may have a *de novo* Xp21 duplication (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism.

Too few affected individuals have been reported to provide an accurate rate of *de novo* duplication; however, most of the affected individuals who have a small duplication inherited it from an unaffected carrier mother [Barbaro et al 2012].

- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.
- The father of an affected male will not have the disorder nor will he be hemizygous for the *NR0B1* duplication; therefore, he does not require further evaluation/testing.

Sibs of a proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an Xp21 duplication, the chance of transmitting it in each pregnancy is 50%. 46,XY sibs who inherit the duplication will be affected; 46,XX sibs who inherit the duplication will be heterozygous and will usually not be affected.
- If the proband represents a simplex case and if the Xp21 duplication cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband

- Individuals with an Xp21 duplication-related nonsyndromic disorder of testicular development are unlikely to reproduce.
- If assisted reproductive technology enables individuals with an Xp21 duplication-related nonsyndromic disorder of testicular development to have children, such individuals will pass the duplication to all of their XX offspring and none of their XY offspring.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the Xp21 duplication, and their offspring, depending on their sex chromosome complement, may be at risk of being heterozygous for the Xp21 duplication or of being affected.

Heterozygote detection. Molecular genetic testing of at-risk female relatives to determine their genetic status requires prior identification of the Xp21 duplication in the proband.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or are heterozygotes (carriers), or who are at increased risk of being heterozygotes (carriers) or affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the genetic cause of a nonsyndromic disorder of testicular development has been identified in an affected family member, prenatal and preimplantation genetic testing for a pregnancy at increased risk are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Accord Alliance**
Phone: 602-492-4144
www.AccordAlliance.org
- **Accord Alliance - DSD Guidelines**
[Clinical Guidelines and Handbook for Parents](#)
- **Accord Alliance- Lend a Helping Hand: a Resource Guide for DSD Care**
www.accordalliance.org/resource-guide
- **DSD Families**
United Kingdom
Email: info@d sdfamilies.org
www.d sdfamilies.org/charity
- **InterNational Council on Infertility Information Dissemination, Inc. (INCIID)**
Phone: 703-379-9178
Fax: 703-379-1593
Email: INCIIDinfo@inciid.org
www.inciid.org

Chapter Notes

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