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Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

Synonym: 46,XX Testicular DSD

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Summary

Clinical characteristics

Nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) are characterized by: the presence of a 46,XX karyotype; external genitalia ranging from typical male to ambiguous; two testicles; azoospermia; absence of müllerian structures; and absence of other syndromic features, such as congenital anomalies outside of the genitourinary system, learning disorders / cognitive impairment, or behavioral issues. Approximately 85% of individuals with nonsyndromic 46,XX testicular DSD present after puberty with normal pubic hair and normal penile size but small testes, gynecomastia, and sterility resulting from azoospermia. Approximately 15% of individuals with nonsyndromic 46,XX testicular DSD present at birth with ambiguous genitalia. Gender role and gender identity are reported as male. If untreated, males with 46,XX testicular DSD experience the consequences of testosterone deficiency.

Diagnosis/testing

Diagnosis of nonsyndromic 46,XX testicular DSD is based on the combination of clinical findings, endocrine testing, and cytogenetic testing. Endocrine studies usually show hypergonadotropic hypogonadism secondary to testicular failure. Cytogenetic studies at the 550-band level demonstrate a 46,XX karyotype. *SRY*, the gene that encodes the sex-determining region Y protein, is the principal gene known to be associated with 46,XX testicular DSD. Approximately 80% of individuals with nonsyndromic 46,XX testicular DSD are *SRY* positive, as shown by use of FISH or chromosomal microarray. Other causes in *SRY*-negative individuals include small copy number variants (CNVs) in or around *SOX3* or *SOX9* and specific heterozygous pathogenic variants in *NR5A1* or *WT1*.

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Management

Treatment of manifestations: Similar to that for other causes of testosterone deficiency. After age 14 years, low-dose testosterone therapy is initiated and gradually increased to reach adult levels. In affected individuals with short stature who are eligible for growth hormone therapy, testosterone therapy is either delayed or given at lower doses initially in order to maximize growth potential. Reduction mammoplasty may be considered if gynecomastia remains an issue following testosterone replacement therapy. Standard treatment for osteopenia, hypospadias, and cryptorchidism. Providers are encouraged to anticipate the need for further psychological support.

Surveillance: Measurement of length/height at each visit. Assessment of mood, libido, energy, erectile function, acne, breast tenderness, and presence or progression of gynecomastia at each visit in adolescence and adulthood. For those on testosterone replacement therapy: measurement of serum testosterone levels every three months (just prior to the next injection) until testosterone dose is optimized; then annual measurement of serum testosterone levels, lipid profile, and liver function tests. Measurement of hematocrit at three, six, and 12 months after initiation of testosterone therapy, then annually thereafter. Digital rectal examination and measurement of serum prostate-specific antigen at three, six, and 12 months after initiation of testosterone therapy in adults, then annually thereafter. Dual-energy x-ray absorptiometry scan every three to five years after puberty or annually, if osteopenia has been identified.

Agents/circumstances to avoid: Contraindications to testosterone replacement therapy include prostate cancer (known or suspected) and breast cancer; oral androgens such as methyltestosterone and fluoxymesterone should not be given because of liver toxicity.

Genetic counseling

The mode of inheritance and recurrence risk to sibs of a proband with a nonsyndromic 46,XX testicular DSD depend on the molecular diagnosis in the proband and the genetic status of the parents.

- *SRY*-positive 46,XX testicular DSD is generally not inherited because it results from *de novo* abnormal interchange between the Y chromosome and the X chromosome, resulting in the presence of *SRY* on the X chromosome and infertility. In the rare cases when *SRY* is translocated to another chromosome or when fertility is preserved, sex-limited autosomal dominant inheritance is observed.
- Pathogenic variants in *NR5A1* are inherited in an autosomal dominant fashion, with incomplete penetrance and variable expressivity. If a fertile parent is heterozygous, they will pass the variant to 50% of their offspring; offspring who are XX are at risk for testicular or ovotesticular DSD.
- To date, all known individuals with CNVs in or around *SOX3* whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo* pathogenic variant. In this scenario, the risk to sibs is low.
- Autosomal dominant inheritance has been documented for familial cases thought to be caused by CNVs in or around *SOX9*. However, only those with a 46,XX karyotype will be affected.
- To date, all known individuals with a pathogenic *WT1* variant that causes nonsyndromic 46,XX testicular DSD whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo* pathogenic variant. In this scenario, the risk to sibs is low.

GeneReview Scope

Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development: Included Disorders
• *SRY*-positive 46,XX testicular disorders/differences of sex development • *SRY*-negative 46,XX testicular disorders/differences of sex development

For synonyms and outdated names see Nomenclature.

Diagnosis

No consensus clinical diagnostic criteria for nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) have been published. However, algorithms have been developed for the evaluation and diagnosis of DSD, including nonsyndromic 46,XX testicular DSD [Délot & Vilain 2021].

Suggestive Findings

Nonsyndromic 46,XX testicular DSD **should be considered** in individuals with the following clinical, supportive laboratory, and imaging findings.

Clinical findings

- Male external genitalia that ranges from typical to ambiguous (penoscrotal hypospadias with or without chordee)
- Two testicles, typically smaller than average for age
- Absence of dysmorphic features and congenital anomalies outside of the genitourinary system
- Normal cognitive development

Supportive laboratory findings

- A 46,XX karyotype using conventional staining methods
- Azoospermia
- Endocrine studies that demonstrate hypergonadotropic hypogonadism secondary to testicular failure:
  - Basal serum concentration of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are moderately elevated (normal range for LH: 1.5-9 mIU/mL in adult males; for FSH: 2.0-9.2 mIU/mL).
  - Serum testosterone concentration is usually decreased, typically with serum testosterone concentration below 300 ng/dL in adults (normal range: 350-1,030 ng/dL in adult males).
  - Human chorionic gonadotropin (hCG) stimulation test typically shows a low-to-subnormal testosterone response, with little or no elevation of serum testosterone concentration after intramuscular injection of hCG.
- Preservation of the hypothalamic-pituitary axis. Gonadotropin-releasing hormone (GnRH) stimulation testing shows a normal LH and FSH response.

  Note: Such testing is not required for diagnosis.
- Testicular biopsy shows a decrease in size and number of seminiferous tubules, peritubular fibrosis, absence of germ cells, and hyperplasia of Leydig cells.

  Note: Such testing is not required for diagnosis.

Imaging findings. No evidence of müllerian structures on pelvic ultrasound or MRI

Establishing the Diagnosis

The diagnosis of nonsyndromic 46,XX testicular DSD **is established** in a 46,XX proband who has the clinical findings listed in Suggestive Findings and/or **one of the following** on molecular genetic testing (see Table 1):

- Presence of *SRY*, frequently detected through chromosomal microarray (CMA), fluorescence in situ hybridization (FISH) for *SRY*, or polymerase chain reaction (PCR) for *SRY*

Note: Some individuals will be diagnosed solely by CMA when there is evidence for two X chromosomes, no Y chromosome, and presence of *SRY*.

- Small copy number variants in or around *SOX3* or *SOX9* affecting only either *SOX3* or *SOX9*, respectively, on CMA or genome sequencing

  Note: (1) Depending on the microarray platform used and the probe coverage in and around *SOX3* and *SOX9,* these variants may not be detected by CMA. (2) It is important to verify with the testing laboratory that they will report variants in the gene desert around *SOX9*, as these may be overlooked and thus not reported.

- Specific heterozygous pathogenic variants in *NR5A1* or *WT1* (See Table 1 and Molecular Genetics.)

In a phenotypic male or an individual with ambiguous genitalia in whom a 46,XX karyotype is already established, molecular genetic testing approaches can include a combination of gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (chromosomal microarray analysis, genome sequencing).

Gene-Targeted Testing

FISH of an *SRY* probe to metaphase chromosomes should be performed first to determine the presence and, if positive, nature of the rearrangement (*SRY* located on an X chromosome vs *SRY* located on an autosome). The inheritance patterns and genetic counseling issues are different for each of these rearrangements.

If *SRY* is not present, the following can be considered next:

- **Sequence analysis** of *NR5A1* and *WT1* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants.

  Note: Only a specific pathogenic variant in *NR5A1* and pathogenic variants in a specific subdomain of *WT1* are known to be causative of nonsyndromic 46,XX testicular DSD at this time (see Table 1 and Molecular Genetics).

- **A DSD multigene panel** that includes *NR5A1*, *WT1*, and other genes of interest (see Differential Diagnosis) 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.

Comprehensive Genomic Testing

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (sometimes including the regulatory regions around *SOX3* and *SOX9*) that cannot be detected by sequence analysis, and small chromosomal rearrangements that may not be detected by karyotype.

- ***SOX3*.** Deletions just upstream of the open reading frame of *SOX3* [Sutton et al 2011] not including adjacent genes or duplications in *SOX3* [Sutton et al 2011, Moalem et al 2012] have been reported.

- ***SOX9.*** Small duplications or triplications in regulatory regions of *SOX9* (in mosaic or nonmosaic form) have been reported (reviewed in Croft et al [2018b]); they are thought to affect core *SOX9* enhancers located in the gene desert up to two megabases (Mb) upstream of *SOX9* [Croft et al 2018a].

Note: A balanced chromosomal translocation involving the 17q24.3 region has also been reported [Croft et al 2018b], but this should be detectable on karyotype.

Genome sequencing does not require the clinician to determine which gene is likely involved. Unlike exome sequencing, genome sequencing may able to detect copy number and single-nucleotide variants that are in noncoding areas of the genome, including in regulatory regions.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development by Phenotype

Gene [1, 2]	Proportion of Nonsyndromic 46,XX Testicular DSD by Phenotype Attributed to Pathogenic Variants in or around Gene		Proportion of Pathogenic Variants [3] Detectable by Method			
	Typical male genitalia	Ambiguous genitalia	Sequence analysis [4]	CMA [5]	GS [6]	FISH for *SRY*
NR5A1	Very rare [7]	Rare [7]	100% [8]	None reported [9]	100% [8]	NA
SOX3	Rare [10]	Very rare [11]	None reported	<100% [12]	Unknown	NA
SOX9	Very rare [10]	Rare [10]	None reported	<100% [12, 13]	Unknown	NA
SRY	80% [14]	Rare	100% [15]	100%	100%	100%
WT1	Very rare [16]	Very rare [16]	100% [17]	None reported [9]	100% [17]	NA

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Nonsyndromic 46,XX Testicular DSD by Phenotype Attributed to Pathogenic Variants in or around Gene		Proportion of Pathogenic Variants [3] Detectable by Method			
	Typical male genitalia	Ambiguous genitalia	Sequence analysis [4]	CMA [5]	GS [6]	FISH for *SRY*
Unknown	NA					

CMA = chromosomal microarray; DSD = disorders/differences of sex development; FISH = fluorescent in situ hybridization; NA = not applicable; GS = genome sequencing

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on variants detected in these genes.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here. Sequencing will typically detect presence of a gene but not chromosomal location.

5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the regions surrounding *SOX3* and *SOX9*. CMA will typically detect presence or absence of a chromosomal region but not the location of that region in relationship to other chromosomal regions.

6. Genome sequencing is typically performed by next-generation sequencing of sheared genomic DNA. Genome sequencing techniques have nonstandardized, highly variable coverage. Unlike exome sequencing, genome sequencing has the ability to identify structural variants and chromosome breakpoints in noncoding regions. The coverage of the genome is less than 100% and varies by laboratory.

7. Bashamboo et al [2016], Baetens et al [2017], Igarashi et al [2017], Knarston et al [2019]

8. To date, the only pathogenic variants in *NR5A1* identified as causing nonsyndromic 46,XX testicular DSD affect the Arg92 codon.

9. Due to the mechanism of disease causation, copy number variants in this gene are unlikely to lead to nonsyndromic 46,XX testicular DSD.

10. Croft et al [2018b]

11. Sutton et al [2011], Moalem et al [2012], Vetro et al [2015]

12. Depending on the microarray platform used and the probe coverage in and around *SOX3* and *SOX9*, these variants may not be detected by CMA.

13. It is important to verify with the testing laboratory that they will report variants in the gene desert around *SOX9*, as these may be overlooked and thus not reported.

14. Fechner et al [1993], McElreavey et al [1993], Boucekkine et al [1994]

15. As implied by the title of this table, sequence analysis that detects the present of *SRY* only leads to nonsyndromic 46,XX DSD in individuals with a known 46,XX chromosome complement and not to those with a 46,XY chromosome complement.

16. Gomes et al [2019], Eozenou et al [2020]

17. The only pathogenic variants described in individuals with this phenotype specifically affect the ZF4 domain (see Genetically Related Disorders and Molecular Genetics).

Clinical Characteristics

Clinical Description

By definition, nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) are not associated with dysmorphic features, congenital anomalies outside of the genitourinary system, learning disorders / cognitive impairment, or behavioral issues.

Approximately 85% of males with a 46,XX sex chromosome complement present after puberty with typical male pubic hair and penile size but small testes, gynecomastia, and sterility resulting from azoospermia [Zenteno-Ruiz et al 2001]. These typically represent individuals with nonsyndromic 46,XX testicular DSD, but ovotesticular DSD cannot be excluded as testicular biopsy is not clinically warranted and thus rarely performed.

Differences of the penis. Most affected individuals have an orthotopic urethral meatus and no abnormalities of phallic size (i.e., typical male external genitalia).

- Approximately 15% of individuals have ambiguous genitalia, typically penoscrotal hypospadias with or without chordee, noted at birth [Zenteno-Ruiz et al 2001].
- Anterior/distal hypospadias (atypical urethral opening) is also uncommon.

Testes. At birth, testes are typically descended but may be smaller and softer than usual. The testes may become firmer with age. A minority have cryptorchidism (undescended testes).

There has only been one case report of a germ cell tumor in an individual with nonsyndromic 46,XX testicular DSD who presented with ambiguous genitalia [Carcavilla et al 2008]. Leydig cell tumors have rarely been reported [Kim et al 2010, Osaka et al 2020]. As these appear to be rare events, no consensus tumor screening protocol has been recommended to date for individuals with 46,XX testicular DSD.

Decreased testosterone production. The natural history of individuals with nonsyndromic 46,XX testicular DSD, if untreated, is similar to the typical consequences of testosterone deficiency:

- Low libido and possible erectile dysfunction
- Decrease in secondary sexual characteristics, such as sparse body hair, infrequent need to shave, and reduced muscle mass
- Increase in fat mass with lower muscle strength
- Increased risk of osteopenia
- Increased risk of depression

Gynecomastia. Affected individuals frequently develop gynecomastia during puberty, the risk of which is related to the underlying cause (see Phenotype Correlations by Gene). Breast reduction surgery can be offered if the condition is of concern to the individual.

Fertility. Individuals with 46,XX testicular DSD are infertile, as they lack the AZF loci on the long arm of the Y chromosome (Yq) that allow normal spermatogenesis. Even in *SRY*-positive individuals, only genetic material from the short arm of the Y chromosome (Yp) is translocated onto another chromosome (most commonly the short arm of the X chromosome).

Gender roles and gender identity are reported as male for the common, unambiguous presentation, but systematic psychosexual assessment has not been performed on a significant number of individuals with 46,XX testicular DSD.

Phenotype Correlations by Gene

***SRY*-positive nonsyndromic 46,XX testicular DSD**

- Typically, these individuals do not have hypospadias.
- The finding of ambiguous genitalia is uncommon.
- Gynecomastia is much less common compared to those who have *SRY*-negative nonsyndromic 46,XX testicular DSD [Ergun-Longmire et al 2005].

***SRY*-negative nonsyndromic 46,XX testicular DSD of unknown cause**

- Affected individuals tend to present with ambiguous genitalia at birth, such as penoscrotal hypospadias and cryptorchidism, and, if untreated, almost always develop gynecomastia around the time of puberty.
- Affected individuals may have shorter-than-average height.

***SOX3*-related nonsyndromic 46,XX testicular DSD**

- Shorter-than-average stature has been described.
- Three individuals without genital ambiguity were incidentally diagnosed while being evaluated for developmental delay or gender dysphoria [Sutton et al 2011, Vetro et al 2015] (see Differential Diagnosis for discussion of syndromic forms of DSD).

***SOX9*-related nonsyndromic 46,XX testicular DSD.** As gonadal biopsy is not routinely performed, it is unclear what percentage of individuals with copy number variants in and around *SOX9* have testicular (vs ovotesticular) DSD (see Genetically Related Disorders).

***WT1*-related nonsyndromic 46,XX testicular DSD.** Of six reported individuals with *WT1*-related testicular DSD, only one had palpable gonads and typical male genitalia [Gomes et al 2019, Eozenou et al 2020, Sirokha et al 2021].

Penetrance

Heterozygous pathogenic variants in *NR5A1* that lead to the predicted p.Arg92Trp protein change demonstrated incomplete penetrance in 46,XX individuals, with fertile XX phenotypic females described [Bashamboo et al 2016, Baetens et al 2017, Knarston et al 2019].

Nomenclature

At an international consensus conference on the management of intersexuality held in October 2005 under the auspices of the Lawson Wilkins Pediatric Endocrine Society (USA) and the European Society for Pediatric Endocrinology, a multidisciplinary panel of experts proposed that the names "XX male syndrome" and "true hermaphrodite" be replaced by the names "46,XX testicular DSD" and "46,XX ovotesticular DSD," respectively [Lee et al 2006]. Recent evolutions suggest that the DSD acronym should be taken to mean "differences of sex development" in an effort to lessen stigma often associated with these conditions [Délot & Vilain 2021].

Prevalence

The prevalence of nonsyndromic 46,XX testicular DSD is estimated at 1:20,000 males.

Genetically Related (Allelic) Disorders

Allelic Nonsyndromic Disorders

Nonsyndromic 46,XX testicular and 46,XX ovotesticular (defined as the presence of both testicular and ovarian tissue in an individual) disorders/differences of sex development (DSD) may represent the same genetic entity, as both phenotypes are represented in families with 46,XX males. However, it is critical to differentiate them, as their potential outcomes differ, requiring different management. The presence of ovarian tissue, however minimal, in a self-identified boy may lead to feminization of physical characteristics (reduced hair, gynecomastia, menstrual flow), a possible indication for surgical excision of the ovarian portion of the gonad. Conversely, the presence of testicular tissue in a self-identified girl could eventually lead to unwanted hirsutism and may increase tumor risk.

Differences between 46,XX ovotesticular DSD and 46,XX testicular DSD include the following:

- Individuals with ovotesticular DSD (formerly known as "true hermaphrodites") have both testicular and ovarian tissue either as an ovotestis or as an ovary and a contralateral testis, whereas the gonads of individuals with 46,XX testicular DSD consist only of testicular tissue. The type of gonadal tissue can be established by gonadal biopsy. The possibility of bias of sampling of a gonadal biopsy that may miss the ovarian portion of the gonads needs to be considered.

- Ovotesticular DSD may be associated with the presence of a uterus or a hemi-uterus; individuals with nonsyndromic 46,XX testicular DSD have no müllerian structures.
- Endocrine investigations may reveal estrogen production in individuals with ovotesticular DSD.

All known genetic causes of nonsyndromic 46,XX testicular DSD can also lead to 46,XX ovotesticular DSD:

- ***NR5A1.*** Heterozygous pathogenic variants that lead to the predicted p.Arg92Trp protein change are associated with variable phenotypes, including ovotesticular DSD.
- ***SOX3.*** 46,XX ovotesticular DSD was reported in one individual with a 774-kb insertion translocated from chromosome 1 to a region 82 kb distal to *SOX3*, resulting in upregulation of *SOX3* expression [Haines et al 2015]. In this individual, ultrasound of bilateral descended gonads in a rugated scrotum suggested the gonads were testes; on biopsy, one of the gonads was found to contain ovarian tissue, resulting in a diagnosis of ovotesticular DSD [Haines et al 2015]. The translocation involving *SOX3* was inherited from a fertile mother. The discrepancy in phenotypes between the mother and proband could be attributed to differential X inactivation in the developing gonad, but this could not be demonstrated. Testicular DSD was suspected in the other five individuals with *SOX3*-associated 46,XX DSD reported to date, but histologically demonstrated in only one [Sutton et al 2011].
- ***SOX9.*** *SOX9*-associated duplications appear to be more frequently associated with ovotesticular DSD than with testicular DSD. The two phenotypes have not been reported in the same family.
- ***SRY.*** *SRY* translocations are much more frequently associated with nonsyndromic 46,XX testicular DSD than with ovotesticular DSD.
- ***WT1.*** Testicular DSD appears to be more frequent than ovotesticular DSD in 46,XX individuals with pathogenic variants affecting the ZF4 domain of *WT1*; of the nine individuals reported to date, four have histologically demonstrated testicular DSD (with two suspected) and two have documented ovotesticular DSD (with one suspected).

Table 2 summarizes allelic nonsyndromic DSD conditions.

Table 2. Allelic Nonsyndromic Disorders/Differences of Sex Development Conditions

Gene [1]	Condition	Molecular Pathogenesis	Clinical Characteristics / Comment
NR5A1 [2]	46,XY gonadal dysgenesis (OMIM 612965)	Heterozygous loss-of-function variants	Broad spectrum: isolated male infertility, ambiguous genitalia, anorchia, female w/ primary amenorrhea
	46,XX premature ovarian insufficiency (OMIM 612964)	Heterozygous loss-of-function variants	Primary or secondary amenorrhea; irregular menstruation
	46,XX ovotesticular DSD	p.Arg92Trp variant	See Differences between 46,XX ovotesticular DSD and 46,XX testicular DSD.
SOX3	46,XX ovotesticular DSD	774-kb insertion translocated from chr 1 to a region 82 kb distal to *SOX3*, → upregulation of *SOX3* expression [3]	
SOX9	46,XX ovotesticular DSD	See footnote 4.	
SRY	46,XY complete gonadal dysgenesis (OMIM 400044)	Hemizygous loss-of-function variant	Female external genitalia w/internal müllerian structures (uterus & fallopian tubes) but streak gonads w/o germ cells; affected persons most commonly come to medical attn at adolescence due to delayed puberty & amenorrhea.
	46,XX ovotesticular DSD	See footnote 5.	See Differences between 46,XX ovotesticular DSD and 46,XX testicular DSD.

Table 2. continued from previous page.

Gene [1]	Condition	Molecular Pathogenesis	Clinical Characteristics / Comment
WT1	46,XX ovotesticular DSD	Heterozygous loss-of-function variants affecting the ZF4 domain	• See Differences between 46,XX ovotesticular DSD and 46,XX testicular DSD. • Atypical genitalia; nonpalpable gonads; gonadoblastoma & dysgerminoma in 1 person. [6]

chr = chromosome; DSD = disorders/differences of sex development

1. Genes are listed in alphabetic order.

2. Heterozygous pathogenic variants in *NR5A1* are associated with a wide range of DSD phenotypes in XY individuals, including dysgenic testes with female phenotype and fertile XY fathers (reviewed in Suntharalingham et al [2015]). Heterozygous pathogenic variants in *NR5A1* are often inherited from XX mothers. Affected XX individuals can have a male phenotype due to testicular or ovotesticular DSD [Bashamboo et al 2016, Baetens et al 2017, Igarashi et al 2017, Knarston et al 2019].

3. Haines et al [2015]

4. 46,XX ovotesticular DSD can also be caused by small duplications of regions upstream of *SOX9* similar to those associated with the forms that present in adulthood with infertility (reviewed in Croft et al [2018b]). The duplicated regions overlap with but may be on average slightly larger than the regions duplicated in individuals presenting in adulthood with infertility.

5. Most commonly as the result of abnormal interchange between an X and Y chromosome resulting in translocation of *SRY* onto the X chromosome. Phenotypic variability may result from differential X inactivation of the chromosome carrying Y material in different tissues.

6. Eozenou et al [2020]

Allelic Syndromic Disorders

SOX3. Larger duplications of approximately six megabases (Mb) have been described in two individuals with 46,XX testicular DSD associated with developmental delay [Sutton et al 2011, Vetro et al 2015].

Table 3 summarizes allelic syndromic conditions.

Table 3. Other Allelic Syndromic Disorders

Gene	Condition	Molecular Pathogenesis	Clinical Characteristics
SOX3	Panhypopituitarism, X-linked (OMIM 312000)	Duplication or expansion of polyalanine tract	Panhypopituitarism has been described in a few 46,XY persons w/*SOX3* duplications (their heterozygous 46,XX mothers were not affected).
SOX9	Campomelic dysplasia (CD) [1]	Heterozygous loss-of-function variant	• Skeletal dysplasia; distinctive facies; Pierre Robin sequence w/cleft palate; shortening & bowing of long bones; clubfeet • Many affected infants die in neonatal period due to laryngotracheomalacia & respiratory compromise • Ambiguous genitalia or typical female external genitalia are seen in most XY persons. DSD is not a feature of 46,XX persons w/CD.

Table 3. continued from previous page.

Gene	Condition	Molecular Pathogenesis	Clinical Characteristics
WT1	Denys-Drash syndrome (See *WT1* Disorder.) [2]	Heterozygous variants in exons 8 or 9 encoding ZF2 & ZF3 domains	In Denys-Drash & Frasier syndromes, 46,XY children typically present w/ambiguous or female external genitalia, gonadal dysgenesis, nephrotic syndrome, Wilms tumor &/or gonadoblastoma.
	Frasier syndrome (See *WT1* Disorder.) [2]	Heterozygous splice site variants	
	Meacham syndrome (See *WT1* Disorder.) [2]	Mutational spectrum overlap w/Denys-Drash syndrome	Meacham syndrome is assoc w/congenital diaphragmatic hernia, congenital heart disease, & retention of & anomalies in müllerian structures.
	WAGR syndrome (See *PAX6*-Related Aniridia.) [2]	Contiguous gene syndrome due to haploinsufficiency of *WT1*, *PAX6*, & other genes	WAGR syndrome incls Wilms tumors, aniridia, genitourinary anomalies, & DD.
	Isolated nephrotic syndrome (See *WT1* Disorder.) [2]	Mutational spectrum overlap w/Denys-Drash syndrome	

DD = developmental delay
1. See also OMIM 114290.
2. See also OMIM *WT1* Clinical Synopsis Table.

Differential Diagnosis

Nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) must be differentiated from ovotesticular DSD as their potential outcomes differ, thus affecting management; see Genetically Related Disorders.

Other disorders to consider in the differential diagnosis of nonsyndromic 46,XX testicular DSD are summarized in Table 4. Sex chromosome aneuploidies, which represent the most common disorders in the differential diagnosis, can be distinguished from 46,XX testicular DSD by karyotype and by FISH testing.

Table 4. Disorders to Consider in the Differential Diagnosis of Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

Differential Category	Etiology	Phenotype
Sex chromosome aneuploidies	47,XXY (& variants: 48,XXXY; 49,XXXXY; 46XY/47,XXY mosaicism)	• Klinefelter syndrome (males w/hypogonadism, small testes, gynecomastia) • Unlike 46,XX testicular DSD, Klinefelter syndrome is often characterized by normal or tall stature, speech delay, learning disorders, & behavioral issues.
	46,XX/46,XY	May present w/external genitalia ranging from typical male to ambiguous to typical female
	45,X/46,XY	Affected persons often present as male & may have short stature; may be clinically indistinguishable from 46,XX testicular DSD.

Table 4. continued from previous page.

Differential Category	Etiology	Phenotype
Syndromic forms of 46,XX testicular DSD	*RSPO1*	Biallelic pathogenic variants are assoc w/palmoplantar hyperkeratosis with squamous cell carcinoma of skin & 46,XX testicular DSD. [1]
	Yp translocation assoc w/partial or complete Xp monosomy	Rare 46,XX males in whom the translocation of Y material to the X chromosome has resulted in loss of X material may present w/syndromic form associating an XX karyotype & male or ambiguous genitalia w/characteristics of partial monosomy Xp, as in microphthalmia with linear skin defects syndrome (MIDAS complex), an X-linked disorder generally lethal in XY persons.
	Balanced translocation involving *SOX9* [2]	46,XX testicular DSD w/dysmorphic facial features
	Deletion of multiple genes around *SOX3* or Mb-size duplications incl *SOX3* [3]	46,XX testicular DSD & DD (w/o ambiguous genitalia)
	NR2F2	Frameshift variant in or deletion of *NR2F* can cause testicular or ovotesticular DSD assoc w/cardiac malformations. [4]
Prenatal exposure of 46,XX fetuses to androgens	*CYP21A2*	• Biallelic pathogenic variants are assoc w/21-hydroxylase deficiency (most common cause of congenital adrenal hyperplasia); excessive adrenal androgen biosynthesis results in virilization in all persons & salt wasting in some. • Virilized females may have an enlarged clitorophallic structure & urogenital sinus; uterus & ovaries are normal.
	Externally administered androgens (e.g., danazol) or androgens endogenously produced by the mother	Virilization resulting in an infant w/ambiguous genitalia that may look similar to those of a male w/46,XX testicular DSD & ambiguous genitalia

DD = developmental delay; Mb = megabase
1. See OMIM 610644.
2. 46,XX,t(12;17)(q14.3;q24.3) [Refai et al 2010] and 46,XX,t(11;17)(p13;q24.3) [Vetro et al 2015]
3. Sutton et al [2011], Vetro et al [2015]
4. See OMIM 618901.

Management

No clinical practice guidelines for nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of the condition and needs in an individual diagnosed with nonsyndromic 46,XX testicular DSD, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

System/Concern	Evaluation	Comment
Constitutional	Measurement of length/height	To assess for short stature

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Endocrinology	Measurement of LH, FSH, & total testosterone levels	In those age >10 yrs
	Assessment of libido, energy, erectile function, acne, breast tenderness, & presence of gynecomastia	In adolescents & adults
	Baseline DXA scan in adolescents & adults	To assess bone mineral density
Urology	Physical exam for evidence of undervirilization	Incl assessment of length & width of phallus; location of urethral meatus; location of gonads through palpation & size measurement w/orchidometer
	Digital rectal exam & measurement of PSA [1]	In adults, prior to initiating testosterone replacement therapy [1] (See Table 6.)
Psychology	Assessment of mood & gender identity	By mental health professional
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of nonsyndromic 46,XX testicular DSD to facilitate medical & personal decision making
Individual & family support/ resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

DSD = disorders/differences of sex development; DXA = dual-energy x-ray absorptiometry; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MOI = mode of inheritance; PSA = prostate-specific antigen

1. Abnormalities in either of these may indicate the presence of prostate cancer; in this scenario, supplemental testosterone therapy may be contraindicated.

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

Manifestation/Concern	Treatment	Considerations/Other
Short stature	Growth hormone therapy may be considered.	Referral to endocrinologist recommended
Low or absent serum testosterone levels [1]	• Low-dose testosterone replacement therapy can be initiated after age 14 yrs. [2, 3] • Testosterone enanthate [4] is given IM [5] every 3-4 wks, starting at 100 mg & ↑ by 50 mg every 6 mos to 200-400 mg. • In adulthood, treatment should plateau at best possible dosage, typically 50-400 mg every 2-4 wks.	• If person has short stature & is eligible for growth hormone therapy, testosterone therapy should be either delayed or given at lower doses initially to maximize growth potential. • Side effects incl pain assoc w/injection & large variations of serum testosterone concentration between injections, resulting in ↑ risk of mood swings.
Gynecomastia	Reduction mammoplasty may be considered if gynecomastia is causing psychological distress.	Regression of gynecomastia may occur w/testosterone replacement therapy.
Osteopenia	Standard treatment per endocrinologist	May incl calcium, exercise, vitamin D, biphosphonates, or calcitonin
Undervirilization	Standard therapy per urologist	May incl orchidopexy &/or hypospadias repair

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Psychological distress	Referral to mental health professional	Sensitivity is necessary when conveying information to persons w/nonsyndromic 46,XX testicular DSD about genetic cause of the disorder & assoc sterility.

IM = intramuscularly
1. Prior to initiating treatment with supplemental testosterone in adults, perform a digital rectal examination and measurement of prostate-specific antigen (PSA), abnormalities of which would be a contraindication to the treatment.
2. Physicians should check for the most current preparations and dosage recommendations before initiating testosterone replacement therapy.
3. Initial high doses of testosterone should be avoided to prevent priapism.
4. Injection of testosterone enanthate is the preferred method of replacement therapy because of low cost and easy, at-home regulation of dosage.
5. Alternative delivery systems that result in more stable dosing include transdermal patches (scrotal and nonscrotal) and transdermal gels. Testosterone-containing gels, however, are associated with the risk of interpersonal transfer, which can be reduced by the use of newer hydroalcoholic gels.

Surveillance

Table 7. Recommended Surveillance for Individuals with Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

System/Concern	Evaluation	Frequency
Short stature	Measurement of length/height	At each visit
Low testosterone levels	Assessment of mood, libido, energy, erectile function, acne, breast tenderness, & presence or progression of gynecomastia	At each visit in adolescence & adulthood
For those on testosterone replacement therapy	Measurement of serum testosterone levels	• Every 3 mos (prior to next injection) to evaluate nadir testosterone concentrations [1] • Once optimal dose is established, annual measurements are sufficient.
	Digital rectal exam & measurement of PSA in adults [2]	3, 6, & 12 mos after initiation of testosterone therapy; then annually
	Measurement of hematocrit [3]	3, 6, & 12 mos after initiation of testosterone therapy; then annually
	Lipid profile & liver function tests	Annually
Osteopenia	DXA scan	Every 3-5 yrs after puberty or annually if osteopenia has been identified

DXA = dual-energy x-ray absorptiometry; PSA = prostate-specific antigen
1. Concentrations lower than 200 ng/dL or higher than 500 ng/dL may require adjustment of total dose or frequency.
2. To evaluate for the presence of an overt prostate cancer, which would be a contraindication to supplemental testosterone treatment.
3. Increased hematocrit may lead to risk of hypoxia and sleep apnea.

Agents/Circumstances to Avoid

Contraindications to testosterone replacement therapy include prostate cancer (known or suspected) and breast cancer.

Oral androgens such as methyltestosterone and fluoxymesterone should not be given (especially for long-term therapy) because of liver toxicity.

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 in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this condition.

Genetic Counseling

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 and Risk to Sibs of a Proband

The mode of inheritance and recurrence risk to sibs of a proband with a nonsyndromic 46,XX testicular disorder/difference of sex development (DSD) depend on the molecular diagnosis in the proband and the genetic status of the parents (see Table 8). The reports of cryptic mosaic/chimeric translocations of *SRY* to the X chromosome seen only in gonads but not blood [Inoue et al 1998, Queipo et al 2002] complicate evaluation of recurrence risk and genetic counseling.

Table 8. Mode of Inheritance and Recurrence Risk for Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development

Molecular Diagnosis in Proband	Genetic Mechanism	Genetic Status of Proband's Parents	Recurrence Risk in Sibs of a Proband
***SRY*-positive 46,XX testicular DSD**	Almost all probands have a *de novo* translocation of *SRY* to an X chromosome. Karyotype of the father of a proband can be evaluated for rare possibility that the father has an extra X-linked copy of *SRY.* [1]	Parents are unaffected & are not carriers.	Low (<1%)
		The XY father has 2 copies of *SRY* (1 translocated to the X chromosome & 1 on the Y chromosome).	XX sibs will have 46,XX testicular or ovotesticular DSD; XY sibs will not be affected.
	SRY translocation to an autosome. An unaffected father may carry the translocation. Carrier status of the father should be assessed to evaluate recurrence risk.	Parents are unaffected & are not carriers.	Not ↑ over empiric risk in general population [2]
		The father is a carrier of a translocated *SRY*.	XX sibs have a 50% chance of inheriting the translocated *SRY* & having 46,XX testicular or ovotesticular DSD; XY sibs will not be affected.
***NR5A1*-related 46,XX testicular DSD**	Recurrent missense variant p.Arg92Trp, *de novo* or inherited in an AD fashion, w/incomplete penetrance & variable expressivity. Genetic status of both parents should be assessed to guide genetic counseling about recurrence risk.	At least 1 fertile 46,XY father has transmitted the variant to affected children. Heterozygous pathogenic variants in *NR5A1* are often inherited from XX mothers.	If a fertile parent is heterozygous, they will pass the variant to 50% of their offspring, who are at risk of testicular or ovotesticular DSD if XX. At least 1 sib w/46,XY karyotype has been reported, with a phenotype of gonadal dysgenesis & female anatomy.
***SOX3*-related 46,XX testicular DSD**	Microdeletions just upstream of the open reading frame of *SOX3* or microduplications in *SOX3.* These alterations have been *de novo* in all persons reported to date.	To date, all reported parents are unaffected & are not carriers.	To date, no sibs have been affected.

Table 8. continued from previous page.

Molecular Diagnosis in Proband	Genetic Mechanism	Genetic Status of Proband's Parents	Recurrence Risk in Sibs of a Proband
SOX9-related 46,XX testicular DSD	Rearrangement/duplication involving *SOX9*. [3] Transmission through an unaffected 46,XY father has been demonstrated in at least 2 families w/ testicular DSD & 3 w/ovotesticular DSD. Carrier status of the father should be assessed to evaluate recurrence risk.	Parents are unaffected & are not carriers.	Not ↑ over empiric risk in general population [2]
		The father is heterozygous for a CNV in or around *SOX9*. All reported 46,XY carriers have been fertile, anatomically typical males. One such XY father (the father of a proband w/ovotesticular DSD) was reported to have inherited the duplication from his fertile 46,XX mother.	The risk to the sibs of inheriting the CNV is 50%. Persons w/ 46,XX karyotype who inherit the CNV are at risk of having 46,XX testicular (or ovotesticular) DSD. Persons w/46,XY karyotype will be typical fertile males.
_WT1_-related 46,XX testicular DSD	Frameshift & missense variants affecting the ZF4 domain of *WT1*. These alterations have been *de novo* in all persons reported to date.	To date, all reported parents are unaffected & not carriers.	One XY sib w/the recurrent p.Arg500Gln variant presented w/Meacham syndrome, male external genitalia, anorchia, & diaphragmatic hernia. No recurrences have been reported in the other 7 families to date.
SRY-negative 46,XX testicular DSD not caused by _SOX9_, _SOX3_, _NR5A1_, or _WT1_ pathogenic variants	Unknown	If the family history suggests an AR [4] MOI, both parents are presumed to be carriers of 1 causative pathogenic variant.	In AR inheritance, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, & a 25% chance of being unaffected & not a carrier.

AD = autosomal dominant; AR = autosomal recessive; CNV = copy number variant; DSD = disorders/differences of sex development; MOI = mode of inheritance

1. Abbas et al [1993] reported a fertile 46,XY male with a copy of *SRY* translocated to his X chromosome and one copy of *SRY* on his normal Y chromosome. He had two affected children: a son who had *SRY*-positive 46,XX testicular DSD and a daughter with *SRY*-positive 46,XX ovotesticular DSD.

2. This risk could be theoretically increased in case of paternal germline mosaicism.

3. Small duplication or triplication of the promoter region of *SOX9*; a balanced chromosomal translocation involving the 17q24.3 region; or duplication of the entire *SOX9* gene (reviewed in Croft et al [2018b]).

4. Although recurrence in sibs has suggested autosomal recessive inheritance (e.g., McElreavey et al [1993]), it is not known if autosomal recessive inheritance is the correct explanation for the recurrence pattern observed.

Offspring of a proband. Individuals with nonsyndromic 46,XX testicular DSD are infertile.

Related Genetic Counseling Issues

Management of infertility. A management option for infertility in couples where the male has 46,XX testicular DSD is artificial insemination of the female partner with donor sperm.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

Prenatal Testing and Preimplantation Genetic Testing

Pregnancies known to be at increased risk. Once the genetic cause of 46,XX testicular DSD has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Pregnancies not known to be at increased risk. In most cases, the suspicion of 46,XX testicular DSD arises during pregnancy when the karyotype (done for an unrelated reason) or the result of a noninvasive prenatal test is discordant with the phenotypic sex observed by ultrasound examination.

An *SRY*-positive result decreases (but does not exclude) the likelihood of ambiguous genitalia. The main issues with prenatal diagnosis of 46,XX testicular DSD are:

- The unknown reliability of the determination of the anatomic sex by ultrasound examination;
- The phenotypic variability associated with most known etiologies;
- The difficulty in prenatally diagnosing or ruling out all the conditions that could be associated with discordant phenotypic and chromosomal sex.

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.

- **MedlinePlus**
  46,XX testicular disorder of sex development
- **Accord Alliance**
  Phone: 602-492-4144
  www.AccordAlliance.org
- **Differences of Sex Development - Translational Research Network**
  DSD-TRN
- **InterNational Council on Infertility Information Dissemination, Inc. (INCIID)**
  Phone: 703-379-9178
  Fax: 703-379-1593
  Email: INCIIDinfo@inciid.org
  www.inciid.org
- **RESOLVE: The National Infertility Association**
  7918 Jones Branch Drive
  Suite 300
  McLean VA 22102
  Phone: 703-556-7172
  Fax: 703-506-3266
  Email: info@resolve.org
  www.resolve.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NR5A1	9q33.3	Steroidogenic factor 1	NR5A1 database	NR5A1	NR5A1
SOX3	Xq27.1	Transcription factor SOX-3	SOX3 @ LOVD	SOX3	SOX3
SOX9	17q24.3	Transcription factor SOX-9	SOX9 database	SOX9	SOX9
SRY	Yp11.2	Sex-determining region Y protein	SRY database	SRY	SRY
WT1	11p13	Wilms tumor protein	WT1 database	WT1	WT1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development (View All in OMIM)

184757	NUCLEAR RECEPTOR SUBFAMILY 5, GROUP A, MEMBER 1; NR5A1
278850	46,XX SEX REVERSAL 2; SRXX2
300833	46,XX SEX REVERSAL 3; SRXX3
313430	SRY-BOX 3; SOX3
400045	46,XX SEX REVERSAL 1; SRXX1
480000	SEX-DETERMINING REGION Y; SRY
607102	WT1 TRANSCRIPTION FACTOR; WT1
608160	SRY-BOX 9; SOX9
617480	46,XX SEX REVERSAL 4; SRXX4

Molecular Pathogenesis

Approximately 80% of individuals with nonsyndromic 46,XX testicular disorders/differences of sex development (DSD) have the condition due to the presence of a small Y chromosome fragment (including *SRY*) in the genome that resulted from an abnormal terminal X-Y exchange during paternal meiosis. This abnormal recombination involves highly homologous loci (recombination hot spots) on the sex-specific part of the X and Y chromosomes [Weil et al 1994].

Mechanism of disease causation

- ***NR5A1.*** The *NR5A1* c.274C>T (p.Arg92Trp) pathogenic variant has been shown to repress the female-specific WNT signaling pathways [Knarston et al 2019].
- ***SOX3.*** Duplications or translocation in regulatory regions of *SOX3*, a gene very structurally similar to *SRY* and not normally expressed in gonadal tissue, are thought to trigger ectopic expression of *SOX3* in XX developing gonadal tissues, leading to a male developmental pathway [Sutton et al 2011].
- ***SOX9.*** Duplications and triplications in the regulatory regions of *SOX9* are thought to trigger overexpression of *SOX9*, the immediate downstream target of *SRY* in the male developmental pathway, to levels sufficient to override repression of the ovarian pathway and drive the formation of testes or ovotestes in the absence of *SRY*.
- ***SRY*** is the primary sex-determination gene, triggering the male developmental pathway in the bipotential gonad [Sinclair et al 1990]. Presence of Y chromosome material including *SRY*, most frequently translocated onto the X chromosome (rare translocations to autosomes have been described), triggers the

male gonadal differentiation cascade, but absence of the other Y-chromosome genes results in azoospermia and infertility.

- ***WT1*** pathogenic variants in the fourth zinc finger domain (ZF4) interfere with the pro-ovarian beta-catenin pathway and activate the pro-testis *SOX9*-dependent pathway in vitro [Eozenou et al 2020].

Table 9. Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
NR5A1	• Only the p.Arg92Trp pathogenic variant is clearly diagnostic. • Variable expressivity / reduced penetrance in families make genetic counseling difficult.
SOX3	None
SOX9	CNVs affecting *SOX9* expression are in a gene desert & may not be identified by automated algorithms. [2]
SRY	• Only the presence of a copy of *SRY* in a 46,XX genome, not single-nucleotide variants in *SRY*, is relevant to 46,XX testicular DSD etiology. • *SRY* may be present in mosaic form in blood, & cases have been reported where *SRY* is found in the gonad only, not in blood [Inoue et al 1998, Queipo et al 2002].
WT1	Only variants affecting the ZF4 domain have been assoc w/nonsydromic 46,XX testicular DSD.

CNV = copy number variant; DSD = disorders/differences of sex development
1. Genes are listed in alphabetic order.
2. At least one case of a 46,XX individual who was mosaic for *SOX9*-associated duplications has been reported [Huang et al 1999].

Table 10. Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change (Alias [2])	Predicted Protein Change (Alias [2])	Comment [References]
NR5A1	NM_004959.5 NP_004950.2	c.274C>T	p.Arg92Trp	Recurrent pathogenic variant [Bashamboo et al 2016, Baetens et al 2017, Igarashi et al 2017, Knarston et al 2019]
WT1	NM_024426.6 NP_077744.4	c.1499G>A (c.1484G>A)	p.Arg500Gln (p.Arg495Gln)	Recurrent pathogenic variant [Eozenou et al 2020]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Genes are listed in alphabetic order.
2. Variant designation that does not conform to current naming conventions

Chapter Notes

Author Notes

Eric Vilain is a founder of the NIH-funded DSD-TRN (Disorders/Differences of Sex Development Translational Research Network). Emmanuèle Délot serves as the national coordinator and chair of the Publications & Research committee for the network. Both have investigated the genetics and mechanisms of DSD, including 46,XX testicular DSD, for more than 20 years.

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