

Prenatal Testing for SRY Gene Variants: 46,XY Complete or Partial Gonadal Dysgenesis or 46,XX Testicular Disorder of Sex Development

Disorder also known as: Testis-Determining Factor (TDF/TDY); Swyer Syndrome; 46,XY Disorder of Sex Development (DSD)

Clinical Features:

46,XY complete gonadal dysgenesis (CGD) is marked by a lack of testicular development, streak gonads, the presence of well-developed Mullerian structures (a uterus and fallopian tubes), underdeveloped breasts, and female external genitalia. Individuals often are not diagnosed until puberty when they present with amenorrhea and the absence of secondary sexual characteristics; however, the diagnosis may be suspected in utero due to an inconsistency between karyotype (46,XY) and ultrasound findings (female). In rare cases, SRY variants have been associated with 46,XY partial gonadal dysgenesis (also called 46,XY disorder of sex development or 46,XY DSD). 46,XY DSD is characterized by the presence of ambiguous genitalia, dysgenetic testes, and absent to fully developed Mullerian structures. Both 46,XY CGD and 46,XY DSD are associated with an increased incidence of gonadoblastoma and germinoma.

46,XY gonadal dysgenesis is a genetically heterogeneous disorder with autosomal, X-, and Y-linked forms.¹ The Y-linked form is caused by pathogenic variants or deletions of the SRY gene (also known as TDF or testis determining factor), which is located on chromosome Yp11.3. Typically, the Y-linked form of XY complete gonadal dysgenesis is sporadic, although approximately 30% of all identified SRY variants are inherited.²

Individuals with 46,XX testicular DSD is characterized by a normal female karyotype and ambiguous or normal male external genitalia with two testicles, azoospermia, and absent Mullerian structures.

Variants in the SRY gene may be suspected when the fetal karyotype is 46,XY but ultrasound reveals apparently female or ambiguous external genitalia or when the fetal karyotype is 46,XX but ultrasound reveals apparently male or ambiguous external genitalia. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variants can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Inheritance Pattern/Genetics:

Y-Linked

Test Methods:

GeneDx offers prenatal whole genome chromosomal microarray or prenatal targeted array analysis for concern with 46,XY gonadal dysgenesis or 46,XX testicular DSD to determine whether the SRY gene is present or absent (see GenomeDx information sheet for more details: <http://www.genedx.com/site/genomedx>). Additionally, for concern with 46,XY gonadal dysgenesis, using genomic DNA, analysis is performed by bi-directional sequencing of the complete coding region of the SRY gene. For known familial variants, the relevant portion of the SRY gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

Test Sensitivity:

Approximately 20-30% of individuals with 46,XY CGD harbor a deletion or a variant of the SRY gene. Specifically, deletions of the SRY gene detectable by array are identified in 10-15% of individuals with 46,XY CGD, and an additional 10-15% of individuals with 46,XY CGD have a variant identifiable by sequencing.³ The sensitivity of SRY gene analysis in prenatal cases ascertained based on fetal ultrasound/karyotype inconsistency is currently unknown.

In approximately 80% of individuals with 46,XX testicular DSD, the presence of the SRY gene is confirmed by chromosomal microarray or FISH.⁷ The SRY region is typically present on the X chromosome. In the remaining 20% of cases, the cause of 46,XX testicular DSD is typically not known.

References:

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