Sequencing and Presence/Absence Testing of the SRY Gene in 46,XY Complete or Partial Gonadal Dysgenesis or 46,XX Disorder of Sex Development

Disorder also known as: Testis-Determining Factor (TDF/TDY); Swyer Syndrome

Clinical Features:
46,XY complete gonadal dysgenesis (CGD) is marked by 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 with 46,XY CGD are typically raised female and present at puberty 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] GeneDx also offers sequencing of the NR5A1 (SF-1) gene, which causes autosomal dominant 46,XY gonadal dysgenesis with or without adrenal insufficiency.

GeneDx also offers SRY Presence/Absence testing to determine the presence or absence of the SRY gene in individuals with 46,XX testicular DSD who have a 46,XX karyotype and ambiguous or normal male external genitalia with two testicles, azoospermia, and absent Mullerian structures.

Genetics:
Pathogenic variants in the SRY gene are inherited in a Y-linked manner. The SRY gene contains no introns and produces a 900-base-pair transcript. Complete deletions of the SRY gene are identifiable by FISH, PCR, or other methods. They occur due to abnormal X-Y recombination during paternal meiosis, resulting in the replacement of the normal Yp chromosome material with chromosome material from Xp.

In individuals with 46,XY CGD, the majority of SRY variants identifiable by sequencing are missense or nonsense substitutions located within the high mobility group (HMG) box domain of the gene, although small deletions and insertions have also been reported.[6] In contrast, SRY variants in individuals with 46,XY DSD are typically located outside of the HMG box in the 5' or 3' end of the gene, although a variant in the HMG box has been reported.[5]

Test Methods:

Gene Sequencing: For individuals with 46,XY gonadal dysgenesis, bi-directional sequence analysis of the entire coding region of the SRY gene is available using genomic DNA obtained from buccal (cheek) brushes or blood (1-5mL in EDTA).

Presence/Absence Testing: To determine whether the SRY gene is present or absent in an individual with a 46,XX karyotype, PCR amplification and analysis on an agarose gel for the SRY gene is performed on the patient sample and on a normal 46,XY control sample. Additionally, GeneDx offers SRY FISH analysis of the SRY gene.

Test Sensitivity:

Approximately 20-30% of individuals with 46,XY CGD harbor a pathogenic deletion or a variant of the SRY gene. Specifically, deletions of the SRY gene detectable by FISH, PCR, or other methods are identified in 10-15% of individuals with 46,XY CGD, and an additional 10-15% of individuals with 46,XY CGD have a pathogenic variant identifiable by sequencing.[3] Rarely, pathogenic variants of the SRY gene have also been identified in individuals with 46,XY DSD.[2,4,5]

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