Genetic Testing of the NR5A1 (SF-1) Gene in 46,XX Disorder of Sex Development

Disorder also known as: 46,XY DSD; XY sex reversal with or without adrenal failure; Gonadal dysgenesis

Clinical Features:
Pathogenic variants in the NR5A1 gene result in a 46,XY disorder of sex development (DSD) with or without adrenal insufficiency. At the severe end of the spectrum, individuals with NR5A1 variants have presented with primary adrenal failure and 46,XY complete gonadal dysgenesis characterized by female external genitalia, severe testicular dysgenesis, and the presence of Mullerian structures or in patients presenting at puberty with 46,XY primary amenorrhea. At the milder end of the spectrum, NR5A1 variants have been reported in individuals with normal adrenal function and 46,XY partial gonadal dysgenesis resulting in ambiguous genitalia, bilateral testes, and no evidence of Mullerian structures. Variants in the NR5A1 gene have also been identified in several patients with severe (penoscrotal) hypospadias and undescended testes, and in males with idiopathic infertility.

Maternally inherited NR5A1 variants have been described, and female variant carriers have had apparently normal adrenal and ovarian function.\(^1\)\(^6\) However, an NR5A1 variant was identified in a 46,XX female with adrenal insufficiency.\(^7\) Variants also were identified in 46,XX females with premature ovarian failure due to primary ovarian insufficiency.\(^8\)

Genetics:
NR5A1 is a transcription factor that regulates expression of genes involved in sexual differentiation, reproduction, and steroidogenesis.\(^2\) The gene is located on chromosome 9q33 and contains seven exons spanning approximately 30-kb. It encodes a protein of 461 amino acid that contains two DNA binding domains, a hinge region, and a ligand-binding domain.\(^9\)

Pathogenic variants in the NR5A1 gene are typically inherited in an autosomal dominant manner, often due to de novo variants. The inheritance may appear to be sex-limited in some families.\(^6\) Autosomal recessive inheritance has also been reported.

To date, more than 30 variants have been reported in the NR5A1 gene. No variant hotspots have been identified, and variants are scattered throughout the gene. The majority of variants are missense changes, although nonsense variants, small deletions, and small insertions have also been identified. Rarely, deletions of the entire NR5A1 gene have been reported in individuals with 46,XY DSD.\(^10\) Genotype-phenotype correlations are not well established at this time.
Test Methods:
Analysis is performed by bi-directional sequencing of the six coding exons (exons 2-7) and the exon/intron splice junctions of the NR5A1 gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
46,XY disorders of sex development are genetically heterogeneous. Previous studies have identified NR5A1 variants in 13-33% of patients with 46,XY partial or complete gonadal dysgenesis and normal adrenal function. NR5A1 variants have also been reported in 2 of 17 (~12%) patients with 46,XY gonadal dysgenesis and adrenal failure. Additionally, NR5A1 variants were identified in 3/60 (5%) of males with hypospadias, including 3/20 (15%) with penoscrotal hypospadias and undescended testes. A recent study also identified NR5A1 variants in 7/315 (~2%) of males with isolated idiopathic spermatogenic failure.

Recently, NR5A1 variants were identified in 2 of 25 (8%) 46,XX females with sporadic primary ovarian insufficiency and in four families with both primary ovarian insufficiency and 46,XY DSD. An NR5A1 variant has been identified in one 46,XX female with apparently isolated adrenal insufficiency, although NR5A1 variants appear to be a rare cause of primary adrenal failure in the absence of gonadal dysgenesis.

References: