

Prenatal testing for the NR5A1 Gene in 46,XY Disorder of Sex Development

Disorder also known as: SF1 gene; 46,XY DSD; XY sex reversal with or without adrenal failure; Gonadal dysgenesis

Clinical Features:

Children and Adults: 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^{1,7}. However, an NR5A1 variant was identified in a 46,XX female with adrenal insufficiency⁶. Variants also were identified in 46,XX females with premature ovarian failure due to primary ovarian insufficiency⁷.

Prenatal Ultrasound Findings: Variants in the NR5A1 gene may be suspected when the fetal karyotype is 46,XY but ultrasound reveals apparently female or ambiguous external genitalia. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Genetics:

Typically autosomal dominant, often due to de novo variants. May be sex-limited in some families⁵. Autosomal recessive inheritance has also been reported¹.

Test Methods:

Using genomic DNA, 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. For known familial variants, the relevant portion of the NR5A1 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:

46,XY disorders of sex development are genetically heterogeneous. The sensitivity of NR5A1 gene analysis in prenatal cases ascertained based on fetal ultrasound/karyotype inconsistency is currently unknown. For postnatal cases, previous studies have identified NR5A1 variants in 13-33% of patients with 46,XY partial or complete gonadal dysgenesis and normal adrenal function^{5,2,11}. NR5A1 variants have also been reported in 2 of 17 (~12%) patients with 46,XY gonadal dysgenesis and adrenal failure.⁴ Additionally, NR5A1 variants were identified in 3/60 (5%) of males with hypospadias, including 3/20 (15%) with penoscrotal hypospadias and undescended testes.³ A recent study also identified NR5A1 variants in 7/315 (~2%) of males with isolated idiopathic spermatogenic failure.⁴ 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.⁷ An NR5A1 variant has been identified in one 46,XX female with apparently isolated adrenal insufficiency (Biaison-Lauber et al., 2000), although NR5A1 variants appear to be a rare cause of primary adrenal failure in the absence of gonadal dysgenesis.¹²

References:

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