

## Prenatal testing for SRD5A2 Gene Variants: 5- $\alpha$ Reductase Deficiency

**Disorder also known as:** Pseudovaginal perineoscrotal hypospadias (PPSH)

### **Clinical Features:**

5- $\alpha$  reductase deficiency is a 46,XY disorder of sex development (DSD) caused by reduced or absent function of the steroid 5- $\alpha$  reductase type 2 enzyme, which converts testosterone (T) into dihydrotestosterone (DHT) during embryogenesis. Individuals with 5- $\alpha$  reductase deficiency have normal Wolffian duct differentiation, but at birth the appearance of the external genitalia ranges from normal female to undermasculinized male. The classic presentation is ambiguous genitalia characterized by perineoscrotal hypospadias with pseudovagina, microphallus, and cryptorchidism. A recent study indicated that the most common phenotype is cliteromegaly, which was present in ~50% of individuals, followed by hypospadias associated with microphallus, which was reported in ~33% of patients.<sup>1</sup> While most patients have ambiguous genitalia noted in infancy, individuals with female external genitalia may not present until puberty with primary amenorrhea, a lack of breast development, and virilization of the external genitalia.

If the diagnosis of 5- $\alpha$  reductase deficiency is not made, the majority of infants are assigned a female gender based on the appearance of the external genitalia; however, significant virilization of the external genitalia occurs at puberty unless a gonadectomy is performed. An estimated 56-63% of individuals with 5- $\alpha$  reductase deficiency that are assigned a female gender have been reported to change to male gender identity at puberty,<sup>10</sup> so early diagnosis is important to assist with gender assignment. While most patients with 5- $\alpha$  reductase deficiency exhibit abnormally high levels of baseline and/or hCG-stimulated T:DHT ratios, individuals with partial enzyme deficiencies have been reported with normal T:DHT ratios. Therefore, in some cases it can be difficult to differentiate 5- $\alpha$  reductase deficiency from partial androgen insensitivity syndrome (AIS) and other 46,XY disorders of sex differentiation based on clinical and biochemical studies.

Variants in the SRD5A2 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.

### **Inheritance Pattern/Genetics:**

Autosomal recessive.

## Test Methods:

Using genomic DNA, analysis is performed by bidirectional sequencing of coding exons (1-5) and flanking splice sites of the SRD5A2 gene. If sequencing identifies a variant on only one allele, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. For known familial variants, the relevant portion of the SRD5A2 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:

SRD5A2 is the only gene known to be associated with 5- $\alpha$  reductase deficiency. The sensitivity of SRD5A2 gene analysis in prenatal cases ascertained based on fetal ultrasound/karyotype inconsistency is currently unknown. For postnatal cases, pooling data from three small studies including patients from a variety of ethnic backgrounds, 41/54 (76%) patients with a clinical diagnosis of 5- $\alpha$  reductase deficiency had two identifiable variants in SRD5A2, while only a single variant was identified in 9/54 (16%) of patients.<sup>2,3,4</sup> Two SRD5A2 variants have also been identified in 3/81 (4%) 46,XY Japanese individuals with micropenis<sup>5</sup> and 9/90 (10%) 46,XY Chinese patients with hypospadias, most of whom also had micropenis.<sup>6</sup>

## References:

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