Prenatal Testing for AR Gene Variants: Androgen Insensitivity Syndrome (AIS)

Disorder also known as: Testicular Feminization syndrome (TFM); Reifenstein syndrome

Clinical Features:
Children and Adults: Androgen insensitivity syndrome may be complete or partial. Patients with AIS may come to attention in utero or at birth because of inconsistency between prenatal karyotype (male) and ultrasound findings of a female fetus, or at birth because of ambiguous genitalia. Alternatively, patients may present during the pubertal years with a presumed inguinal hernia (abdominal or inguinal testes), absence of pubic/auxiliary hair, or lack of onset of menses. The mature phenotype is often “voluptuously” feminine with very well-developed breasts and luxuriant scalp hair. In the partial form, patients may exhibit hypospadias, micropenis, or fusion of the labial folds, associated with the occurrence of virilization at puberty. Heterozygous females may exhibit patchy changes in hair distribution and irregular menses due to skewed inactivation of the X-chromosome. Of note, Kennedy disease is an independent disorder due to an expansion of a CAG repeat in the AR gene and is not diagnosed with this test.
Prenatal Ultrasound Findings: Androgen insensitivity syndrome may be suspected when the fetal karyotype is 46,XY but ultrasound reveals apparently female or ambiguous genitalia. Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial pathogenic variantscan be offered targeted molecular testing regardless of ultrasound findings, if desired.

Genetics:
X-linked recessive.

Test Methods:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding region (exons 1-8) and the flanking splice sites of the AR gene. For known familial variants, the relevant portion of the AR 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 83-95% of individuals with complete AIS are expected to have a variant in the AR gene identifiable by sequencing. The detection rate for individuals with milder phenotypes (i.e. partial androgen insensitivity and mild androgen insensitivity) is not well established but is

likely less than 50%.[1,2]Additionally, 5-6% of males with hypospadias have been found to harbor an identifiable variant in the AR gene.[3,4,5] The sensitivity of AR gene analysis in prenatal cases ascertained based on an inconsistency between the fetal gender by ultrasound and by karyotype is currently unknown.

References:

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