AR Gene Analysis in Androgen Insensitivity Syndrome (AIS) / Sequencing and Deletion/Duplication

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

Clinical Features:
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 because of a presumed inguinal hernia (abdominal or inguinal testes), absence of pubic/auxiliary hair, or lack of onset of menses. The mature phenotype is often characterized by well-developed breasts and luxuriant scalp hair. In the partial form, patients may exhibit hypospadias, micropenis, or fusion of the labial folds and undergo virilization at puberty. 46,XX individuals who are heterozygous carriers of an AR variant typically do not exhibit any clinical differences in sexual differentiation, although they may have patchy changes in hair distribution and irregular menses due to skewed X chromosome inactivation.

Of note, Kennedy disease is an independent disorder caused by an expansion of a CAG repeat in the AR gene and is not diagnosed with this test.

Genetics:
Androgen insensitivity syndrome (AIS) has an x-linked recessive pattern of inheritance.

Test Sensitivity:
Approximately 95-97% of individuals with AIS are expected to have a variant in the AR gene identifiable by sequencing, while 3-5% will have a deletion or duplication.[9] 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]

Variant Spectrum:
Many distinct variants scattered across the AR gene have been identified in both complete and partial androgen insensitivity syndrome. The vast majority of the variants are missense substitutions, although nonsense and splice-site variants, whole and partial gene deletions, and two partial gene duplications also have been reported.[8,1,6,7]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and is analyzed for sequence variants. Reported clinically significant variants are confirmed by an appropriate method. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants are not routinely reported but are available upon request.

In 46,XY individuals, deletions of one or more exons would be detectable by sequencing. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for duplications in 46,XY individuals and to evaluate for deletions and duplication in 46,XX individuals.

References:

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