AR Gene Analysis in Androgen Insensitivity Syndrome (AIS)

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 "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 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 Methods:
Using genomic DNA obtained from a venous blood sample in EDTA (buccal kits are not accepted for this test), the coding sequence of the AR gene (exons 1-8) and flanking splice sites are PCR amplified and bi-directional sequence analysis is performed. If no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for 46,XX females to evaluate for a deletion or duplication of one or more exons of the AR gene. In 46,XY individuals, deletions of one or more exons would be detectable by sequencing, but ExonArrayDx is available to evaluate for duplications. Prenatal variant analysis of the entire AR gene is available for fetal specimens when prenatal ultrasound suggests female genitalia in a fetus with a 46,XY karyotype.

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] Large deletions of one or more exons of the AR gene have been reported in multiple families, and rarely partial gene duplications have been described, although the sensitivity of deletion/duplication testing is not well established.[1,6,7] Likewise, the sensitivity of AR gene analysis in prenatal cases ascertained based on fetal ultrasound/karyotype inconsistency is currently unknown.

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]

References:

1. Ahmed et al., (2000) JCEM. 85:658-665.
2. Batch et al., (1992) Hum Molec Genet 1:497-503.
3. Hiort et al., (1994) Eur J Pediatr 153:317-321.
4. Albers et al., (1997) J Pediatr 131:386-392.
5. Wang et al., (2004) Eur J Hum Genet 12:706-712.
6. Avila et al., (2002) JCEM 87:182-188.
7. Hannema et al., (2004) JCEM 89:5815-5822.
8. Gottlieb et al (2004) Hum Mutat 23:527-533.
9. Gottlieb B, Beitel Lk, Trifiro MA. Androgen Insensitivity Syndrome. 1999 Mar 24 [Updated 2014 Jul 10]
10. Pagon RA, Adam, MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.