

Androgen Insensitivity Syndrome (AIS) via Androgen Receptor (AR) Gene Sequencing --Test #736

Brief Description of Clinical Features: Male sexual differentiation requires the Androgen Receptor (AR) and its ligands—Testosterone and Dihydroxytestosterone (DHT) (reviewed by Wilson and Davies *Reproduction* 133:331-359, 2007). Testosterone, which is secreted by the developing testes beginning at 9 weeks of gestation, stimulates Wolffian duct differentiation into epididymis, vas deferens and seminal vesicles. DHT, derived from testosterone via the enzymatic activity of 5 α -reductase type 2, stimulates prostate development and masculinization of the primordial external genital into penis and scrotum (Brinkmann et al. *Mol Cell Endocrinol* 179:105-109, 2001). Both androgens exert their effect through binding and activation of the AR. In individuals with a 46,XY karyotype, defects in AR signaling result in Androgen Insensitivity Syndrome (AIS). AIS symptoms range from complete insensitivity (CAIS), whereby patients have female external genitalia, a short, blind ending vagina and no Wolffian duct derived structures, to partial insensitivity (PAIS), whereby patients can have a predominately female appearance with mild cliteromegaly, ambiguous genitalia, or an undervirilized male appearance (Galani et al. *Hormones* 7:217-229, 2008). Given the complex nature of genital anomalies, recommendations for treatment and management of AIS should rely on an elaborate and individualized approach (Dacou-Voutetakis *Nat Clin Pract* 3:668-669, 2007). Genetic testing for the molecular cause of AIS is recognized as an invaluable aspect of this approach.

Genetics: Most patients with clinical features of AIS have mutations in the *AR* gene, and this gene should be tested first. To date over 600 mutations have been described throughout the *AR* gene (Gottlieb et al. *Hum Mutat* 23:527-533, 2004). Nonsense and frameshift mutations consistently cause CAIS, while weaker mutations, such as missense and regulatory (i.e. those in the promoter, introns, and 3' untranslated region) mutations, cause more variable symptoms and PAIS. Importantly, all documented *AR* mutations, and their respective phenotype, can be found in the Androgen Receptor Gene Mutations Database (ARDB, www.mcgill.ca/androgendb/), making it possible for physicians and genetic counselors to offer a statistically relevant phenotype prognosis for most identified mutations. The *AR* gene is located on the X chromosome, so in most cases (~70%) the pattern of inheritance is X-linked recessive. However, an apparently high mutation rate within the *AR* gene also results in relatively frequent occurrence (~30%) of *de novo* mutations and somatic mosaicism (Gottlieb et al. 2004). Identifying patients with *de novo* mutations and somatic mosaicism has important consequences for sex assignment and genetic counseling (for example, see Kohler et al. *J Clin Endocrinol Metab* 90:106-111, 2005).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 8 coding exons of the *AR* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one exon (Test #100; \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000023.10 mRNA: NM_000044.2 Protein: NP_000035.2 CCDS 14387.1

Indications for Test: Candidates for this test are patients with a presumptive diagnosis of AIS (Boehmer et al. *J Clin Endocrinol Metab* 86:4151-4160, 2001). *This test is not designed to quantify the number of CAG or CCG trinucleotide repeats in exon 1, and is not appropriate for diagnosis of patients with Spinal and Bulbar Muscular Atrophy (SBMA).*

Sensitivity of Test: This test is predicted to identify a causative mutation in 65% of all patients with AIS (Boehmer et al. 2001).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price:	Sequencing of the AR Gene:	\$ 780
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x13	83898 \$ 220	Sequencing x13 83904 \$ 320
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 120

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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