

46,XY Disorder of Sex Development (DSD) via *HSD17B3* Gene Sequencing --Test #735

Brief Description of Clinical Features: A Disorder of Sex Development (DSD) refers to a congenital condition in which the development of chromosomal, gonadal, or anatomical sex is atypical (Hughes et al. *Arch Dis Child* 91:554-563, 2006). Three subtypes of DSD are generally recognized: Sex Chromosome DSD, 46,XX DSD and 46,XY DSD. 46,XY DSD (OMIM 612965) is defined by a normal 46,XY karyotype in conjunction with atypical development of anatomical sex organs. Patients with 46,XY DSD can present with completely undervirilized external female genitalia (Sinnecker type 5), predominately female genitalia (Sinnecker type 4), ambiguous genitalia (Sinnecker type 3), or micropenis and hypospadias (Sinnecker type 2), although the most frequent presentation is with female external genitalia, labial fusion and a blind ending vagina, with or without clitoromegaly (Sinnecker types 5 and 4) (Boehmer et al. *J Clin Endocrinol Metab* 84:4713-4721, 1999). The early fetus possesses all the precursors for both female (Mullerian) and male (Wolfian) reproductive tracts. Induction of the Wolfian tract, including the urethra, prostate, penis and scrotum, relies on the activities of testosterone and dihydrotestosterone (DHT) hormones (Wilson and Davies *Reproduction* 133:331-359, 2007). Five critical enzymes are required for the biosynthesis of testosterone and DHT from cholesterol, and deficiencies in at least two of these enzymes are known to cause defects in Wolfian induction, and symptoms of 46,XY DSD (George et al. *Horm Res Paediatr* 74:229-240, 2010). The 17 β -hydroxysteroid dehydrogenase type 3 (17 β HSD-3) enzyme, encoded by the *HSD17B3* (OMIM 605573) gene, converts Δ 4-androstenedione to testosterone, while 5 α -reductase type 2 enzyme, encoded by the *SRD5A2* (OMIM 607306) gene, converts testosterone to DHT.

Genetics: Deficiency of the 17 β HSD-3 enzyme leads to an autosomal recessive form of DSD in 46,XY individuals, which was described as early as 1971 (Saez et al. *J Clin Endocrinol Metab* 32:604-610, 1971). In 46,XX individuals, however, 17 β HSD-3 deficiency has no apparent effect on female sex development, and these individuals present as normal asymptomatic females (Mendoca et al., *J Clin Endocrinol Metab* 84:802-804, 1999). To date, at least 27 pathogenic mutations in the *HSD17B3* gene have been reported to cause 17 β HSD-3 enzyme deficiency (George et al. 2010), all of which are detected by this sequencing test. Most of the mutations are rare, although a few founder mutations have been described for Arab (i.e. p.Arg80Gln) and Dutch (i.e. p.Asn74Thr and c.325+4A>T) populations, and descendants of the Ottoman Empire, including Greek, Turkish and Syrian patients (i.e. c.655-1G>A) (Boehmer et al. 1999).

Description of This Particular Test: This test involves bidirectional DNA sequencing of coding exons 1-11 of the *HSD17B3* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100; \$190) or two exons (Test #200; \$340) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000009.11 mRNA: NM_000197.1 Protein: NP_000188.1 CCDS 6716.1

Indications for Test: Candidates for this test are undervirilized male infants with normal Wolfian duct structures, absent Mullerian ducts, and normal adrenal steroid biosynthesis *or* assigned females who unexpectedly virilize at puberty (Lee et al. *Clin Endocrinol* 67:20-28, 2007). High levels of Δ 4-androstenedione and low levels of testosterone are also indicative of 17 β HSD-3 deficiency (George et al. 2010).

Sensitivity of Test: The clinical sensitivity of this test is unknown at this time.

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 <i>HSD17B3</i> Gene:	\$ 690
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x11	83898 \$ 190	Sequencing x11 83904 \$ 280
Separation x1	83894 \$ 40	Interpretation/Report x1 83912 \$ 110

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

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