

Male and Female Infertility via *FSHB* Gene Sequencing --Test #734

Brief Description of Clinical Features: Infertility affects 10-20% of couples worldwide and is generally attributed to males and females equally (Marchbanks et al. *Am J Epidemiol* 130:259-267, 1989). The follicle stimulating hormone-receptor signaling pathway is required for ovarian maturation and folliculogenesis in females and sperm production in males (reviewed in Layman & McDonough, *Mol Cell Endocrinol* 161:9-17, 2000). The basic elements of this pathway include a follicle stimulating hormone (FSH) ligand and an FSH receptor (FSHR). The FSH ligand is a heterodimer comprised of non-covalently joined α and β peptide chains. The α -subunit is encoded by the Chorionic Gonadotropin, Alpha polypeptide (*CGA*) gene while the β -subunit is encoded by Follicle-Stimulating Hormone, Beta polypeptide (*FSHB*) gene. The *CGA* subunit is common to luteinizing hormone (LH), human chorionic gonadotropin (hCG), thyroid stimulating hormone (TSH) and FSH, but the *FSHB* subunit confers specificity of the hormone for FSHR. Binding of FSH to its receptor induces a cascade of events in ovarian granulosa cells and male Sertoli cells, which culminates in the transcription of genes required for folliculogenesis and spermatogenesis, respectively. Loss-of-function mutations, then, in either *FSHB* (OMIM 136530) or *FSHR* (OMIM 136435; see also the description for *FSHR* Test #732, <http://preventiongenetics.com/ClinicalTesting/TestsByGene.htm>) lead to failed gametogenesis in both sexes. Women with mutations in *FSHB* commonly display symptoms of delayed puberty, partial breast development and primary amenorrhea, while men with mutations often undergo normal puberty but have azoospermia (Layman et al. *J Clin Endocrinol Metab* 87:3702-3707, 2002).

Genetics: Infertility associated with *FSHB* mutations is most often inherited in an autosomal recessive pattern, with the heterozygous family members exhibiting normal fertility (Layman et al. *N Eng J Med* 337:607-611, 1997; Phillip et al. *N Eng J Med* 338:1729-1732, 1998). However, in one reported case, the heterozygous mother of a child with primary amenorrhoea and infertility had been amenorrhoeic and infertile for six years prior to the unexpected conception of her child (Matthews et al. *Nat Genet* 5:83-86, 1993), indicating that in some cases, *FSHB* haploinsufficiency may lead to a mild, subfertility phenotype. To date, five distinct pathogenic mutations in the *FSHB* gene have been documented: two are missense mutations (p.Cys51Gly and p.Cys82Arg), two are frameshifts (i.e. small deletions), and one is a nonsense mutation (p.Tyr94Stop) (see www.hgmd.org). In addition, a promoter polymorphism (c.-211G>T; rs10835638) was found to significantly reduce FSH serum levels, and may be associated with reduced fertility in men (Grigorova et al. *J Clin Endocrinol Metab* 95:100-108, 2009).

Description of This Particular Test: This test involves bidirectional DNA sequencing of both *FSHB* coding exons (2 & 3) and the promoter region, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single exon (Test #100; \$190) in family members of patients with known mutations, or to confirm research results.

Reference Sequences: Genomic: NC_000011.9 mRNA: NM_001018080.1 Protein: NP_001018090.1 (CCDS 7868.1)

Indications for Test: Candidates for this test are women with primary or secondary amenorrhea and men with azoospermia.

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>FSHB</i> Gene:	\$ 390
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x3	83898 \$ 90	Sequencing x3 83904 \$ 130
Separation x1	83894 \$ 30	Interpretation/Report x1 83912 \$ 70

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

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