

Ovarian Hyperstimulation Syndrome via *FSHR* Gene Sequencing --Test #732

Brief Description of Clinical Features: Over one million couples worldwide seek reproductive assistance each year because of infertility (Chandra et al. U.S. Vital and Health Statistics, Series 23, Number 25, 2005; Nyboe Andersen et al. *Hum Reprod* 24:1267-1287, 2009). In at least 75% of the cases, ovarian stimulation, to induce the development of multiple dominant follicles and maturation of many oocytes, is an integral part of the treatment regimen. Typically, ovarian stimulation is achieved by administering exogenous human Menopausal Gonadotropin (hMG), i.e. a natural mixture of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG) (Macklon et al. *Endocrine Rev* 27:170-207, 2006). Ovarian Hyperstimulation Syndrome (OHSS; OMIM 608115) is an iatrogenic complication due to the exogenous administration of hMG and affects upwards of 5% of all women undergoing treatment for infertility (Delvigne & Rozenberg, *Hum Reprod Update* 8:559-577, 2002; Abramov et al. *Hum Reprod* 14:2181-2183, 1999). In addition, OHSS can spontaneously occur in women during the third month of an otherwise normal pregnancy. In these cases, increased endogenous levels of hCG from the ongoing pregnancy is thought to be the cause (Elchalal & Schenker, *Hum Reprod* 12:1129-1137, 1997). The primary symptoms of OHSS are abdominal discomfort, nausea, vomiting and diarrhea due to enlarged polycystic ovaries. In the most severe instances, rupture and hemorrhaging of ovarian cysts, organ failure and death can occur (Delvigne & Rozenberg, *Hum Reprod Update* 9:77-96, 2003).

Genetics: OHSS can be caused by dominant mutations in the Follicle Stimulating Hormone Receptor gene (*FSHR*; OMIM 136435). Normally, *FSHR* protein is exclusively activated by FSH. However, changes at four different amino acids (Ser128, Thr449, Ile545, and Asp567) of *FSHR* decrease its specificity for FSH and increase its sensitivity to other hormones, such as LH and hCG (De Leener et al. *Hum Mutat* 29:91-98, 2008; De Leener et al. *J Clin Endocrinol Metab* 91:555-562, 2006; Smits et al. *N Engl J Med* 349:760-766, 2003; Vasseur et al. *N Engl J Med* 349:753-759, 2003). Thus, patients who have a heterozygous mutation of one of these four amino acids are likely to develop OHSS during the course of treatment for infertility, particularly if hMG is used to stimulate ovulation. In addition, three mutations within the promoter region of *FSHR* have been documented to influence protein expression, and likely increase the probability of developing OHSS during the course of artificial ovarian stimulation (Wunsch et al. *Fertil Steril* 84:446-453, 2005).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 10 exons of the *FSHR* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. This test also includes the sequencing of a region upstream of the translation start codon (from position -1 to -350) for the detection of documented promoter mutations. As indicated, we will also sequence one exon, or the promoter region, in family members of patients with known mutations, or to confirm research results (Test #100; \$190).

Reference Sequences: Genomic: NC_000002.11 mRNA: NM_000145.2 Protein: NP_000136.2 (CCDS 1843.1)

Indications for Test: Candidates for this test are women who will receive exogenous hMG during the course of treatment for infertility, women with symptoms of spontaneous OHSS, and relatives of patients with known mutations in *FSHR*.

Sensitivity of Test: The sensitivity of this test is currently unknown.

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

Specimen Requirements: See page 4 of the Requisition Form.

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| Price: | Sequencing of the <i>FSHR</i> Gene: | \$ 820 |
| CPT Codes: | | |
| Sample Ascertainment x1 | 83890 \$ 30 | DNA Isolation x1 83891 \$ 40 |
| Amplification x14 | 83898 \$ 240 | Sequencing x14 83904 \$ 350 |
| Separation x1 | 83894 \$ 50 | 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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