

Ovarian Dysgenesis 2 via *BMP15* Gene Sequencing --Test #733

Brief Description of Clinical Features: Premature Ovarian Failure (POF; OMIM 311360) is a condition of female infertility characterized by the cessation of menstruation for at least four consecutive months prior to the age of 40. POF is thought to affect 1-2% of all women under 40 years old (Goswami & Conway *Hum Reprod Update* 11:391-410, 2005). Although there are many potential causes of ovarian failure, Ovarian Dysgenesis (ODG) likely accounts for about half of the known POF cases. The symptoms of ODG include pubertal delay, primary or secondary amenorrhea, and hypoplastic ovaries. Often times, ODG is caused by major alterations of the X chromosome, such as Turner mosaics, large deletions, translocations or trisomy X. However, in patients with a normal 46 XX karyotype, mutations in a few specific genes, including *FSHR*, *BMP15*, and *GDF9*, have been found to cause ODG and POF (Aittomaki et al. *Cell* 82:959-968, 1995; Di Pasquale et al. *Am J Hum Genet* 75:106-111, 2004; Laissue et al. *Eur J Endocrinol* 154:739-744, 2006). ODG Type 2 (ODG2; OMIM 300510), also called X-linked hypergonadotropic ovarian failure, is known to be specifically caused by heterozygous mutations in the Bone Morphogenetic Protein 15 gene (*BMP15*; OMIM 300247).

Genetics: The first patients described with a mutation in the *BMP15* gene were two female siblings with a normal 46 XX karyotype who presented with pubertal delay, primary amenorrhea and streak ovaries (Di Pasquale et al., 2004). Both sisters were heterozygous for a missense variant (p.Tyr235Lys). Interestingly, *BMP15* is encoded on the X chromosome, and the p.Tyr235Lys variant was inherited from the unaffected father. ODG2, then, is an intriguing example of an X-linked dominant disorder, which exclusively affects heterozygous females who inherited the genetic mutation from their father. Consistent with this pattern of inheritance, the p.Tyr235Lys variant was shown to exert a dominant-negative effect on the proliferation of cultured granulosa cells (Di Pasquale et al. 2004), a cell-type restricted to female ovaries. To date, all but one of the additional causative mutations found in *BMP15* have been heterozygous missense (Dixit et al. *Hum Genet* 119:408-415, 2006; Di Pasquale et al. *J Clin Endocrinol Metab* 91:1976-1979, 2006; Laissue et al. *Eur J Endocrinol* 154:739-744, 2006), and at least two of these (p.Arg68Trp and p.Arg138His) clearly exert a dominant-negative effect in an *in vitro* functional assay (Rossetti et al. *Hum Mut* 30:804-810, 2009). The one exception to this pattern of inheritance is the finding of a homozygous nonsense mutation (p.Glu211Stop) in a patient presenting with secondary amenorrhea and POF at the age of 28 (Dixit et al. 2006).

Description of This Particular Test: This test involves bidirectional DNA sequencing of both exons of the *BMP15* gene plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence a single (Test #100) exon in family members of patients with known mutations, or to confirm research results (\$190).

Reference Sequences: Genomic: NC_000023.10 mRNA: NM_005448.1 Protein: NP_005439.1 (CCDS: 14334.1)

Indications for Test: Candidates for this test are women with primary or secondary amenorrhea and normal 46,XX karyotype, and relatives of patients with a verified *BMP15* germline mutation.

Sensitivity of Test: Depending on the population, anywhere from 1 to 10% of women with primary or secondary amenorrhea have been found to have a mutation in the *BMP15* gene (Dixit et al. 2006; Di Pasquale et al. 2006; Laissue et al. 2006).

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>BMP15</i> Gene:	\$ 440
CPT Codes:		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x4	83898 \$ 100	Sequencing x4 83904 \$ 150
Separation x1	83894 \$ 30	Interpretation/Report x1 83912 \$ 90

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

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