

## Short Stature with or without Partial Isolated Growth Hormone Deficiency via *GHSR* Gene Sequencing (Test #628)

**Brief Description of Clinical Features:** Short stature is a multifactorial developmental disorder. Short stature with or without partial isolated growth hormone deficiency (OMIM 604271) is a genetic disorder of growth failure due to defective growth hormone secretagogue receptor (GHSR) (Howard et al. Science 273:974-977, 1996; Pantel et al. J Clin Invest 116:760-768, 2006). It has been reported that a patient with recessive partial isolated growth hormone deficiency due to *GHSR* mutations, had growth delay associated with recurrent abdominal pain, vomiting, ketosis, hypoglycemia and low body mass index (Pantel et al. J Clin Endocrinol Metab 94:4334-4341, 2009). On the other hand, a semidominant transmission with incomplete penetrance of short stature with or without partial isolated growth hormone deficiency has been reported in patients of two unrelated families from Morocco (Pantel et al. 2006).

**Genetics:** Short stature with or without partial isolated growth hormone deficiency caused by mutations in the *GHSR* gene (Pantel et al. 2006). *GHSR* gene encodes a growth hormone secretagogue receptor (GHSR), an orphan 7-transmembrane G-protein coupled receptor that acts on the pituitary gland and the hypothalamus to stimulate growth hormone release (Howard et al. 1996, Smith et al. Endocr Rev 18:621-645, 1997). The GHSR receptor has a constitutive activity, defined as ligand-independent signaling activity, of unknown clinical significance and an endogenous ligand known as ghrelin, a hormone predominantly produced by the stomach to stimulate growth hormone secretion (Holst et al. Mol Endocrinol 17:2201-2210, 2003; Kojima et al. Nature 402:656-660, 1999; Pantel et al. 2006). A mix of missense and nonsense mutations within the *GHSR* gene and its promoter region have been reported (Wang et al. J Clin Endocrinol Metab 89:157-162, 2004; Pantel et al. 2006; Liu et al. J Pharmacol Exp Ther 322:1036-1043, 2007; Mager et al. PLoS One 3:e2941, 2008; Pantel et al. 2009). The missense mutation c.611C>A (p.Ala204Glu), which results in a semidominant transmission with incomplete penetrance of short stature, has been demonstrated to affect the constitutive activity and the cell surface expression of the GHSR receptor but does not affect the specific binding to ghrelin (Pantel et al. 2006; Liu et al. 2007).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 2 coding exons (exons 1-2) and the regulatory region upstream of the *GHSR* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) or pair of exons (Test #200) for family members of patients with known mutations and to confirm previous research results (\$190-340 charge).

**Reference Sequences:** Genomic: NC\_000003.11 mRNA: NM\_198407.1 Protein: NP\_940799.1 (CCDS 3218.1)

**Indications for Test:** Candidates for this test are patients with symptoms consistent with short stature with or without partial isolated growth hormone deficiency and family members of patients who have known *GHSR* mutations.

**Sensitivity of Test:** 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.

**Prices:** Sequencing of *GHSR* gene \$ 550

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x7	83898 \$ 130	Sequencing x7	83904 \$ 200
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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