

## **Laron Syndrome / Pituitary Dwarfism II (Growth Hormone Insensitivity) via *GHR* Gene Sequencing (Test #627)**

**Brief Description of Clinical Features:** Short stature is a multifactorial developmental disorder. Laron Syndrome (also known as Pituitary dwarfism II or Growth hormone insensitivity; OMIM 262500) is a genetic disorder of postnatal growth failure due to defective growth hormone receptor (GHR). Laron syndrome patients fail to generate insulin-like growth factor 1 (IGF1), which is important for signal transduction pathways required for growth (Laron J Clin Endocrinol Metab 89:1031-1044, 2004; Amselem et al. J Clin Invest 87:1098-1102, 1991). Laron syndrome is characterized by severe short stature, severe growth retardation, delayed bone age, truncal obesity, severe hypoglycemia, blue sclerae, hip degeneration and characteristic facies with frontal bossing. Additional biochemical findings include a normal to high serum growth hormone level and a low level of serum IGF-I and its binding protein 3 (IGFBP-3) (Laron 2004; Amselem et al. 1991; Berg et al. Am J Hum Genet 52:998-1005, 1993; Pantel et al. J Clin Endocrinol Metab 88:1705-1710, 2003). Of note, Laron syndrome patients do not response to exogenous growth hormone treatment (Laron 2004; Berg et al. 1993).

**Genetics:** Laron syndrome is an autosomal recessive disorder caused by mutations in the *GHR* gene; however dominant negative mutations leading to skipping of exon 9 have been reported in two different families (Godowski et al Proc. Nat. Acad. Sci. 86:8083-8087, 1989; Ayling et al. Nat Genet 16:13-14, 1997; Lida et al. J Clin Endocrinol Metab 83:531-537, 1998). *GHR* gene encodes a growth hormone receptor (GHR), which consists of an extracellular domain that generates the soluble growth hormone binding protein (GHBP), short transmembrane domain and a cytoplasmic domain required for signal transduction. The GHR receptor dimerizes upon binding to the growth hormone to activate an intracellular signal transduction pathway leading to the synthesis and secretion of insulin-like growth factor 1 (Laron 2004, Huang et al. Mol Endocrinol 18:1471-1485, 2004). A mix of missense, nonsense, splicing, frameshift and gross deletion mutations within the *GHR* gene has been reported (Laron 2004, Amselem et al. 1991, Berg et al. 1993; Pantel et al. 2003; David et al. J Clin Endocr Metab 92: 655-659, 2007; David et al. Eur J Endocrinol 162:37-42, 2010).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of the 9 coding exons (exons 2-10) of the *GHR* 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\_000005.9 mRNA: NM\_000163.2 Protein: NP\_000154.1 (CCDS 3940.1)

**Indications for Test:** Candidates for this test are patients with symptoms consistent with Laron syndrome and family members of patients who have known *GHR* 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 *GHR* gene**    **\$ 820**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x14	83898 \$ 230	Sequencing x14	83904 \$ 350
Separation x1	83894 \$ 60	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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