

## Hypophosphatasia via *ALPL* Gene Sequencing (Test #851)

**Brief Description of Clinical Features:** Hypophosphatasia (HPP) is characterized by defective mineralization of bone and/or teeth in the presence of low activity of serum and bone alkaline phosphatase. Clinical features range from stillbirth without mineralized bone at the severe end to pathologic fractures of the lower extremities in later adulthood at the mild end. At least six clinical forms are currently recognized based on age at diagnosis and severity of features, including: (1) perinatal lethal HPP characterized by respiratory insufficiency and hypercalcemia; (2) perinatal benign HPP with prenatal skeletal manifestations that slowly resolve into the milder childhood or adult form; (3) infantile HPP (OMIM#241500) with onset between birth and age six months of rickets without elevated serum alkaline phosphatase activity; (4) childhood HPP (OMIM#241510) that ranges from low bone mineral density for age with unexplained fractures to rickets; (5) adult HPP (OMIM#146300) characterized by early loss of adult dentition and stress fractures and pseudofractures of the lower extremities in middle age; and (6) odontohypophosphatasia characterized by premature exfoliation of primary teeth and/or severe dental caries as an isolated finding or as part of the above forms of HPP (Mornet & Nunes *GeneReviews* 2010).

**Genetics:** *ALPL* is the only gene known to be associated with HPP. *ALPL* encodes alkaline phosphatase, tissue-nonspecific isozyme (TNSALP), which is present in liver, kidney, and bone. Perinatal and infantile HPP are inherited in an autosomal recessive manner. The milder forms, especially adult and odontohypophosphatasia, may be inherited in an autosomal recessive or dominant manner depending on the effect that the mutation has on TNSALP activity. In recessive HPP, heterozygotes either are asymptomatic, manifesting biochemical but not clinical abnormality, or may manifest milder symptoms depending on the mutation. A good correlation exists between the severity of the phenotype and the residual enzymatic activity (Zurutuza et al. *Hum Mol Genet* 8:1039–1046, 1999; Orimo et al. *J Bone Miner Res* 16:2313–2319, 2001). A variety of mutations in *ALPL* has been reported with the majority being missense changes.

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of all coding exons of the *ALPL* gene plus ~50 bp of flanking non-coding DNA on each side. We will also sequence any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) in family members of patients with known mutations, or to confirm research results.

**Reference Sequences:** **Genomic:** NC\_000001.10                      **mRNA:** NM\_000478.4  
**Protein:** NP\_000469.3    **mRNA and Protein:** CCDS 217.1

**Indications for Test:** Candidates for this test are patients with clinical features consistent with HPP or biochemical abnormality showing reduced activity of serum alkaline phosphatase (ALP) and/or elevated urine phosphoethanolamine (PEA), and family members of patients who have known *ALPL* mutations.

**Sensitivity of Test:** Sequencing of *ALPL* is predicted to detect disease mutations in 95% of cases with severe perinatal and infantile HPP. In milder forms, mutation detection rate is difficult to estimate. Overall, ~50% of cases with a clinical diagnosis of HPP have two *ALPL* mutations and ~40%-45% have one mutation. The milder the disease, the higher the proportion in which only one *ALPL* mutation is detected (Mornet & Nunes *GeneReviews* 2010).

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

**Specimen Requirements:** See page four of the Requisition Form.

**Prices:**                      **Sequencing of *ALPL* gene**                      **\$ 780**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x13	83898 \$230	Sequencing x13	83904 \$340
Separation x1	83894 \$ 40	Interpretation/Report x1	83912 \$100

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

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