

## Hypochondroplasia via *FGFR3* Gene Sequencing (Test #428)

**Brief Description of Clinical Features:** Hypochondroplasia (OMIM#146000) is a relatively common skeletal dysplasia characterized by short stature; stocky build; disproportionately short arms and legs; broad, short hands and feet; mild joint laxity; and macrocephaly (Francomano *GeneReviews* 2005). The skeletal features are very similar to achondroplasia but usually tend to be milder. Children usually present as toddlers or school-age children with failure to grow. As the age of the children increases, limb disproportion and other features become more prominent.

**Genetics:** Hypochondroplasia is inherited in an autosomal dominant manner. The majority of new cases result from *de novo* mutation. *FGFR3* is the only gene known to be associated with hypochondroplasia; however, genetic heterogeneity is suspected. Two recurrent *FGFR3* mutations (c.1620C>A and c.1620C>G) resulting in p.Asn540Lys in exon 13 that encodes the ATP-binding segment of the tyrosine kinase domain have been shown to be common cause of hypochondroplasia (Bellus et al. *Nat Genet* 10:357–359, 1995; Prinos et al. *Hum Mol Genet* 4:2097–2101, 1995). Sequence analysis of *FGFR3* exons 7, 9, 10, 13, and 15 detects other rare *FGFR3* mutations associated with hypochondroplasia. *FGFR3* gene encodes fibroblast growth factor receptor-3, a member of the FGFR family. Like all of the FGFRs, FGFR3 is a membrane-spanning tyrosine kinase receptor with an extracellular ligand-binding domain consisting of three immunoglobulin subdomains, a transmembrane domain, and a split intracellular tyrosine kinase domain (Green et al. *Bioessays* 18:639–646, 1996).

**Description of This Particular Test:** This test involves bidirectional sequencing using genomic DNA of 5 selected coding exons (exon 7, 9, 10, 13, 15) of the *FGFR3* gene plus ~50 bp of flanking non-coding DNA on each side. We will also sequence any single exon (Test #100, \$190) in family members of patients with a known mutation, or to confirm research results.

**Reference Sequences:** Genomic: NC\_000004.11 mRNA: NM\_000142.4 Protein: NP\_000133.1 (CCDS 3353.1)

**Indications for Test:** Candidates for this test are patients with clinical features consistent with hypochondroplasia and family members of patients who have a known *FGFR3* mutation.

**Sensitivity of Test:** This test is predicted to detect disease mutations in >80% of affected individuals (Prinos et al. *Hum Mol Genet* 4:2097–2101, 1995; Prinster et al. *Am J Med Genet* 75:109–112, 1998; Ramaswami et al. *J Pediatr* 133:99–102, 1998; Grigelioniene et al. *Hum Mut* 11:333, 1998; Bellus et al. *Am J Hum Genet* 67:1411–1421, 2000; Thauvin-Robinet et al. *Am J Med Genet A* 119:81–84, 2003).

**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 5 exons (exon 7, 9, 10, 13, 15) in *FGFR3* gene \$ 490**

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x5	83898 \$120	Sequencing x5	83904 \$190
Separation x1	83894 \$ 25	Interpretation/Report x1	83912 \$ 85

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

**Contact:** Dr. Ying Wang, [ying.wang@preventiongenetics.com](mailto:ying.wang@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)