

Achondroplasia/Hypochondroplasia via *FGFR3* Gene Sequencing (Test #429)

Brief Description of Clinical Features: Achondroplasia (ACH, OMIM#100800) is the most common form of inherited disproportionate short stature. It occurs in one in 15,000 to one in 40,000 live births. Achondroplasia is characterized by abnormal bone growth that results in short stature with disproportionately short arms and legs, a large head, and characteristic facial features with frontal bossing and mid-face hypoplasia (Francomano *GeneReviews* 2006). Skeletal features of Hypochondroplasia (HCH, OMIM#146000) are very similar to achondroplasia but usually 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 (Francomano *GeneReviews* 2005).

Genetics: ACH/HCH are 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 ACH/HCH. More than 99% of individuals with achondroplasia have one of two mutations (c.1138G>A, c.1138G>C) in the exon 10 of *FGFR3* gene, both resulting in a p.Gly380Arg substitution in the FGFR3 protein (Shiang et al. *Cell* 78:335–342, 1994; Bellus et al. *Am J Hum Genet* 56:368–373, 1995). Two recurrent *FGFR3* mutations (c.1620C>A and c.1620C>G) both resulting in p.Asn540Lys in exon 13 that encodes the ATP-binding segment of the tyrosine kinase domain have been shown to be a common cause of hypochondroplasia (Bellus et al. *Nat Genet* 10:357–359, 1995; Prinos et al. *Hum Mol Genet* 4:2097–2101, 1995). The *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). The p.Gly380Arg mutation, located in the transmembrane domain, has been shown to result in constitutive activation of the FGF receptor (Deng et al. *Cell* 84:911–921, 1996).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of all coding exons 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 include patients with clinical and radiographic features suggestive of ACH/HCH but tested negative for common ACH/HCH mutations.

Sensitivity of Test: This test is predicted to detect disease mutations in >99% of individuals with ACH and >80% of individuals with HCH.

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 *FGFR3* gene \$ 940

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x17	83898 \$280	Sequencing x17	83904 \$420
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$110

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

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