

## Achondroplasia via *FGFR3* Gene, Exon 10 Sequencing (Test #425)

**Brief Description of Clinical Features:** Achondroplasia (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). This condition can be diagnosed by characteristic clinical and radiographic findings in most affected individuals.

**Genetics:** Achondroplasia is inherited in an autosomal dominant manner with complete penetrance. Over 80% of individuals with achondroplasia have parents with normal stature and have achondroplasia as the result of a *de novo* mutation. More than 99% of individuals with achondroplasia have one of two mutations in the exon 10 of *FGFR3* gene. In about 98% of individuals, the mutation is c.1138G>A, and in about 1% of individuals, the mutation is c.1138G>C, 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). One other amino acid substitution (p.Gly375Cys) encoded within *FGFR3* exon 10 has also been reported to cause this condition (Ikegawa et al. *Hum Genet* 96:309-311, 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 of the target coding exon (exon 10) of the *FGFR3* gene using genomic DNA. The full coding region of the selected exon plus ~50 bp of flanking non-coding DNA on each side are sequenced.

**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 consistent with achondroplasia, those with abnormal prenatal ultrasound showing short fetal limbs and raising the possibility of achondroplasia, and individuals who may be too young to diagnose with certainty or in individuals with atypical findings.

**Sensitivity of Test:** This test is predicted to detect disease mutations in >99% of affected individuals (Shiang et al. 1994, Bellus et al. 1995).

**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 exon 10 in *FGFR3* gene \$ 190

**CPT Codes:**

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x1	83898 \$ 25	Sequencing x1	83904 \$ 35
Separation x1	83894 \$ 15	Interpretation/Report x1	83912 \$ 45

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

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