

Thanatophoric Dysplasia (TD) via *FGFR3* Gene Sequencing (Test #426)

Brief Description of Clinical Features: Thanatophoric dysplasia (TD) is a short-limb dwarfism syndrome that is usually lethal in the perinatal period. TD is divided into type I (OMIM #187600), characterized by micromelia with bowed femurs and, uncommonly, the presence of cloverleaf skull deformity of varying severity; and type II (OMIM #187601), characterized by micromelia with straight femurs and uniform presence of moderate-to-severe cloverleaf skull deformity (Karczeski & Cutting *GeneReviews* 2008). Other features common to type I and type II include: short ribs, narrow thorax, macrocephaly, distinctive facial features, brachydactyly, hypotonia, and redundant skin folds along the limbs. Most affected infants die of respiratory insufficiency shortly after birth. Rare long-term survivors have been reported.

Genetics: TD is inherited in an autosomal dominant manner with complete penetrance. The majority of probands have a *de novo* gene mutation. *FGFR3* is the only gene known to be associated with TD type I and type II. A single *FGFR3* mutation (p.Lys650Glu) in exon 15 has been identified in all individuals with TD type II (Bellus et al. *Am J Hum Genet* 67:1411–1421, 2000). Sequence analysis of selected exons of *FGFR3* (exons 7, 10, 15, and 19 for TD type I; and exon 15 for TD type II) detects up to 99% disease mutations causing TD type I and >99% of mutations causing TD type II (Wilcox et al. *Am J Med Genet* 78:274–281, 1998; Brodie et al. *Am J Med Genet* 84:476–480, 1999; Camera et al. *Am J Med Genet* 104:277–281, 2001). *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 4 selected coding exons (exon 7, 10, 15, 19) 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 newborns with abnormal clinical and radiologic features consistent with TD, and patients with abnormal prenatal ultrasound showing features suggestive of TD in the fetus.

Sensitivity of Test: This test is predicted to detect up to 99% disease mutations causing TD type I and >99% of mutations causing TD type II (Wilcox et al. 1998; Brodie et al. 1999; Camera et al. 2001).

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 4 exons (exons 7, 10, 15, and 19) in *FGFR3* gene \$ 440

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x4	83898 \$110	Sequencing x4	83904 \$160
Separation x1	83894 \$ 20	Interpretation/Report x1	83912 \$ 80

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

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