

Thanatophoric Dysplasia, Types 1 & 2 (*FGFR3*) 13 Mutations

TO CONFIRM A CLINICAL DIAGNOSIS OF THANATOPHORIC DYSPLASIA

Disease Overview

- Thanatophoric dysplasia (TD) is a lethal neonatal skeletal dysplasia.
- Affected individuals have rhizomelic shortening of the long bones, redundant skin folds on the limbs, brachydactyly, platyspondyly, short ribs, narrow thorax, macrocephaly, hypotonia, and characteristic facial features (i.e., frontal bossing, flat facies, low nasal bridge, and proptotic eyes).
- TD is subclassified into types 1 and 2: Type 1 has bent femurs and uncommonly a cloverleaf skull deformity; type 2 always has straight femurs and a cloverleaf skull deformity.
- Death typically occurs due to respiratory insufficiency within hours or days of birth.
- Three long-term survivors requiring ventilatory support and a tracheostomy have been reported. Additional developing characteristics included ventriculomegaly, bilateral hearing loss, seizures, kyphosis, and severe developmental delay.

Epidemiology

One in 20,000 to one in 50,000 births.

Genetics

- Autosomal dominant; mostly de novo mutations, with 100 percent penetrance.
- Cause: fibroblast growth-factor receptor 3 (*FGFR3*) gene mutations.
- Recurrence risk in offspring: not increased over that in the general population in individuals with no clinical features of TD.
- Eleven *FGFR3* mutations (five missense and seven read-throughs of the native stop codon) cause 99 percent of TD1.
- A single *FGFR3* mutation, K650E, is responsible for TD2.
- All mutations result in gain of *FGFR3* function capable of initiating intracellular signal pathways in the absence of ligand binding leading to premature differentiation of proliferative chondrocytes and premature bone maturation.

Indications for Ordering

- First trimester: ultrasound showing increased nuchal translucency, reverse flow in ductus venosus, and long bone shortening.

- Second/third trimester: ultrasound examination revealing limb shortening below the fifth percentile recognizable by 18 weeks gestation; platyspondyly, frontal bossing, ventriculomegaly, narrow chest cavity with short ribs, polyhydramnios, bowed femurs (type 1), cloverleaf skull (in type 2), and well-ossified spine and skull.
- Postnatal: clinical exam consistent with TD (see above).

Interpretation

- A single *FGFR3* mutation is consistent with a diagnosis of TD.
- If no *FGFR3* mutations are identified, this is consistent with a 99 percent risk reduction for TD.

Methodology

- Polymerase chain reaction and single nucleotide extension followed by capillary electrophoresis to detect the following mutations: c.742C>T (p.R248C), c.746C>G (p.S249C), c.1108G>T (p.G370C), c.1111A>T (p.S371C), c.1118A>G (p.Y373C), c.1948A>G (p.K650E), c.2419T>G (p.X807G), c.2419T>A (p.X807R), c.2420G>C (p.X807S), c.2420G>T (p.X807L), c.2421A>T (p.X807C), c.2421A>C (p.X807C), and c.2421A>G (p.X807W).
- Analytic specificity and sensitivity are 99 percent.

Limitations

- Mutations other than those targeted in *FGFR3* will not be detected.
- Clinical sensitivity may be compromised by rare primer-site mutations.

Related Test

Thanatophoric Dysplasia, Types 1 & 2 (*FGFR3*) 13 Mutations, Fetal (0051508)

References

1. Online GeneTests: Thanatophoric Dysplasia. www.genetests.org (accessed on October 21, 2008).
2. Sqn Ldr S Sahu, Wg Cdr P Kaur. Thanatophoric Dysplasia: Antenatal Diagnosis. *MJAFI* 2009; 65:87–8.
3. Defendi, GL. Thanatophoric Dysplasia. <http://emedicine.medscape.com/article/949591-overview#a0101> (accessed on September 2, 2011).

Test Information

0051506 **Thanatophoric Dysplasia, Types I and II (*FGFR3*) 13 Mutations**

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.