Thanatophoric Dysplasia, Types 1 and 2 (FGFR3), 13 Mutations

Thanatophoric dysplasia (TD) is a skeletal dysplasia that is often suspected based on clinical and/or radiographic findings of micromelia (marked shortening of the limbs) and dysmorphic features. There are two subtypes of TD; type 1 presents with bent femurs and rarely includes skull deformity (craniosynostosis) while type 2 is characterized by straight femurs and cloverleaf skull deformity.[1] Targeted testing for pathogenic variants can confirm a clinical diagnosis of TD in fetuses and neonates. TD is caused by pathogenic variants in the *FGFR3* gene, and the majority of pathogenic variants are de novo. The condition is almost always lethal, with death occurring due to respiratory insufficiency shortly after birth.

Tests to Consider

Thanatophoric Dysplasia, Types 1 and 2 (FGFR3) 13 Mutations 0051506

Method: Polymerase Chain Reaction/Fragment Analysis

Use to confirm clinical diagnosis of TD type 1 or type 2

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

Method: Polymerase Chain Reaction/Fragment Analysis

Use to confirm diagnosis in a fetus with clinical suspicion of TD type 1 or type 2

See Related Tests

Disease Overview

Symptoms

- Severe shortening of the extremities (bowed femurs in TD type 1)
- Redundant skin folds on limbs
- Short ribs/narrow thorax
- Hypotonia
- Brachydactyly with trident hand
- Macrocephaly
- Dysmorphic facial features (eg, frontal bossing, flat facies, low nasal bridge, proptotic eyes)
- Craniosynostosis (cloverleaf skull) in TD type 2

Prenatal Findings

Trimester	Ultrasound Findings
First	• Increased nuchal translucency • Reverse flow in ductus venosus • Long bone shortening
Second/third	• Limb shortening <5%; recognizable on ultrasound by ~18 wks gestation • Bent femurs in TD type 1 • Cloverleaf skull in TD type 2 • Narrow thorax • Polyhydramnios • Well-ossified skull and spine

Genetics

Gene

FGFR3

Incidence

1/20,000[1]

Inheritance

Autosomal dominant

Most cases are caused by de novo pathogenic variant in *FGFR3*; often associated with advanced paternal age.

Penetrance

100%

Test Interpretation

Sensitivity/Specificity

Analytical Sensitivity/Specificity

99%

Clinical Sensitivity

99%

Variants

Disease Type/Pathogenic Variant[a]	
TD Type 1	**TD Type 2**
c.742C>T (p.R248C)	c.1948A>G (p.K650E)
c.746C>G (p.S249C)	
c.1108G>T (p.G370C)	
c.1111A>T (p.S371C)	
c.1118A>G (p.Y373C)	
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)	
c.2421A>G (p.X807W)	

[a]13 pathogenic variants cause 99% of TD cases.

Results

Result	Variant Detected	Interpretive Data
Positive	One pathogenic variant detected	Diagnosis of TD confirmed
Negative	No pathogenic variant detected	Not predicted to be affected with TD

Limitations

- Diagnostic errors can occur due to rare sequence variations.
- Variants other than those targeted in FGFR3 are not detected.

References

1. French T, Savarirayan R. Thanatophoric dysplasia. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2022. [Last update: June 2020; Accessed: Apr 2022]

Related Information

Skeletal Dysplasias
Skeletal Dysplasia Panel
Achondroplasia (FGFR3) 2 Mutations

Related Tests

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication, Fetal 2012010

Method: Massively Parallel Sequencing

Skeletal Dysplasia Panel, Sequencing and Deletion/Duplication 2012015

Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Achondroplasia (FGFR3) 2 Mutations 0051266

Method: Polymerase Chain Reaction/Fluorescence Resonance Energy Transfer (FRET)

Achondroplasia (FGFR3) 2 Mutations, Fetal 0051265

Method: Polymerase Chain Reaction/Fluorescence Monitoring

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review April 2022 | Last Update May 2022