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

Indications for Ordering

- Confirm clinical diagnosis of thanatophoric dysplasia (TD) type 1 or type 2
- Confirm diagnosis in at-risk fetus or those with ultrasonographic features consistent with TD type 1 or type 2

Test Description

Polymerase chain reaction and fluorescence resonance energy transfer for variants in *FGFR3* gene

- 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)

Tests to Consider

Primary tests

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

- Confirm clinical diagnosis of TD type 1 or type 2

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

- Confirm diagnosis in at-risk fetus or those with ultrasonographic features consistent with TD type 1 or type 2

Related tests

Achondroplasia (*FGFR3*) 2 Mutations 0051266

- Confirm clinical or suspected diagnosis of achondroplasia

Achondroplasia (*FGFR3*) 2 Mutations, Fetal 0051265

- Confirm diagnosis in at-risk fetus or those with ultrasonographic features consistent with achondroplasia

Disease Overview

Incidence – 1/20,000-50,000

Symptoms

- Lethal neonatal skeletal dysplasia for most newborns
  - Death typically occurs due to respiratory insufficiency in first hours/days after birth
- Two types
  - Type 1 has bent femurs with no skull deformity
  - Type 2 always has straight femurs and cloverleaf skull deformity
- Rhizomelic shortening of the extremities
- Redundant skin folds on limbs
- Short ribs/narrow thorax
- Hypotonia
- Lumbar lordosis
- Macrocephaly
- Facial abnormalities
  - Frontal bossing
  - Flat facies
  - Low nasal bridge
  - Proptotic eyes
- In survivors (rare)
  - Long-term ventilatory support is required
  - Ventriculomegaly
  - Bilateral hearing loss
  - Kyphosis
  - Severe developmental delay
- Prenatal findings
  - First trimester – ultrasound (US) showing
    - Increased nuchal translucency
    - Reverse flow in ductus venosus
    - Long bone shortening
  - Second/third trimester – US showing
    - Limb shortening <5% recognizable by 18 weeks gestation
    - Bent femurs in TD type 1
    - Cloverleaf skull in TD type 2
    - Narrow thorax
    - Polyhydramnios
    - Well-ossified skull and spine

Genetics

Gene – *FGFR3*

Inheritance – autosomal dominant

Penetrance – 100%

De novo variants – most cases

Variants

- 13 pathogenic variants – account for 99% of TD cases
  - 12 pathogenic variants cause TD type 1
  - K650E pathogenic variant is always responsible for TD type 2

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 99%
- Analytical sensitivity/specificity – 99%

Results

- Positive – single variant detected
  - Confirms diagnosis of TD
- Negative – no 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

Karczeski B, Cutting GR. Thanatophoric Dysplasia. 2004 May 21 [Updated 2013 Sep 12]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1366/)