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

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
Penetration – 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