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
  o Death typically occurs due to respiratory insufficiency in first hours/days after birth
  o 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