Achondroplasia (*FGFR3*), 2 Mutations

**Indications for Ordering**

Achondroplasia mutation(s)
- Confirm clinical or suspected diagnosis of achondroplasia

Achondroplasia mutation(s), fetal
- Confirm diagnosis for fetus with suspected achondroplasia

**Test Description**

Polymerase chain reaction/fluorescence resonance energy transfer hybridization to detect two pathogenic variants in the *FGFR3* gene
  - c.1138G>A (p.G380R)
  - c.1138G>C (p.G380R)

**Tests to Consider**

**Primary tests**

- Achondroplasia (*FGFR3*) 2 Mutations 0051266
- Achondroplasia (*FGFR3*) 2 Mutations, Fetal 0051265
  - Confirm diagnosis in at-risk fetuses or those with ultrasonographic features consistent with achondroplasia

**Related tests**

- Thanatophoric Dysplasia, Types 1 and 2 (*FGFR3*) 13 Mutations 0051506
  - Confirm clinical diagnosis of thanatophoric dysplasia type 1 or type 2
- Thanatophoric Dysplasia, Types 1 and 2 (*FGFR3*) 13 Mutations, Fetal 0051508
  - Confirm diagnosis in at-risk fetuses or those with ultrasonographic features consistent with thanatophoric dysplasia type 1 or type 2

**Disease Overview**

**Incidence** – 1/25,000

**Symptoms**
- Short extremities due to rhizomelic shortening
- Short stature
- Short/broad hands and feet; trident hands
- Mild joint laxity
- Hypotonia
- Lumbar lordosis
- Macrocephaly
- Facial findings
  - Frontal bossing
  - Midface hypoplasia
- Ultrasound is normal until >20 weeks of gestation, when long bones begin to show shortening of <5th percentile
- 7% risk of death due to brain stem compression from foramen magnum and spinal canal stenosis
- Two mutated alleles (homozygous or compound heterozygous) causes a more severe disease
  - Usually lethal in the prenatal period

**Genetics**

**Gene** – *FGFR3*

**Inheritance** – autosomal dominant

**Penetrance** – 100%

**De novo variants** – 80% of cases

**Structure/function**
- Encodes a transmembrane tyrosine kinase receptor that is a regulator of bone growth
- Gain-of-function variants lead to altered bone growth and characteristic skeletal findings

**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity – two pathogenic variants, c.1138G>A and c.1138G>C, account for >99% of cases (Pauli, 2012)
- Analytical sensitivity/specificity – >99%

**Results**
- Negative – no pathogenic variant detected
  - Not predicted to be affected with achondroplasia
- Positive
  - Heterozygous for c.1138G>A or c.1138G>C
    - Confirmed achondroplasia
  - Homozygous or compound heterozygous – two pathogenic variants detected
    - Severe disease that is usually lethal in the prenatal period
Limitations

- Diagnostic errors can occur due to rare sequence variations
- Variants other than c.1138G>A (p.G380R) and c.1138G>C (p.G380R) are not detected

References