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 mutations 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 mutations – 80% of cases

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

Test Interpretation

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

Results
- Negative – no mutation 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 mutations detected
    - Severe disease that is usually lethal in the prenatal period

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

References

- Baujat G, Legeai-Mallet L, et al. Achondroplasia. Best Pract Res Clin Rheumato. 2008;22(1):3-18
- Pauli RM. Achondroplasia. 1998 Oct 12 [Updated 2012 Feb 16]. 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/NBK1152/)