Hypochondroplasia (FGFR3), 2 Mutations

Indications for Ordering

Confirm a diagnosis of hypochondroplasia in individuals with clinical or radiological evidence of the condition

Test Description

Polymerase chain reaction/fluorescence monitoring to detect two pathogenic variants in the FGFR3 gene
  - c.1620C>A (p.N540K)
  - c.1620C>G (p.N540K)

Tests to Consider

Primary tests

Hypochondroplasia (FGFR3) 2 Mutations 0051367
Achondroplasia (FGFR3) 2 Mutations 0051266
  - Confirm a clinical or suspected diagnosis of achondroplasia

Disease Overview

Incidence – 1/15,000-40,000

Symptoms
  - Extreme clinical variability makes diagnosis before 3 years of age difficult
  - Skeletal findings and medical complications are similar but less severe than achondroplasia
  - Rhizomelic or mesomelic shortening of long bones
  - Short stature
  - Short/broad hands and feet; trident hands
  - Mild joint laxity
  - Lumbar lordosis
  - Macrocephaly
  - Facial abnormalities
    - Frontal bossing
    - Midface hypoplasia
  - Developmental delay

Radiologic findings
  - Shortening of long bones with metaphyseal flaring
  - Narrowing of inferior lumbar interpediculer distances
  - Mild brachydactyly
  - Short/broad femoral neck
  - Squared/shortened ilia

Genetics

Gene – FGFR3

Inheritance – autosomal dominant
Penetration – 100%

De novo variants – most cases
  - Risk of recurrence in offspring of unaffected parents is <0.01%

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 – 70% (Bober, 2013)
  - Analytical sensitivity/specificity – 99%

Results
  - Positive
    - Heterozygous for either c.1620C>A or c.1620C>G
      - Confirmed hypochondroplasia
    - Homozygous or compound heterozygous – two pathogenic variants detected
      - A more severe disease is predicted
  - Negative
    - No pathogenic variant detected
      - Likelihood of hypochondroplasia is reduced, but still possible

Limitations
  - Diagnostic errors can occur due to rare sequence variations
  - Variants other than FGFR3 c.1620C>A and c.1620C>G are not detected

References