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 mutations 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 interpedicular distances
- Mild brachydactyly
- Short/broad femoral neck
- Squared/shortened ilia

Genetics

Gene – *FGFR3*

Inheritance – autosomal dominant

Penetrance – 100%

De novo mutations – 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 mutations 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 mutations detected
    - A more severe disease is predicted
- Negative
  - No mutation detected
    - Likelihood of hypochondroplasia is reduced, but still possible

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Mutations other than *FGRF3* c.1620C>A and c.1620C>G are not detected

References

- Bober MB, Bellus GA, et al. Hypochondroplasia. 1999 Jul 15 [Updated 2013 Sep 26]. 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/NBK1477/)
- Heuertz S, Le Merrer M, et al. Novel FGFR3 mutations creating cysteine residues in the extracellular domain of the receptor cause achondroplasia or severe forms of hypochondroplasia." Eur J Hum Genet. 2006;14:1240-1247