

Hypochondroplasia (*FGFR3*) 2 Mutations

TO CONFIRM A CLINICAL DIAGNOSIS OF HYPOCHONDROPLASIA

Disease Overview

- Hypochondroplasia is a non-lethal skeletal dysplasia characterized by short extremities due to rhizomelic or mesomelic shortening, short stature, short/broad hands and feet, mild joint laxity, lumbar lordosis, and macrocephaly.
- There is no single radiologic or clinical feature unique to hypochondroplasia. Common radiologic findings include: shortening of long bones with mild metaphyseal flaring, narrowing of inferior lumbar interpedicular distances, mild brachydactyly, short/broad femoral neck, and squared/shortened ilia.
- Skeletal findings and medical complications are usually similar but less severe than achondroplasia (e.g., midface hypoplasia, frontal bossing, trident hands, and mild or absent motor milestone delays).
- Extreme clinical variability and established locus heterogeneity complicate the diagnosis of hypochondroplasia, especially in children under 3 years of age.
- Diagnosis of sporadic or familial cases is not feasible by prenatal ultrasound.

Epidemiology

Incidence is one in 15,000–40,000.

Genetics

- Hypochondroplasia is autosomal dominant.
- Penetrance is 100 percent; height range in mild hypochondroplasia may overlap that of the general population, but radiographic changes are present.
- Majority of cases are sporadic; recurrence risk in offspring is <0.01 percent for unaffected parents. An association with advanced paternal age has been reported.
- Gain of function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, a negative regulator of bone growth, leads to the characteristic skeletal findings.
- Seventy percent of cases are caused by an A or G nucleotide substitution for C at position 1620, resulting in a lysine-for-asparagine substitution (N540K).
- Locus heterogeneity has been established through linkage analysis, which demonstrates that similar phenotypes result from mutations in currently unidentified genes.
- Compound heterozygotes for N540K/achondroplasia mutation have a severe skeletal phenotype and potential for significant medical problems.
- The clinical presentation of N540K homozygotes, homozygotes for non-*FGFR3* hypochondroplasia mutations, or compound heterozygotes for N540K/non-*FGFR3* mutations have not been described.

Indication for Ordering

Confirm a clinical diagnosis of hypochondroplasia.

Interpretation

- When neither the c.1620C>A nor the c.1620C>G mutation is present, the risk for hypochondroplasia is reduced but not eliminated.
- If a sample is heterozygous for either the c.1620C>A or c.1620C>G mutation, confirmation for a clinical diagnosis of hypochondroplasia is provided.

Methodology

- Mutations in the *FGFR3* gene (c.1620C>A, c.1620C>G) are assayed by polymerase chain reaction and fluorescence resonance energy transfer.
- Clinical sensitivity is 70 percent.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- *FGFR3* gene mutations, other than c.1620C>A and c.1620C>G, will not be detected.
- Mutations in other genes that may cause hypochondroplasia, or similar clinical findings, are not detected.
- Rare diagnostic errors may occur due to primer site mutations.

Related Tests

- Achondroplasia Mutation ([0051266](#))
- Achondroplasia Mutation, Fetal ([0051265](#))
- Thanatophoric Dysplasia, Types I and II (*FGFR3*) 13 Mutations ([0051506](#))
- Thanatophoric Dysplasia, Types 1 & 2 (*FGFR3*) 13 Mutations, Fetal ([0051508](#))

References

1. GeneTests: Hypochondroplasia. www.genetests.org (accessed May 4, 2007).
2. Zoltan V, Francomano CA, Wilkin DJ. The molecular and genetic basis of fibroblast growth factor receptor 3 disorders: the achondroplasia family of skeletal dysplasias, Muenke craniosynostosis, and Crouzon syndrome with acanthosis nigricans. *Endocr Rev* 2000; 21(1):23–39.
3. Rousseau, F. et al. Clinical and genetic heterogeneity of hypochondroplasia. *J Med Gen* 1996; 33:749–52.

Test Information

0051367 **Hypochondroplasia**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.