

Achondroplasia (*FGFR3*) 2 Mutations

TO DIAGNOSE ACHONDROPLASIA

Disease Overview

- Achondroplasia is a skeletal dysplasia characterized by short stature, shortening of the proximal long bones, large head with frontal bossing, limited elbow extension, and bowed legs.
- Although affected individuals have normal intelligence and most have a normal life span, there is a 7 percent risk for death in infancy from obstructive apnea due to midface hypoplasia or brainstem compression. Large head size also increases risk for intracranial bleeding during vaginal delivery.
- Infants present with mild to moderate hypotonia and hyperextensibility of the knees and other joints.
- Affected adults with symptomatic spinal stenosis often experience back pain, which may progress to lower extremity pain and debilitating consequences.
- Currently, there is no effective therapy to stimulate bone growth in patients with achondroplasia.

Epidemiology

One in 25,000 births worldwide.

Genetics

- Autosomal dominant inheritance with 100 percent penetrance; 80 percent of cases are de novo.
- The Fibroblast Growth Factor Receptor 3 (*FGFR3*) gene is located on chromosome 4p16.3.
- Two mutations, c.1138G>A and c.1138G>C, result in a G380R (glycine to arginine) amino acid substitution accounting for greater than 99 percent of cases with the classical features of achondroplasia.
- *FGFR3* encodes a transmembrane tyrosine kinase receptor with an extracellular ligand-binding domain expressed in resting and proliferating chondrocytes.
- *FGFR3* is a negative regulator of enchondral bone growth. *FGFR3* signaling is essential in chondrocyte differentiation and proliferation through pathways that down regulate growth-promoting molecules. *FGFR3* signaling also inhibits both the proliferation and terminal differentiation of growth plate chondrocytes and synthesis of extracellular matrix.

Indications for Ordering

- Confirmation of a diagnosis of achondroplasia.
- Prenatal diagnosis for pregnancies of average-sized adults with ultrasound findings suggestive of achondroplasia.
- Prenatal diagnosis for pregnancies of affected couples who want to be sure the fetus did not inherit a lethal combination of two mutations.

- Prenatal diagnosis for pregnancies with one affected parent to determine if the fetus is affected and could benefit from extra care during delivery.

Additional Testing Information

To test individuals for a specific *FGFR3* mutation a copy of the lab report detailing the familial mutation must be provided. Please provide the relationship of the family member to the individual being tested.

Interpretation

- Negative: The *FGFR3* c.1138G>A and c.1138G>C mutations were not detected.
- Heterozygous: One copy of either the c.1138G>A or c.1138G>C mutation detected is diagnostic for achondroplasia.
- Homozygous or Compound Heterozygous: Two copies of the c.1138G>A or c.1138G>C mutations, or one c.1138G>A mutation and one c.1138G>C mutation are lethal in the perinatal period.

Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect the c.1138G>A and c.1138G>C (G380R) mutations.
- Clinical sensitivity and specificity are 99 percent.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- Mutations in the *FGFR3* gene, other than c.1138G>A and c.1138G>C, are not evaluated.
- Rare diagnostic errors may occur due to primer-site mutations.

Related Tests

- Achondroplasia (*FGFR3*) 2 Mutations, Fetal (0051265)

References

1. Achondroplasia. <http://www.genetests.org>. (accessed on October 20, 2010).
2. Laederich MB, Horton WA. Achondroplasia: pathogenesis and implications for future treatment. *Curr Opin Pediatr* 2010;22:516–23.
3. Baujat G, et al. Achondroplasia. *Best Pract Res Clin Rheumatol* 2008;22(1):3–18.

Test Information

0051266

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

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