SickKids | Genome Diagnostics

ACHONDROPLASIA/HYPOCHONDROPLASIA

Achondroplasia (ACH) is characterized by abnormal bone growth that results in short stature with disproportionately short arms and legs, a large head, and characteristic facial features. Intelligence and life span are usually unaffected, although compression of the spinal cord and/or upper airway obstruction during infancy may result in medical complications.

Hypochondroplasia (HCH) is also characterized by short stature with disproportionately short arms and legs. The skeletal features are very similar to Achondroplasia but usually tend to be milder. Medical problems common to Achondroplasia occur less frequently in Hypochondroplasia, however deficits in mental capacity may be more common.

GENETICS

Achondroplasia and Hypochondroplasia are autosomal dominant disorders caused by mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene located on chromosome 4 (4p16.3). Both conditions occur as a result of different changes in the *FGFR3* gene.

Most cases of ACH or HCH are a result of a new mutation, as the parents are not affected and have average stature. In these cases the risk of having another affected child is low. A person with ACH or HCH whose partner is average-sized has a 50% chance of having a child with the same condition. When both parents are affected, there is a 75% chance of having an affected child. The severity of the disorder in these children will vary, depending on the type and number of mutations inherited.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with ACH or HCH
- Pregnancies at high risk due to abnormal ultrasound findings or a family history of ACH or HCH

TEST METHODS

- Direct mutation detection assay using PCR to test for the following mutations in the *FGFR3* gene:

Disorder	*FGFR3* Gene Mutation
ACH	c.1138G>A (p.Gly380Arg)
	c.1138G>C (p.Gly380Arg)
	c.1123G>T (p.Gly375Cys)
HCH	c.1620C>A (p.Asn540Lys)
	c.1620C>G (p.Asn540Lys)
	c.1619A>C (p.Asn540Thr)
	c.1612A>G (p.Ile538Val)

TEST SENSITIVITY

The mutations indicated above account for more than 99% of those present in individuals affected with Achondroplasia, and 70% of those present in individuals affected with Hypochondroplasia. A small fraction of people with ACH and ~30% of people with HCH have different mutations in the *FGFR3* gene that are not detected by this test.

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

FGFR3 Gene Mutation	Explanation
None detected	This result does not support a diagnosis of Achondroplasia or Hypochondroplasia
Mutation detected (Gly380Arg or Gly375Cys)	This result supports a diagnosis of Achondroplasia
Mutation detected (Asn540Thr, Asn540Lys or Ile538Val)	This result supports a diagnosis of Hypochondroplasia

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/ ACH Item # 100800, HCH Item # 146000

GeneReviews online clinical information resource - ACH: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=achondroplasia or HCH: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hypochondroplasia

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of ACH or HCH.

2. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

3. Other mutation combinations are possible in addition to those listed. These combinations are very rare and usually result in a more serious phenotype.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.