

## What is hypophosphatasia?

Hypophosphatasia is an inherited disease characterized by defective mineralization of bones and teeth, with variable severity and age at onset.<sup>1,2</sup> Individuals with hypophosphatasia have defects in an enzyme called alkaline phosphatase, which is essential for the process of mineralization.<sup>3</sup> During mineralization, minerals such as calcium and phosphorus are deposited in developing bones and teeth.<sup>3</sup> Symptoms of hypophosphatasia are due to an inadequate or defective mineralization process.<sup>1</sup>

## What are the symptoms of hypophosphatasia and what treatment is available?

Hypophosphatasia is classified into six overlapping clinical subtypes based on age at diagnosis. The most severe form occurs prenatally and is characterized by marked skeletal defects in utero and stillbirth or death soon after birth.<sup>1</sup> Less severely affected individuals show symptoms in later infancy or childhood.<sup>1</sup> Mild forms are seen in adulthood, with some affected adults showing only tooth abnormalities.<sup>1</sup> Signs and symptoms may include:<sup>1,2,4</sup>

- Skeletal abnormalities similar to rickets
- Premature craniosynostosis (skull abnormality), leading to intracranial hypertension
- Abnormally shaped chest with respiratory complications
- Poor feeding and failure to gain weight
- Hypercalcemia, leading to recurrent vomiting and kidney problems
- Short stature
- Bone and joint malformations
- Osteomalacia (softening of bones)
- Recurrent bone fractures
- Osteoarthritis
- Early loss of primary and secondary teeth
- Odontohypophosphatasia (malformed teeth)

There is no cure for hypophosphatasia. Treatment is supportive and may include medications, surgery for orthopedic issues, proactive dental care, and enzyme replacement therapy in appropriate cases.<sup>4</sup>

## How is hypophosphatasia inherited?

Hypophosphatasia is caused by mutations in the *ALPL* gene and may be inherited in either an autosomal recessive or an autosomal dominant pattern.<sup>1,2</sup> Severe, early onset disease is autosomal recessive and milder disease with a later onset may be either autosomal recessive or dominant.<sup>2,4</sup>

In the autosomal recessive pattern of inheritance, an individual who inherits one copy of an *ALPL* gene mutation is a carrier and is not expected to have related health problems. An individual who inherits two *ALPL* mutations, one from each parent, is expected to be affected with hypophosphatasia.

In the autosomal dominant pattern of inheritance, an individual who inherits one copy of an *ALPL* gene mutation is expected to be affected with hypophosphatasia.

If both members of a couple are carriers of mutations in the same gene, the risk for an affected child is at least 25% in each pregnancy and may be 50%, depending on the inheritance pattern associated with the familial mutations; therefore, it is especially important that the reproductive partner of a carrier be offered testing.

## Who is at risk for hypophosphatasia?

Hypophosphatasia can occur in individuals of all races and ethnicities. It is more common in Caucasian populations; in the Canadian Mennonite population, the carrier frequency is 1 in 25.<sup>4</sup>

Having a relative who is a carrier or who is affected can increase an individual's risk to be a carrier. Consultation with a genetics health professional may be helpful in determining carrier risk and appropriate testing.

### What does a positive test result mean?

If a gene mutation is identified, an individual should speak to a physician or genetics health professional about the implications of the result and appropriate testing for the reproductive partner and at-risk family members.

### What does a negative test result mean?

A negative result reduces, but does not eliminate, the possibility that an individual carries a gene mutation. The likelihood of being a carrier is also influenced by family history, medical symptoms, and other relevant test results.

### Where can I get more information?

Genetics Home Reference: <http://ghr.nlm.nih.gov/condition/hypophosphatasia>

National Organization for Rare Disorders (NORD): <http://rarediseases.org/rare-diseases/hypophosphatasia/>

Osteogenesis Imperfecta Foundation: <http://www.oif.org/site/PageServer?pagename=Hypophosphatasia>

Soft Bones: <http://www.softbones.org/>

### References

1. Hypophosphatasia. *Genetics Home Reference*. Available at <http://ghr.nlm.nih.gov/condition/hypophosphatasia>. Accessed February 4, 2016.
2. Mornet E. Hypophosphatasia. *Orphanet J Rare Dis* 2007, 2:40.
3. *ALPL*. *Genetics Home Reference*. Available at <http://ghr.nlm.nih.gov/gene/ALPL>. Accessed February 4, 2016.
4. Mornet E and Nunes ME. Hypophosphatasia. *GeneReviews*. Available at <http://www.ncbi.nlm.nih.gov/books/NBK1150>. Accessed February 4, 2016.