

# Hypophosphatasia

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[Abstract](#)

[Keywords](#)

[Disease name / synonyms](#)

[Definition / diagnostic criteria](#)

[Differential diagnosis](#)

[Etiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Antenatal diagnosis](#)

[Epidemiology](#)

[Genetic counseling](#)

[Management including treatment](#)

[References](#)

## Abstract

*Hypophosphatasia is a rare inherited disorder characterized by defective bone and teeth mineralization and deficiency of serum and bone alkaline phosphatase activity. The frequency of the disease has been estimated to 1/100,000 for severe forms. The symptoms are highly variable in their clinical expression, which ranges from stillbirth without mineralized bone to early loss of tooth without bone symptoms. The transmission of severe forms is autosomal recessive while milder forms may be transmitted as dominant or recessive autosomal traits. The diagnosis is based on serum alkaline phosphatase assay and molecular analysis of the tissue nonspecific alkaline phosphatase (ALPL) gene. Currently, there is no treatment of the disease.*

## Keywords

Hypophosphatasia, ALPL gene, alkaline phosphatase, bone disease, mineralization

## Disease name / synonyms

- Hypophosphatasia
- Phosphoethanolaminuria
- Rathbun disease
- HOPS

## Definition / diagnostic criteria

Hypophosphatasia is an inherited disorder characterized by defective bone and teeth mineralization and deficiency of serum and bone alkaline phosphatase activity.

## Differential diagnosis

- Hypophosphatasia
- Osteogenesis imperfecta
- Rickets

- Achondrogenesis

## Etiology

The disease is due to mutations in the liver/bone/kidney alkaline phosphatase gene (ALPL; OMIM# 171760) encoding the tissue-nonspecific alkaline phosphatase (TNSALP). TNSALP is a phosphomonoesterase of 507 residues, anchored at its carboxyl terminus to the plasma membrane by a phosphatidylinositol-glycan moiety (Jemmerson *et al.* 1987). The enzyme is physiologically active in its dimeric form and cleaves extracellular substrates pyridoxal-5'-phosphate (PLP), phosphoethanolamine (PEA) and inorganic pyrophosphates (PPi). Its exact

function in bone and dental mineralization is still unclear but probably involves hydrolysis of PPI (Hessle *et al.* 2002), and perhaps mammalian-specific activities such as collagen and calcium binding (Mornet *et al.* 2001). The *TNSALP* gene is located on chromosome 1p36.1 (Greenberg *et al.* 1990) and consists of 12 exons distributed over 50 kb (Weiss *et al.* 1988). The gene is subject to high allelic heterogeneity (Mornet 2000) and more than 138 distinct mutations have been described (see for review the *TNSALP* gene mutation database at the internet address <http://www.sesep.uvsq.fr/Database.html>). Most of them (82%) are missense mutations. This variety of mutations results in highly variable clinical expressivity and in a great number of compound heterozygous genotypes. Attempts to assess the relative importance of missense mutations and the genotype-phenotype relationship were performed on the basis of clinical data from patients, transfection studies (Sugimoto *et al.* 1998, Fukushi *et al.* 1998, Shibata *et al.* 1998, Cai *et al.* 1998, Zurutuza *et al.* 1999, Taillandier *et al.* 2000, Watanabe *et al.* 2002, Ishida *et al.* 2003), computer-assisted modeling (Zurutuza *et al.* 1999, Mornet *et al.* 2001), and studies of the biochemical properties of ALP in cultured fibroblasts of patients (Fedde *et al.* 1996) or transfected cells (Di Mauro *et al.* 2002).

### Clinical description

Hypophosphatasia (OMIM 146300, 241500, 241510) is characterized by defective bone and teeth mineralization and deficiency of serum and bone alkaline phosphatase activity. Clinical expression ranges from stillbirth without mineralized bone to pathologic fractures developing only late in adulthood (Whyte MP, 1994). Depending on the age at diagnosis, five clinical forms are currently recognized: perinatal (lethal), infantile, childhood, adult and odontohypophosphatasia. A rare benign prenatal form characterized by *in utero* detection but much better prognosis than other prenatal forms was more recently described and define the sixth clinical form of hypophosphatasia (Moore *et al.* 1999, Pauli *et al.* 1999).

### Lethal perinatal form

In the lethal perinatal form the patients show markedly *in utero* impaired mineralization. They have skin-covered osteochondral spurs protruding from the forearms or legs (Shohat *et al.* 1991). These spurs are often diagnostic for hypophosphatasia. Some infants survive a few days but have respiratory complications due to

hypoplastic lungs and rachitic deformities of the chest. Other symptoms include apnea, seizures, and marked shortening of the long bones. In the rare prenatal benign form, despite prenatal symptoms, there is a spontaneous improvement of skeletal defects.

### Infantile form

Patients with the infantile form may appear normal at birth; however, the clinical signs of hypophosphatasia appear during the first 6 months. This form also has respiratory complications due to rachitic deformities of the chest. Despite the presence of an open fontanelle, premature craniosynostosis is a common finding that may result in increased intracranial pressure. Radiographs show widespread demineralization and rachitic changes in the metaphyses. Hypercalcemia also is present, explaining a history of irritability, poor feeding, anorexia, vomiting, hypotonia, polydipsia, polyuria, dehydration, and constipation. Increased excretion of calcium may lead to renal damage. In infants who survive, there is often spontaneous improvement in mineralization and remission of clinical problems, with the exception of craniosynostosis (Whyte *et al.* 1986). Short stature in adulthood and premature loss of deciduous teeth are also common but the long-term outlook is good (Cole 2003).

### Childhood form

Skeletal deformities, such as dolichocephalic skull and enlarged joints, a delay in walking, short stature, and waddling gait accompany the childhood form. Signs of intracranial hypertension or failure to thrive are typical (Whyte 1994, Fallon *et al.* 1984, Kozlowski *et al.* 1976). A history of fractures and bone pain usually exists as well. Focal bony defects near the ends of major long bones may be observed and help point to the diagnosis. Premature loss of dentition is common with the incisor teeth often being the first affected. Spontaneous remission of bone disease is well known, but the disease may re-appear in middle or late adulthood.

### Adult form

The adult form presents during middle age. The first complaint may be foot pain, which is due to stress fractures of the metatarsals. Thigh pain, due to pseudofractures of the femur, also may be a presenting symptom. There is also a predilection for chondrocalcinosis and marked osteoarthropathy later in life. Upon obtaining an in-depth history, many of these patients will

reveal that they had premature loss of their deciduous teeth (Whyte 1979; Whyte 1982).

### **Odontohypophosphatasia**

Odontohypophosphatasia is characterized by premature exfoliation of fully rooted primary teeth and/or severe dental caries, often not associated with abnormalities of the skeletal system. The anterior deciduous teeth are more likely to be affected and the most frequent loss involves the incisors (Beumer *et al.* 1973). Dental X-rays show reduced alveolar bone, enlarged pulp chambers and root canals. Although the only clinical feature is dental disease, biochemical findings are generally indistinguishable from those in patients with mild forms of hypophosphatasia (adult and childhood). Odontohypophosphatasia should be considered in any patient with a history of early unexplained loss of teeth or abnormally loose teeth on dental examination (Cole 2003).

### **Diagnostic methods**

In addition to clinical and radiographic examinations (see clinical description), hypophosphatasia diagnosis is based on laboratory assays, and since 1990s, molecular biology which appears to be very effective.

### **Laboratory assays**

Total serum alkaline phosphatase activity is markedly reduced in hypophosphatasia. So, the diagnosis can be suggested in individuals in whom serum ALP activity is clearly and consistently subnormal. In general, the more severe the disease, the lower the serum ALP activity level appropriate for age (White 1994). However, ALP activity is only a helpful diagnostic indicator because other conditions may also show this finding: early pregnancy, drugs administration, hypothyroidism, anemia, celiac disease etc. It must be also noticed that serum ALP dramatically varies with age and sex.

Increased urinary phosphoethanolamine (PEA) level supports a diagnosis of hypophosphatasia but is not pathognomonic. It is also observed in a variety of other conditions, including several metabolic bone diseases, and some hypophosphatasia patients may have normal PEA excretion.

Increased pyridoxal 5'-phosphate (PLP) may be a sensitive marker for hypophosphatasia (Whyte *et al.* 1994).

Heterozygous carriers of the severe forms are usually clinically normal but often show modestly reduced serum ALP activity and increased urinary phosphoethanol-amine (PEA) (Rasmussen 1983).

### **Molecular biology**

Screening for mutations in the *TNSALP* gene is essential to confirm the hypophosphatasia diagnosis when biochemical and clinical data are not clear enough, or to offer molecular prenatal diagnosis to families affected by severe forms of the disease (see below). Indeed, clinical and biochemical data may not always distinguish hypophosphatasia from other skeletal diseases such as osteogenesis imperfecta. Some patients presenting with atypical radiographic pictures and borderline laboratory values were diagnosed with hypophosphatasia on the basis of *TNSALP* mutations. Mutation screening may be performed by SSCP or DGGE followed by sequencing of exons exhibiting variants (Orimo *et al.* 1994, Orimo *et al.* 1997, Goseki-Sone *et al.* 1998, Mornet *et al.* 1998, Watanabe *et al.* 1999, Mumm *et al.* 2002), by direct sequencing of the cDNA (Henthorn *et al.* 1992, Greenberg *et al.* 1993, Fedde *et al.* 1996) or by direct sequencing of genomic sequences (Taillandier *et al.* 1999, Taillandier *et al.* 2000, Spentchian *et al.* 2003). The exons are small and few in number, making relatively easy the analyses. However, the fact that the mutations are spread over all the exons often means that the whole coding sequence has to be analyzed. In addition, some mutations remain undetectable despite of exhaustive sequencing of the coding sequence, intron-exon borders and untranslated exons. This may be due to mutations lying in intronic or regulatory sequences, but also to the expression of heterozygous mutations, especially in moderate (childhood, adult and ondoto-) hypophosphatasia. By using sequencing, approximately 95% of mutations are detected in severe (perinatal and infantile) hypophosphatasia. There is no reason to believe that this rate is lower in moderate forms, although the estimation is blurred by the patients in whom the disease is expressed at the heterozygous state.

### **Antenatal diagnosis**

Prenatal assessment of severe hypophosphatasia by mutation analysis of chorionic villus DNAs is now well documented (Henthorn *et al.* 1995, Orimo *et al.* 1996, Mornet *et al.* 1999) and is routinely performed in at least one laboratory. It seems that mutation analysis is more reliable than alkaline phosphatase assay of chorionic villus at least for heterozygote detection where low ALP values may be misinterpreted (Mornet *et al.* 1999). Prenatal and postnatal diagnoses were also reported by using linked or intragenic

polymorphisms (Greenberg *et al.* 1990, Iqbal *et al.* 1999).

### Epidemiology

The birth prevalence of severe hypophosphatasia was estimated to be 1/100,000 on the basis of pediatric hospital records in USA (Fraser 1957). The incidence of moderate forms was never estimated but it is expected to be much higher, due to the number of patients with dominant forms carrying the same mutations than those found in recessive hypophosphatasia.

### Genetic counseling

Genetic counseling of hypophosphatasia is complicated by the inheritance that may be autosomal dominant or autosomal recessive, the existence of an uncommon prenatal benign form (Pauli *et al.* 1999, Moore *et al.* 1999), the variable expression of the disease in heterozygotes and the probable effect of other genes that may modulate the hypophosphatasia phenotype (modifier genes). Except for rare cases (Pauli *et al.* 1999, Lia-Baldini *et al.* 2001), severe forms of the disease (perinatal and infantile) are transmitted as an autosomal recessive trait, while both autosomal recessive and autosomal dominant transmission have been shown in clinically milder forms (Whyte *et al.* 1979, Whyte *et al.* 1982, Eastman *et al.* 1983 and Eberic *et al.* 1984). Therefore, the risk of recurrence of severe forms is 25%. In moderate forms, it may be 25% (recessive transmission), 50% (dominant transmission) or still different (less than 50%) due to the variable expressivity of dominant forms (Lia-Baldini *et al.* 2001, Hérasse *et al.* 2003). The mutations detected in dominant forms and responsible for moderate hypophosphatasia are also found in severe recessive hypophosphatasia, associated to other mutations (Hu *et al.* 2000, Lia-Baldini *et al.* 2001, Hérasse *et al.* 2003). Dominance is sometimes difficult to demonstrate by using familial analysis, since expression of the disease may be highly variable, with parents of even severely affected children showing no or extremely mild symptoms of the disease (Whyte 1994; Pauli *et al.* 1999). This may be attributable both to the progressive improvement of affected patients from infancy to adulthood (Robinow 1971; Whyte 1989; Fedde *et al.* 1996; Lepe *et al.* 1997) and to epigenetic factors involved in the variable expression of the disease. Testing patient's relatives is useful since heterozygotes may express a mild form of the disease. In regard to the frequency of the disease, testing

spouses of carriers is not primordial unless there is an history of consanguinity.

### Management including treatment

At this time, there is no efficient treatment of hypophosphatasia. Treatments with zinc and magnesium (catalytic ions of the enzyme), and pyridoxal 5'-phosphate were reported not to improve significantly the patient's condition. However, the high clinical heterogeneity and the fact that the disease is rare make almost impossible controlled clinical trials. More promising was the attempt of MP Whyte's group (Saint-Louis, MI, USA) to treat an 8-month-old girl affected with highly severe hypophosphatasia by bone marrow cell transplantation (Whyte *et al.* 2003). The patient was given T-cell-depleted, haplo-identical marrow from her healthy sister and significant and prolonged clinical and radiographic improvement were observed.

Another interesting way of treatment would be to act onto the expression of the plasma cell membrane glycoprotein-1 (*PC-1*) gene, an antagonist of the *TNSALP* gene (Hessle *et al.* 2002). Indeed, it has been shown in mice that inactivation of *pc-1* gene in *tnsalp*-knock-out mice allows to restore the normal bone phenotype (Hessle *et al.* 2002).

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