



Rare Diseases of Bone Development

Clinical features, causes, diagnoses, treatments

Hypophosphatasia

Osteogenesis Imperfecta

Familial Hypophosphatemia

Hereditary Hyperphosphatasia

141 Hawkins Place, #267
Boonton, New Jersey 07005
www.softbones.org

Hypophosphatasia

Also Called

HPP

Rathbun Disease

Overview of HPP

A rare, inherited inborn error of metabolism that results in impaired bone mineralization. Bones are soft and fracture easily and heal slowly. Signs and symptoms vary greatly among affected individuals, ranging from very mild to severe and life-threatening. The disease is life-long.

Cause of HPP

Gene mutation resulting in the inability to manufacture alkaline phosphatase (ALP), an enzyme needed for proper bone mineralization.

Gene Defect in HPP

Mutations in the ALPL gene result in faulty coding for tissue non-specific alkaline phosphatase (TNSALP). Sometimes the gene is called the TNSALP gene. The defective gene can be inherited as dominant or recessive, depending on the form of HPP.¹ The U.S incidence of the gene mutation is 1/200 people.²

Incidence and Prevalence of HPP

Incidence of severe HPP is estimated at 1 per 100,000 live births. Incidence of less severe forms is thought to be greater. Population prevalence of HPP is unknown—mild manifestations can be undiagnosed or misdiagnosed.¹

Hallmarks of HPP

Soft, fragile bones that are prone to fracture and heal slowly

Bowed legs and other skeletal deformities

Premature loss of primary teeth

Other Potential Clinical Features of HPP

Pulmonary insufficiency/respiratory difficulty

Short stature

Bone pain

Poor muscle tone

Loss of adult teeth

Severity of HPP

Varies in severity. Mild HPP can manifest as only dental abnormalities. Severe HPP can be life-threatening. The more severe forms are detected earlier in life. Perinatal HPP detected via ultrasound view of short limbs, abnormal chest shape, soft skull bones. Those most severely affected will fail to form a mineralized skeleton and will have a life span of days.

Variants of HPP

- **Perinatal HPP**
The most severe form, perinatal HPP is visible prenatally via fetal ultrasound. Newborns have short limbs, abnormal chest shape, and soft skull bones. Life expectancy is days or weeks. Those most severely affected fail to form a mineralized skeleton in utero and are stillborn.
- **Infantile HPP**
Signs and symptoms become apparent within the first six months. First sign may be failure to thrive. Skull bones may fuse prematurely, resulting in the appearance of a wide head. Rickets and deformities of the chest and ribs can occur. Hyperkalemia can cause vomiting, constipation, weakness, diminished muscle tone, and poor feeding.
- **Childhood HPP**
Less severe than the infantile form, but often causes delayed development and delayed attainment of such milestones as sitting, crawling, or walking. Primary (baby) teeth fall out earlier than expected (before the age of five); children may have bowed legs and a misshapen skull, wrists, or ankles.
- **Adult HPP**
Typically diagnosed in middle age; can be mistaken for osteoporosis. Affected adults may have had rickets as children, lost baby teeth early, and may be of short stature with bowed or deformed legs. Other features may include waddling gait, pain, and fatigue. The risk of recurrent fractures, particularly in the feet, increases as adult bones soften. Many affected individuals lead a full life. Adult HPP is not considered life-threatening.
- **Odontohypophosphatasia**
Mildest form of HPP. Dental manifestations only; no skeletal signs or symptoms.
- **Pseudohypophosphatasia**
A rare form in which symptoms are present, but patients have normal levels of serum ALP.



- **Benign Prenatal Hypophosphatasia**

Prenatal HPP, visible on fetal ultrasound, that spontaneously improves later in the pregnancy or at birth. A very rare form of HPP.

Diagnosis of HPP³

Bone x-rays

Laboratory testing for serum ALP

Laboratory testing for vitamin B-6 (high)

Gene testing for ALPL gene

Treatment of HPP

Strensiq (asfotase alfa, Alexion) enzyme-replacement therapy for some indications in the United States, Japan, Canada, and EU.

Organizations for HPP

Soft Bones Foundation

<https://www.softbones.org/>

Osteogenesis Imperfecta

Also Called

OI

Brittle Bone Disease

Overview

A group of rare, connective-tissue disorders that results in fragile, brittle bones that can fracture upon minimal trauma.

Cause of OI

Gene defect that affects the quality or quantity of type 1 collagen, a protein that helps support and maintain bone, cartilage, tendons, and other musculoskeletal structures.

Gene Defect in OI

Mutations in the COL1A1 or COL1A2 dominant genes—which contain the instructions for forming type 1 collagen—are responsible for 90 percent of the incidence of OI. The remaining cases result from mutations of other genes, which can have either dominant or recessive inheritance.⁴

Incidence and Prevalence of OI⁵

Incidence is estimated at 1 in every 30,000 to 60,000 live births, depending on the type of OI. The prevalence in the U.S. population is estimated at 20,000 to 50,000 individuals. OI occurs equally in males and females and occurs in all racial groups.

Hallmarks of OI

Frequent broken bones from infancy through puberty

Fracture frequency drops off in early adulthood, then increases in later adulthood

Bone deformity

Short stature

Other Potential Clinical Features of OI

Appearance and severity vary widely; features may vary with age and can vary widely among sub-types, within sub-types, and within the same family, but some of the most widely seen features are:

Loose joints (joint laxity)

Muscle weakness

Early hearing loss

Bluish tint in whites of the eyes

Loose teeth that fall out prematurely

Respiratory problems resulting from bone deformities

Severity of OI

Classified as mild, moderate, or severe. Individuals with the most severe forms have a shortened life span. With good medical management and supportive care, the majority of people with OI lead healthy, productive lives with an average life span.

Variants of OI

Fifteen subtypes have been identified. Ascertaining the subtype is important for treatment decisions and care needs, but the types are not always clear-cut. An individual may not show every feature within one subtype or may exhibit features of multiple subtypes. Denoted by Roman numerals, subtypes vary in prevalence and severity. The most prevalent are Type I through Type VI.

- **Type I OI** is the most prevalent and the mildest. Affected individuals may show no outward signs, have minimal or no bone deformity, and reach expected height. Lifetime fractures are limited, and life expectancy does not appear to be affected.
- **Type II OI** is the most severe. Babies are born with multiple fractures, an unusually soft skull, and an unstable neck. Because of respiratory problems, nearly all die at birth or shortly afterward
- **Type III OI** varies in its presentation and severity. Babies are born with fractures; lifetime fractures could total in the hundreds. Other manifestations include short stature, curved spine, bone deformities, and a barrel-shaped rib cage. Life span may be shortened due to respiratory problems.
- **Type IV OI** is considered moderate, with clinical features varying from almost as mild as Type I to nearing the severity of Type III. It's characterized by short stature, frequent fractures that typically level off after puberty, and some bone deformity. Life expectancy is usually normal.
- **Type V OI** is similar to Type IV, except with the addition of a few distinct features like hypertrophic calluses at fracture sites and limited range of motion of the forearm. It's considered a moderate form of the disease.
- **Type VI** is extremely rare. Similar to Type IV, with the addition of a distinguishing bone-mineralization defect that is discovered via bone biopsy.

Diagnosis of OI

Clinical observation

Medical history

Genetic testing

Bone x-rays

DXA

Prenatal ultrasound for severe forms

Rule out HPP

Treatment of OI

OI is incurable. Disease management is focused on minimizing fractures to improve quality of life. Treatment plans are individualized based on the severity of the disease and may include surgery, physical therapy, and/or medication. Drug treatments indicated for OI are under investigation, but several currently available osteoporosis drugs are frequently prescribed off-label.

Organizations for OI

Osteogenesis Imperfecta Foundation

<http://www.oif.org/>

Familial Hypophosphatemia

Also Called

XLH
Hypophosphatemia
Phosphatemic rickets
Vitamin D-Resistant Rickets
Renal hypophosphatemia

Overview of Familial Hypophosphatemia

A rare, genetic disorder that impairs phosphate transport to cells and manifests as a soft-bone condition called osteomalacia. Vitamin-D metabolism in the kidneys can also be affected, further exacerbating bone weakness.

Cause of Familial Hypophosphatemia

A gene defect that interferes with the kidneys' ability to conserve phosphate and activate vitamin-D production. The resulting low levels of phosphate and vitamin-D impair bone mineralization, thus leaving the affected individual with soft, weak bones.

Gene Defect in Familial Hypophosphatemia

Mutations of the PHEX gene, located on the X chromosome, are responsible for most cases. PHEX mutations increase the levels of a phosphate-regulating hormone that triggers the kidneys to 1) over-excrete phosphate in the urine, and 2) inhibit activation of vitamin-D. The resulting condition is known as X-linked hypophosphatemia (XLH). PHEX is a dominant gene; thus XLH can occur in both males and females.

Less commonly, familial hypophosphatemia is inherited through an autosomal dominant mutation, with the ensuing condition referred to as autosomal dominant familial hypophosphatemic rickets (ADHR). Another variant is inherited as an autosomal recessive trait (ARHR).

Incidence and Prevalence of Familial Hypophosphatemia

The incidence of XLH is estimated at 1 in 20,000 individuals. Based on that incidence, it can be estimated that 16,000 individuals in the United States currently have familial hypophosphatemia. ADHR and ARHR occur with far less frequency.

Hallmarks of Familial Hypophosphatemia

Bowed legs (rickets) at young age
Concave chest
Short stature
Progressive softening of bones (osteomalacia)

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Long-shaped head relative to head width
Spontaneous tooth abscesses
Late eruption of teeth

Other Potential Clinical Features of Familial Hypophosphatemia

Bone pain
Muscle pain and weakness
Stiffness in the back, hips, and shoulders
Hearing loss
Dental caries

Severity of Familial Hypophosphatemia

Varies substantially. The most severely affected individuals have limited mobility. About five percent of people with XLH have no bone symptoms at all and may go undiagnosed.⁶ The disease is incurable and life-long.

Variants of Familial Hypophosphatemia

- X-linked hypophosphatemia (XLH): The most common inherited cause of rickets, caused by an X-linked gene mutation.
- Autosomal dominant hypophosphatemic rickets (ADHR): Less common; inherited through autosomal dominant gene transmission.
- Autosomal recessive hypophosphatemic rickets (ARHR): Least common; inherited through autosomal recessive gene transmission.

Diagnosis of Familial Hypophosphatemia

Serum phosphate level (lower than reference value)⁷
24-hour urine phosphate excretion (higher than ref. value)⁸
Serum magnesium, calcium, and potassium
Bone x-rays
Genetic testing to determine if the state of hypophosphatemia—low serum phosphate—is a consequence of genetic inheritance or is secondary to another disease or condition.

Treatment of Familial Hypophosphatemia

Nutritional supplementation with phosphate salts and activated forms of vitamin D can help replace intrinsically low levels but will not cure the disease.
Supportive measures to ease pain and aid mobility
Tooth sealants to protect against abscesses
Surgery for severely deformed legs

**Organizations for Familial Hypophosphatemia**

XLH Network

<https://xlhnetwork.org/>

Hereditary Hyperphosphatasia

Also Called

Chronic congenital idiopathic hyperphosphatasemia
Familial idiopathic hyperphosphatasia
Familial osteoectasia
Hyperostosis corticalis deformans juvenilis
Juvenile Paget's disease

Overview of Hereditary Hyperphosphatasia

A rare genetic bone disorder characterized by progressive skeletal malformations, mostly in the long bones of the arms and legs. It becomes apparent in infancy or early childhood.

Cause of Hereditary Hyperphosphatasia

Deficiency of the osteoprotegerin protein, resulting in rapid bone turnover—the continual process of bone resorption (break-down) and osteogenesis (depositing new bone). In normal physiology, bone turnover is a tightly regulated, complex sequence of cellular events. In hereditary hyperphosphatasia, deficiency of osteoprotegerin, needed for healthy bone turnover, upsets the balance, and bone turnover becomes too prevalent.⁹

Gene Defect in Hereditary Hyperphosphatasia

Through autosomal recessive heredity, mutations of the TNFRSF11B gene are responsible for about two-thirds of cases. TNFRSF11B codes for the osteoprotegerin protein, which regulates the cells responsible for bone resorption.

Incidence and Prevalence of Hereditary Hyperphosphatasia

Hereditary hyperphosphatasia is extremely rare. The number of individuals who have been identified with the disease since it was first reported in the medical literature in 1956 hovers around 50.⁹

Hallmarks of Hereditary Hyperphosphatasia

Widening and bowing of the long bones of the legs
Thickening of long bones of limbs
Difficulty walking
Short stature
Thickening of the upper part of skull (calvaria)

Other Potential Clinical Features of Hereditary Hyperphosphatasia

Pain
Fractures
Muscle weakness

Curvature of the spine (front-to-back and side-to-side)

Sensorineural hearing loss

Damage to optic nerve and retina

Severity of Hereditary Hyperphosphatasia

The severity and variety of symptoms vary, but severity generally increases in adolescence.¹⁰

Variants of Hereditary Hyperphosphatasia

As the condition is exceedingly rare, the prevalence is too small to identify variants

Diagnosis of Hereditary Hyperphosphatasia

Clinical evaluation

X-rays

Blood test (elevated levels of serum alkaline phosphatase)

Urine tests (biochemical markers of bone turnover)

Treatment of Hereditary Hyperphosphatasia

Treatment is mostly supportive, based on an individual's symptoms. Some affected individuals are treated with bisphosphonates, which reduce bone turnover by inhibiting bone resorption. Some investigational drugs are also under study.

Organizations for Hereditary Hyperphosphatasia

Although there are no identified organizations dedicated solely to Hereditary hyperphosphatasia, additional information can be obtained at these groups:

Genetic and Rare Diseases (GARD) Information Center

<https://rarediseases.org/organizations/genetic-and-rare-diseases-gard-information-center/>

National Organization for Rare Disorders

<https://rarediseases.org/rare-diseases/hereditary-hyperphosphatasia/>

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