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Hypophosphatasia

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Summary

Disease characteristics. Hypophosphatasia is characterized by defective mineralization of bone and/or teeth in the presence of low activity of serum and bone alkaline phosphatase. Clinical features range from stillbirth without mineralized bone at the severe end to pathologic fractures of the lower extremities in later adulthood at the mild end. At least six clinical forms are currently recognized based on age at diagnosis and severity of features, including: perinatal (lethal) hypophosphatasia characterized by respiratory insufficiency and hypercalcemia; perinatal (benign) hypophosphatasia with prenatal skeletal manifestations that slowly resolve into the milder childhood or adult form; infantile hypophosphatasia with onset between birth and age six months of rickets without elevated serum alkaline phosphatase activity; childhood hypophosphatasia that ranges from low bone mineral density for age with unexplained fractures to rickets; adult hypophosphatasia characterized by early loss of adult dentition and stress fractures and pseudofractures of the lower extremities in middle age; and odontohypophosphatasia characterized by premature exfoliation of primary teeth and/or severe dental caries as an isolated finding or as part of the above forms of hypophosphatasia.

Diagnosis/testing. Although formal diagnostic criteria are not established, all forms of hypophosphatasia (except pseudohypophosphatasia) share in common reduced activity of unfractionated serum alkaline phosphatase (ALP) and presence of either one or two pathologic mutations in *ALPL*, the gene encoding alkaline phosphatase, tissue-nonspecific isozyme (TNSALP). *ALPL* is the only gene known to be associated with hypophosphatasia.

Management. *Treatment of manifestations:* Perinatal lethal type: expectant management and family support. Infantile types: respiratory support, treatment of hypercalcemia/hypercalciuria; treatment of seizures with vitamin B_6; routine treatment of craniosynostosis. All other types: routine dental care starting at age one year; NSAIDs for osteoarthritis, bone pain, and osteomalacia; internal fixation for pseudofractures and stress fractures. *Surveillance:* dental visits twice yearly starting at age one year; monitoring children with infantile type for increased

intracranial pressure secondary to craniosynostosis. *Agents/circumstances to avoid:* bisphosphonates, excess vitamin D

Genetic counseling. Perinatal and infantile hypophosphatasia are inherited in an autosomal recessive manner. The milder forms, especially adult and odontohypophosphatasia, may be inherited in an autosomal recessive or autosomal dominant manner depending on the effect that the *ALPL* mutation has on TNSALP activity. In autosomal recessive hypophosphatasia, heterozygotes (carriers) either are asymptomatic, manifesting biochemical but not clinical abnormality, or may manifest milder symptoms depending on the mutation. Although *de novo* mutations have been reported, in most instances each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an "asymptomatic" carrier, and a 25% chance of being unaffected and not a carrier. In autosomal dominant hypophosphatasia, most probands have an affected parent; *de novo* mutations have not been reported. Each child of an individual with the autosomal dominant form of hypophosphatasia has a 50% chance of inheriting the mutation. For both modes of inheritance, prenatal diagnosis for pregnancies at increased risk is possible if disease-causing mutation(s) of an affected family member is (are) known. Recurrence of perinatal and infantile hypophosphatasia may reliably be identified by prenatal ultrasound examination.

Diagnosis

Clinical Diagnosis

Hypophosphatasia is characterized by defective mineralization of bone and/or teeth in the context of low activity of serum and bone alkaline phosphatase.

Although formal diagnostic criteria are not established, all forms of hypophosphatasia share in common:

- Reduced serum alkaline phosphatase (ALP) activity (except pseudohypophosphatasia, in which serum alkaline phosphatase activity is normal)
- Presence of either one or two pathologic mutations in *ALPL*, the gene encoding alkaline phosphatase, tissue-nonspecific isozyme (TNSALP).

At least six clinical forms are currently recognized based on age at diagnosis and severity of features (see Table 1). Clinical features include the following:

- **Prenatal long-bone bowing** with osteochondral spurs and pretibial dimpling
- **Infantile rickets without elevated serum alkaline phosphatase activity.** These features can include growth failure, craniotabes, craniosynostosis, blue sclerae, costochondral enlargement ("rachitic rosary"), scoliosis, thickening of wrists and ankles, bowing of long bones, lax ligaments, and hypotonia.
- **Hypercalcemia and hypercalciuria** during the first year of life
- **Pathologic fractures** and bone pain. Growing children may have a predilection to metaphyseal fractures; however, epiphyseal and diaphyseal fractures are also seen. In adults, metatarsal fractures and femoral pseudofractures prevail.
- **Premature loss of deciduous teeth** beginning with the incisors. Dental caries and early loss or extraction of adult teeth is also seen.
- **Family history** of any of the forms of hypophosphatasia consistent with autosomal recessive inheritance or autosomal dominant inheritance with variable expressivity

The radiographic signs of hypophosphatasia vary with age and type, and may be quite distinctive. Perinatal lethal hypophosphatasia is radiographically distinct. In milder cases, the

combination of clinical, laboratory, and radiographic findings are required for diagnosis because the radiographic signs are not pathognomonic.

- **Osteopenia, osteoporosis, or low bone mineral content for age** detected by dual-energy x-ray absorptiometry (DEXA). Bone mineral content increases with age, and there may be improvement during adolescence with recurrence in middle age.
- **Infantile rickets.** Findings include undermineralized bones, widened-appearing sutures, brachycephaly, rachitic costochondral rib changes, poorly ossified epiphyses, flared metaphyses (resulting in enlarged wrists, knees, and ankles), and bowed legs.
- **Alveolar bone loss** resulting in premature loss of deciduous teeth. This most typically involves the anterior mandible, with the central incisors lost first. However, any teeth may be affected (see Figure 1A).
- **Focal bony defects of the metaphyses** resembling radiolucent "tongues" (see Figure 1B). This feature is fairly specific for childhood hypophosphatasia.
- **Metatarsal stress fractures** in childhood and adult hypophosphatasia
- **Osteomalacia with lateral pseudofractures (Looser zones)** in adult hypophosphatsia (see Figure 1C)

Table 1. Clinical Features of Hypophosphatasia by Type

Type	Inheritance [1]	Cardinal Features	Dental Features	Clinical Diagnosis
Perinatal (lethal)	AR	Hypomineralization, osteochondral spurs	N/A	Radiographs, prenatal ultrasound examination
Perinatal (benign)	AD	Long-bone bowing, benign postnatal course	±	Prenatal ultrasound examination, clinical course
Infantile [2]	AR	Craniosynostosis, hypomineralization, rachitic ribs, hypercalciuria	Premature loss, deciduous teeth	Clinical course, radiographs, laboratory findings
Childhood	AR or AD	Short stature, skeletal deformity, bone pain/ fractures	Premature loss, deciduous teeth (incisors)	Clinical course, radiographs, laboratory findings
Adult [3]	AD	Stress fractures: metatarsal, tibia; chondrocalcinosis	±	Clinical course, radiographs, laboratory findings
Odontohypo-phosphatasia	AD	Alveolar bone loss	Exfoliation (incisors), dental caries	Clinical course, dental panorex, laboratory findings

1. AR = autosomal recessive; AD = autosomal dominant
2. Rare reported cases of infantile hypophosphatasia that have normal serum alkaline phosphatase activity (in vitro) have been designated "pseudohypophosphatasia." The biochemical and molecular basis of pseudohypophosphasia remains unclear.
3. Persons with adult hypophosphatasia may give a history of features typically reported in childhood, infantile, and even prenatal hypophosphatasia.

Testing

Total serum alkaline phosphatase (ALP) activity: low. In all the types of hypophosphatasia, serum ALP activity is low.

- Laboratories within a country and between countries use different methods and thus have very different reference ranges; the gende- and age-specific reference range determined by each reference laboratory should be used. See Table 2 for the lowest normal reference values for a major North American reference laboratory.

  Note: The values in Table 2 are not relevant for other laboratories.
- TNSALP activity requires Zn^{++} and Mg^{++}, so EDTA tubes should not be used.

- Transient increases in serum ALP activity in affected individuals invariably occur during pregnancy. Small increases in serum ALP activity may be seen with liver disease and acute fracture or surgery. Thus, serial measurement of serum ALP activity may be necessary when the diagnosis is suspected in toddlers with unexplained fractures.
- Quantitation of the activity of the bone isoform of ALP in serum is generally unnecessary; however, in the setting of liver disease, the serum activity of ALP may be "falsely" normal. The bone isoform is heat labile, the liver isoform heat stable.

Table 2. Typical Lowest Normal Reference Values for Serum Alkaline Phosphatase Activity in North America

Age	Lowest Normal Total Serum or Plasma Alkaline Phosphatase Activity (U/L)	
	Male	Female
0-30 days	60	
1-11 months	70	
1-3 years	125	
4-11 years	150	
12-13 years	160	110
14-15 years	130	55
16-19 years	60	40
>20 years	40	

Adapted from ARUP laboratories

Note: (1) Full reference values depend on the method used and population sampled. The low normal total serum or plasma alkaline phosphatase activity is specific to the laboratory from which measurement of alkaline phosphatase activity is ordered and differs between laboratories. (2) Empiric historical references for the laboratory employed should be preferentially used.

Urine concentration of phosphoethanolamine (PEA): elevated. This is the most commonly obtained secondary screen for hypophosphatasia. It may be obtained as part of a urine amino acid chromatogram.

- An elevated urine concentration of PEA supports the diagnosis of hypophosphatasia; however, the concentration in urine may be elevated with other metabolic bone disease and may be normal in affected individuals.

  Note: Finding an elevated urine concentration of proline adds specificity in interpretation of test results.
- Asymptomatic heterozygotes may have reduced serum ALP activity and increased urine PEA concentration.

Serum concentration of pyridoxal 5'-phosphate (PLP): elevated

- This biologically active metabolite of vitamin B_6 may be the most sensitive indicator of hypophosphatasia [Cole et al 1986].
- Use of vitamin supplements within a week of assaying serum concentration of PLP may lead to false positive results.

Serum concentration of calcium, ionized calcium, and inorganic phosphate: normal

- Normal levels distinguish hypophosphatasia from other forms of rickets.
- Hypercalciuria may be present with or without elevated serum concentration of calcium.

- Although inorganic phosphate concentration in serum or urine is most typically normal, it may be elevated and thus is too variable to be used in diagnosis.

Serum concentration of vitamin D (25-hydroxy and 1,25-dihydroxy) and parathyroid hormone (nPTH): normal

Urine inorganic pyrophosphate (PPi): elevated

- This is a sensitive marker in affected individuals and asymptomatic heterozygotes.
- The test is available on a research basis only.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *ALPL*, the gene encoding alkaline phosphatase, tissue-nonspecific isozyme (TNSALP), is the only gene known to be associated with hypophosphatasia.

Clinical testing

- **Targeted mutation analysis.** Some mutations are common in particular populations or regions, and may therefore be tested by targeted mutation analysis:
  - c.1559delT and c.979T>C (p.Phe310Leu), in severely and mildly affected individuals in Japan [Orimo et al 2002, Michigami et al 2005]
  - c.571G>A (p.Glu174Lys), in mildly affected individuals of European ancestry [Hérasse et al 2002]
  - c.1001G>A (p.Gly317Asp), in severely affected individuals of the Canadian Mennonite community [Greenberg et al 1993]
  - c.1133A>T (p.Asp361Val), in mildly affected North Americans of European ancestry [Mumm et al 2007]
- **Sequence analysis** of *ALPL* genomic DNA to detect mutations altering either sequence or mRNA stability identifies 95% of mutations in severe perinatal and infantile hypophosphatasia.

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in Hypophosphatasia

Test Method	Mutations Detected [1]	Mutation Detection Frequency by Phenotype	Test Availability
Targeted mutation analysis	Mennonite mutation: c.1001G>A (p.Gly317Asp) Common European mutations: c.571G>A (p.Glu174Lys), c.1133A>T (p.Asp361Val) Common Japanese mutations: c.1559delT, c. 979T>C (p.Phe310Leu)	p.Glu174Lys: ~30% of those of European ancestry with mild disease [2]	Clinical Testing
Genomic DNA sequence analysis	Nonsense mutations, missense mutations, splice-site mutations, small deletions and insertions, of *ALPL*	Perinatal: ~95% [3, 4] Infantile: ~95% [3, 4] Childhood: <95% [4, 5] Adult: <95% [4, 5] Odonto: <95% [4, 5]	

1. Nucleotide numbering given according to Weiss et al (1988) and the Nomenclature Working Group [Antonarakis 1998]: the first nucleotide (+1) corresponds to the A of the ATG initiation codon.
2. Mild disease corresponds to childhood, adult, and odontohypophosphatasia.
3. In individuals with severe (perinatal and infantile) hypophosphatasia, two *ALPL* mutations are identified in approximately 95% of cases of European ancestry.
4. Japanese overall mutation detection rate is the same as European, but c.1559delT accounts for 40.9% of alleles, p.Phe310Leu 13.6% of alleles.
5. In more moderate forms in which one mutant allele is believed sufficient to cause disease, mutation detection rate is more difficult to estimate. Overall, ~50% have two *ALPL* mutations (compound heterozygote or homozygote); about 40%-45% only one identified mutation. The milder the disease, the higher the proportion in which only one *ALPL* mutation is detected in both European and Japanese populations.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a proband

- Clinical suspicion based on history, physical examination, and radiographs
- Routine laboratory testing to screen for hypophosphatasia: unfractionated serum alkaline phosphatase activity

  Note: Serial measurements may be necessary in the presence of conditions which result in elevated serum alkaline phosphatase activity, including acute fracture.
- Confirmation of the diagnosis of hypophosphatasia by one of the following:
  - Specialized evaluation of TNSALP substrates (serum PLP concentration and/or urine PEA concentration)
  - *ALPL* molecular genetic testing

Carrier testing for at-risk relatives in families in which the inheritance is autosomal recessive requires prior identification of the disease-causing mutations in an affected family member.

Note: Carriers are heterozygous for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation(s) in an affected family member.

Genetically Related (Allelic) Disorders

Polymorphisms in *ALPL* define haplotypes associated with bone mineral density variation in postmenopausal women, suggesting that osteopenia may represent the mildest clinical phenotype associated with variation in the *ALPL* gene [Goseki-Sone et al 2005].

Clinical Description

Natural History

The clinical features of hypophosphatasia represent a spectrum ranging from stillbirth without mineralized bone to pathologic fractures of the lower extremities in later adulthood [Whyte 1994].

The clinical classification reflects a continuous spectrum of severity, with pseudohypophosphatasia distinguished by infantile phenotype and normal alkaline phosphatase activity.

Perinatal (lethal) hypophosphatasia is typically identified by prenatal ultrasound examination. Pregnancies may end in stillbirth. Small thoracic cavity and short, bowed limbs are seen in both liveborn and stillborn infants. A flail chest may be present. Infants with perinatal hypophosphatasia may experience pulmonary insufficiency; it is the most frequent cause of death. Hypercalcemia is common and may be associated with apnea or seizures.

Perinatal (benign) hypophosphatasia is typically identified by prenatal ultrasound examination. Postnatally, skeletal manifestations slowly resolve with an eventual childhood or adult hypophospatasia phenotype. All reported cases have been born to mothers who have at least biochemical, if not clinical, evidence of hypophosphatasia [Pauli et al 1999].

Infantile hypophosphatasia cases may be normal at birth. Clinical signs may be recognized between birth and age six months. Clinical features resemble rickets. Clinical severity depends on the degree of pulmonary insufficiency and the complications of hypercalcemia, including irritability, poor feeding, failure to thrive, hypotonia, and more rarely vitamin B_6-dependent seizures (see Management.) Older children may have renal damage.

Pseudohypophosphatasia is characterized by clinical, biochemical, and radiographic findings reminiscent of infantile hypophosphatasia, with the exception that clinical laboratory assays of serum alkaline phosphatase activity are in the normal range.

Childhood hypophosphatasia displays wide variability in clinical presentation, ranging from low bone mineral density for age with unexplained fractures to rickets. Children may have premature loss of deciduous teeth (age <5 years), usually beginning with incisors. More severely affected toddlers have short stature and delay in walking and develop a waddling myopathic gait. Bone and joint pain are typical. Diaphyseal and metaphyseal fractures may occur.

The radiographic appearance of open fontanels and wide sutures is deceptive, because the hypomineralized bone causing this appearance is prone to premature fusion. Thus, craniosynsotosis and intracranial hypertension are potential complications.

Adult hypophosphatasia is sometimes associated with a history of transient rickets in childhood and/or premature loss of deciduous teeth. Early loss of adult dentition is common. Other dental problems in adolescents and adults with hypophosphatasia are more poorly characterized, although enamel hypoplasia and tooth mobility have been described. Adult hypophosphatasia is usually recognized in middle age, the cardinal features being stress fractures and pseudofractures of the lower extremities. Foot pain is common; slow-to-heal stress fractures of the metatarsals are common. Thigh and hip pain may reflect pseudofractures, or "Looser zones," in the lateral cortex of the femoral diaphysis (Figure 1C). Chondrocalcinosis and osteoarthropathy may develop with age. Osteomalacia distinguishes adult hypophosphatasia from odontohypophosphatasia.

Odontohypophosphatasia can be seen as an isolated finding without additional abnormalities of the skeletal system or can be variably seen in the above forms of hypophosphatasia. Premature exfoliation of primary teeth and/or severe dental caries may be seen, with the incisors most frequently lost.

Histologic evaluation. Bone histology reveals rachitic abnormalities of the growth plate. Histochemical testing of osteoclasts reveals lack of membrane-associated ALP activity. Osteoclasts and osteoblasts otherwise appear normal.

Tooth histology reveals a decrease in cementum, which varies with the severity of the disease.

Genotype-Phenotype Correlations

Most patients have a "private" genotype, making the prediction of the phenotype difficult. However, there is a good correlation between the severity of the phenotype and the residual enzymatic activity produced in vitro by the enzyme [Zurutuza et al 1999, Orimo et al 2001].

Genotype-phenotype correlations have been studied by the use of site-directed mutagenesis and 3D modeling of the enzyme [Fukushi et al 1998, Shibata et al 1998, Zurutuza et al 1999, Mornet et al 2001, Watanabe et al 2002, Nasu et al 2006, Brun-Heath 2007]. According to 3D modeling studies, more than 70% of the mutations affect functional domains of the protein, namely the active site, the calcium binding site, the crown domain, and the homodimer interface. Mutations with a dominant negative effect are preferentially located in functional domains, particularly the active site.

Nomenclature

Hypophosphatasia takes its name from low phosphatase activity, rather than reflecting serum concentration of phosphorus.

In classifications of genetic conditions, hypophosphatasia may be considered a metabolic bone disease, a skeletal dysplasia, a metaphyseal dysplasia, a dental disorder, or a disorder of membrane-bound ectoenzyme activity in the extracellular matrix.

Prevalence

Based on pediatric hospital records in Ontario, Canada, the birth prevalence of (autosomal recessive) perinatal and infantile hypophosphatasia was estimated to be 1:100,000 [Fraser 1957].

Applying the Hardy-Weinberg equation to this estimate, the frequency of heterozygotes for deleterious *ALPL* mutations in Ontario, Canada is about 1:150.

In the Canadian Mennonite population, the prevalence of the perinatal lethal form is 1:2500, for a carrier frequency of 1:25.

In Africa, no cases have been reported outside of North Africa; however, clinical ascertainment bias is likely significant. African American cases are rare; it is assumed that mutations in this population represent European admixture.

On the basis of the frequency of heterozygotes, and of the proportion of mutations exhibiting a dominant negative effect [Muller et al 2000, Lia-Baldini et al 2001], it is expected that mild forms of hypophosphatasia (childhood, adult, and odontohypophosphatasia) are more common than severe forms. However, because of incomplete penetrance in these forms, an estimate of the prevalence is difficult to establish.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of hypophosphatasia depends on the age at which the diagnosis is considered. Clinical features that help differentiate hypophosphatasia from other conditions include bone hypomineralization prenatally and immediately postnatally; elevated serum concentrations of calcium and phosphorus postnatally; and of course, persistently low serum alkaline phosphatase activity.

In utero. Early prenatal ultrasound examination may lead to a consideration of osteogenesis imperfecta (OI) type II, thanatophoric dysplasia, campomelic dysplasia, and achondrogenesis types 1A and 1B, as well as hypophosphatasia. Experienced sonographers usually have little difficulty in distinguishing among these disorders. Fetal x-rays are sometimes helpful in recognizing the undermineralization of bone that is more typical of perinatal hypophosphatasia than the other disorders considered in the differential diagnosis.

At birth. Outwardly difficult to distinguish, radiographs readily distinguish osteogenesis imperfecta (OI type II), thanatophoric dysplasia, campomelic dysplasia, and achondrogenesis types IA, IB, and II from hypophosphatasia. In cases in which the diagnosis is in doubt, serum alkaline phosphatase activity and specialized biochemical testing (serum concentration of PLP, urine concentration of PEA) can suggest the diagnosis pending confirmation with molecular genetic testing.

Infancy and childhood. Irritability, poor feeding, failure to thrive, hypotonia, and seizures place the **infantile type** in a broad differential diagnosis that includes inborn errors of energy metabolism, organic acidemia, primary and secondary rickets, neglect, and non-accidental trauma. Providing appropriate pediatric normative reference values are used, **infantile hypophosphatasia** is suspected with low serum alkaline phosphatase activity, making the argument for routine screening of alkaline phosphatase in cases of failure to thrive and suspected non-accidental skeletal injury.

- **Rickets** defines the physical and radiographic features of early hypophosphatasia. However, whether caused by nutritional and/or vitamin D deficiency, vitamin D resistance, or renal osteodystrophy, rickets is readily distinguished from hypophosphatasia by laboratory findings. In rickets, the following are characteristic: elevated serum alkaline phosphatase activity, low serum concentrations of calcium and phosphorus, low serum concentrations of vitamin D, and elevated serum concentration of parathyroid hormone.
- **Osteogenesis imperfecta (OI)** with deformation (typically type III in infancy or type IV later on) may resemble hypophosphatasia clinically.
- **Dentinogenesis imperfecta (DI),** whether part of OI or an isolated finding, is distinguishable from the dental presentation of hypophosphatasia.
- **Cleidocranial dysostosis** is characterized by late closure of fontanels and cranial sutures, aplastic clavicles, delayed mineralization at the pubic rami, and delayed eruption of deciduous and permanent teeth. The skeletal dysplasia is distinguishable from hypophosphatasia on clinical examination and skeletal survey. The dental dysplasia does not result in early tooth loss, and the enamel hypoplasia is readily distinguishable from **odontohypophosphatasia**.
- **Cole-Carpenter syndrome** (OMIM 112240) is characterized by bone deformities, multiple fractures, proptosis, shallow orbits, orbital craniosynostosis, frontal bossing, and hydrocephalus.
- **Hadju-Cheney syndrome** (OMIM 102500) is characterized by failure to thrive, dysmorphic facial features, early tooth loss, genitourinary anomalies, osteopenia, pathologic fractures, Wormian bones, failure of suture ossification, basilar impression, vertebral abnormalities, joint laxity, bowed fibulae, short distal digits, acroosteolysis, and hirsutism.
- **Idiopathic juvenile osteoporosis (IJO)** typically presents in preadolescents with fractures and osteoporosis. The fracture susceptibility and osteoporosis usually resolve spontaneously with puberty. The etiology remains unknown.

- **Renal osteodystrophy** may be confused with late presentation of the **childhood type** associated with renal damage; however, characteristic biochemical findings distinguish the two disorders.
- **Non-accidental trauma (child abuse).** Like osteogenesis imperfecta, patient history, family history, physical examination, routine laboratories, radiographic imaging, and the clinical course all contribute to distinguishing hypophosphatasia from child abuse. Multiple fractures are less typical of hypophosphatasia. The family history may be particularly instructive in that the perinatal lethal type is an autosomal recessive disorder, and the childhood, adult, and odontohypophosphatasia types are autosomal dominant disorders; all have been reported in a single family ascertained by unexplained fracture in a child [Lia-Baldini et al 2001]. Serial measurement of serum alkaline phosphatase activity is usually sufficient to identify hypophosphatasia in this circumstance.

Adult and odontohypophosphatasia

- **Osteoarthritis** and pseudogout (secondary to calcium pyrophosphate dehydrate deposition) are presentations of adult hypophosphatasia, distinguished from the more common disorders by clinical history and laboratory findings.
- **Osteopenia/osteoporosis** needs to be distinguished from adult hypophosphatasia, in that bisphosphonates may be contraindicated (see Management, Agents/ Circumstances to Avoid).
- **Periodontal disease** may be difficult to distinguish from hypophosphatasia, in that alveolar bone loss can be seen with severe gingivitis. However, gingival inflammation is unusual with odontohypophosphatasia. Familial periodontal disease can be inherited in an autosomal dominant manner (OMIM 311750), as part of a connective tissue disorder such as Ehlers-Danlos syndrome, vascular type or Ehlers-Danlos syndrome, periodontal type, or associated with neutropenia, such as *ELA2*-related neutropenia.

  Rarer autosomal recessive disorders associated with premature tooth loss and periodontal disease include Papillon-Lefevre syndrome and Haim-Munk syndrome (HMS), caused by mutations in *CTSC*, the gene encoding cathespin C. The periodontal disease is usually of earlier onset and more severe than that seen with odontohypophosphatasia. Both Papillon-Lefevre syndrome and HMS are usually associated with palmar keratosis, further distinguishing them from odontohypophosphatasia. Measurement of serum alkaline phosphatase activity is reasonable when either disorder is considered.
- **Dentinogenesis imperfecta (DI).** Whether associated with osteogenesis imperfecta or as an isolated condition resulting from *DSPP* gene mutation [Rajpar et al 2002], DI is readily distinguishable from odontohypophosphatasia on biochemical findings.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hypophosphatasia, the following evaluations are recommended:

- Blood urea nitrogen and serum creatinine concentration to assess renal function
- Serum concentration of calcium, phosphorus, magnesium
- Serum concentration of 25(OH) and 1,25(OH)2 vitamin D, nPTH to assess rickets

- Assessment of pulmonary function in infants with the perinatal type to assist in prognosis and distinguishing between the perinatal lethal type and the perinatal benign type
- X-rays of the skull to assess for craniosynostosis in young children with the infantile form of hypophosphatasia

Treatment of Manifestations

Management at all ages focuses on supportive therapy to minimize disease-related complications.

Perinatal types. In the perinatal period, if multidisciplinary assessment identifies the perinatal lethal type, expectant management and family support are appropriate. Molecular genetic testing should be used to confirm the diagnosis, establish recurrence risk for family members, and provide for potential prenatal diagnosis.

Infantile type. Infantile cases have high mortality, with 50% succumbing to respiratory failure caused by undermineralization of the ribs.

Management can further be complicated by recalcitrant hypercalcemia/hypercalciuria.

When present, seizures may respond to treatment with vitamin B_6 (pyridoxine). Pyridoxal phosphate (PLP), one of the natural substrates of alkaline phosphatase, is the active compound by which pyridoxine mediates essential enzyme activity; PLP deficiency in the central nervous system may reduce seizure threshold by reducing neurotransmitter (GABA) synthesis.

Craniosynostosis in infantile cases is variable. When identified, involvement of a neurosurgeon to monitor for complications is prudent. Increased intracranial pressure secondary to craniosynostosis is an indication for surgical release.

Dental care, beginning at age one year (the new universal recommendation for all children, regardless of whether they have an underlying medical condition), is important to preserve primary dentition (to support nutrition) and to preserve or replace secondary dentition.

Osteoarthritis may respond to NSAIDs.

Bone pain and osteomalacia are managed supportively: NSAIDs appear beneficial [Girschick et al 2006]. Hypophosphatasia is a relative contraindication to treatment with bisphosphonates (see Management, Agents/Circumstances to Avoid).

Pseudofractures and stress fractures are difficult to manage; internal fixation has been suggested as the optimal orthopedic management. Foot orthotics may help in management of tarsal fractures and pseudofractures in adults.

Surveillance

Children with hypophosphatasia should be seen by a pediatric dentist twice yearly, beginning at age one year.

Children with the infantile type of hypophosphatasia are at elevated risk for increased intracranial pressure secondary to craniosynostosis, and should be monitored for this complication.

Agents/Circumstances to Avoid

Biphosphonates are relatively contraindicated in hypophosphatasia. Although adverse outcomes have not been identified in children with the severe infantile type [Deeb et al 2000] or in adults with hypophosphatasia and osteomalacia treated with bisphosphonates, theoretical concern has been raised based on the structure of bisphosphonates. The phosphate motifs in bisphosphonates have a similar conformation to inorganic pyrophosphate (PPi), the natural substrate of TNSALP; thus, treatment with bisphosphonates is thought to be analogous to "adding fuel to the fire."

Excess vitamin D can exacerbate hypercalcemia/hypercalciuria in children with infantile hypophosphatasia who have hypercalcemia.

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Autosomal recessive hypophosphatasia is an extremely rare and severe condition; thus, clinical therapies are compassionate and anecdotal. Bone marrow transplantation (i.e., hematopoetic stem cell transplantation) was used to treat an eight-month-old girl with severe hypophosphatasia with prolonged, significant clinical and radiologic improvement [Whyte et al 2003]. Seven years after transplantation, the patient was reported to be active and growing, and to have the clinical phenotype of the more mild childhood form of hypophosphatasia [Cahill et al 2007].

Restoration of a normal bone phenotype is seen in *tnsalp* knockout mice in which a *tnsalp* antagonist gene, *pc-1*, is inactivated. *PC-1* suppression, therefore, may be a potential pharmacologic option in treating human hypophosphatasia [Hessle et al 2002].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Treatment with calcitonin, chlorthiazide, and bisphosphonates has shown little or no efficacy [Deeb et al 2000].

Treatment with cortisone, vitamin B_6, zinc, magnesium, and parathyroid hormone makes no significant clinical difference.

Calcium supplementation or treatment with vitamin D do not offer any benefit as these parameters are usually normal.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Perinatal and infantile hypophosphatasia are inherited in an autosomal recessive manner. The milder forms, especially adult and odontohypophosphatasia, may be inherited in an autosomal recessive or autosomal dominant manner depending on the effect the *ALPL* mutation has on TNSALP activity.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore typically carry one mutant allele.
- Taillandier et al (2005) reported one case of a *de novo* mutation in the second *ALPL* allele in an individual with autosomal recessive hypophosphatasia; thus, parents of an affected individual are not always carriers.
- Heterozygotes (carriers) either are asymptomatic, manifesting biochemical but not clinical abnormality, or may manifest milder symptoms depending on the mutation.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an "asymptomatic" carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic manifesting biochemical but not clinical abnormality, or may manifest milder symptoms depending on the mutation. Determining the mode of inheritance in such families is difficult as mildly affected parents may lead one to consider autosomal dominant inheritance.

Offspring of a proband. The offspring of an individual with hypophosphatasia are obligate heterozygotes (carriers) for a disease-causing mutation in the *ALPL* gene.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Most individuals diagnosed with the autosomal dominant form of hypophosphatasia have inherited the mutation from a parent who may or may not have symptoms. A proband with the autosomal dominant form of hypophosphatasia could have the disorder as the result of a new gene mutation. However, *de novo* mutation in the autosomal dominant form of hypophosphatasia has never been reported, indicating that the proportion of cases caused by *de novo* mutations is very low.
- If the disease-causing mutation found in the proband cannot be detected in DNA extracted from the leukocytes of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include careful review of clinical history and laboratory evaluations for signs of hypophosphatasia. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure by health care professionals to recognize the syndrome and/or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Note: Although most individuals diagnosed with the autosomal dominant form of hypophosphatasia have inherited the mutation from a parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

Offspring of a proband. Each child of an individual with the autosomal dominant form of hypophosphatasia has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

Determining the mode of inheritance can be difficult in some families as dominance is sometimes difficult to demonstrate by using familial analysis. Expression of the disease may be highly variable, with parents of even markedly affected children showing no or extremely mild symptoms of the disease.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Pregnancy with high a priori risk (pregnancy known to be at increased risk based on family history)

- **Molecular genetic testing.** Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele(s) of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

  Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

- **Fetal ultrasonography.** Recurrence of perinatal and infantile hypophosphatasia may reliably be identified by prenatal ultrasound examination. Undermineralization, small thoracic cavity, shortened long bones, and bowing are typical features of autosomal recessive and severe hypophosphatasia. Long bone bowing has been reported prenatally in affected sibs and in children of individuals with childhood or adult hypophosphatasia, but the finding is not diagnostic of hypophosphatasia.

- **Biochemical testing.** Concentration of alkaline phosphatase in amniotic fluid, amniocytes, and chorionic villous samples is prone to misinterpretation (particularly in distinguishing unaffected heterozygotes), such that molecular genetic testing is the preferred method in confirming prenatal diagnosis [Mornet et al 1999].

Pregnancy with low a priori risk (pregnancy not known to be at risk)

- **Fetal ultrasonography.** Although perinatal and infantile hypophosphatasia may be distinguished from other skeletal dysplasias by prenatal ultrasonography, care must be taken in the interpretation of bowed long bones. Undermineralization, small thoracic cavity, shortened long bones, and bowing are typical features of autosomal recessive and severe hypophosphatasia. However, prognosis is difficult to predict based on ultrasound findings alone. Bowed and shortened long bones have been observed on prenatal ultrasound in individuals who ultimately were shown to have benign perinatal, childhood, and adult hypophosphatasia. The bowing resolves postnatally. In such cases when *ALPL* molecular testing has been performed, a single mutation in the *ALPL* gene has been identified.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Hypophosphatasia

Gene Symbol	Chromosomal Locus	Protein Name
ALPL	1p36.1-p34	Alkaline phosphatase, tissue-nonspecific isozyme

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Hypophosphatasia

146300	HYPOPHOSPHATASIA, ADULT TYPE
171760	ALKALINE PHOSPHATASE, LIVER; ALPL
241500	HYPOPHOSPHATASIA, INFANTILE
241510	HYPOPHOSPHATASIA, CHILDHOOD

Table C. Genomic Databases for Hypophosphatasia

Gene Symbol	Locus Specific	Entrez Gene	HGMD
ALPL	ALPL	249 (MIM No. 171760)	ALPL

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The gene consists of 12 exons. Three normal allelic variants are c.455G>A (p.Arg135His), c.787T>C (p.Tyr246His), and c.876A>G (p.Val505Ala). A number of exonic and intronic sequence variations have been reported as polymorphisms in the TNSALP gene mutation database.

Pathologic allelic variants: To date, more than 191 distinct mutations have been described in *ALPL* in persons from North America, Japan, and Europe. A continually updated list of mutations is available online; see www.sesep.uvsq.fr/Database.html. (See also Genomic Databases table.)

The mutations are distributed throughout the 12 exons of the gene. Missense mutations account for 78.7% of mutations with the remainder microdeletions/insertions (11.7%), splicing mutations (4.8%), nonsense mutations (2.7%), gross deletions (1.1%), and a nucleotide substitution affecting the major transcription initiation site. This variety of mutations results in highly variable clinical expression and in a great number of compound heterozygous genotypes.

Normal gene product: The *ALPL* gene encodes alkaline phosphatase, tissue-nonspecific isozyme (TNSALP), the isozyme present in liver, kidney, and bone. The enzyme acts as a (lipid) membrane-bound ectophosphatase with PLP and PEA as natural substrates.

Abnormal gene product: The catalytic activity of mutated proteins is affected and/or the mutated protein is sequestered in cell compartments and consequently unable to reach the cell membrane, its final destination for physiologic activity [Cai et al 1998, Fukushi et al 1998, Shibata et al 1998, Watanabe et al 2002, Brun-Heath et al 2007].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current

as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Hypophosphatasie Europe
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www.hypophosphatasie.com

The MAGIC Foundation
6645 West North Avenue
Oak Park IL 60302
Phone: 800-362-4423; 708-383-0808
Fax: 708-383-0899
Email: info@magicfoundation.org
Hypophosphatasia

International Skeletal Dysplasia Registry
Medical Genetics Institute
8635 West Third St. Suite 665
Los Angeles CA 90048
Phone: 800-CEDARS-1 (800-233-2771)
Fax: 310-423-0462
www.csmc.edu

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Author Notes

Web: www.sesep.uvsq.fr/Database.html

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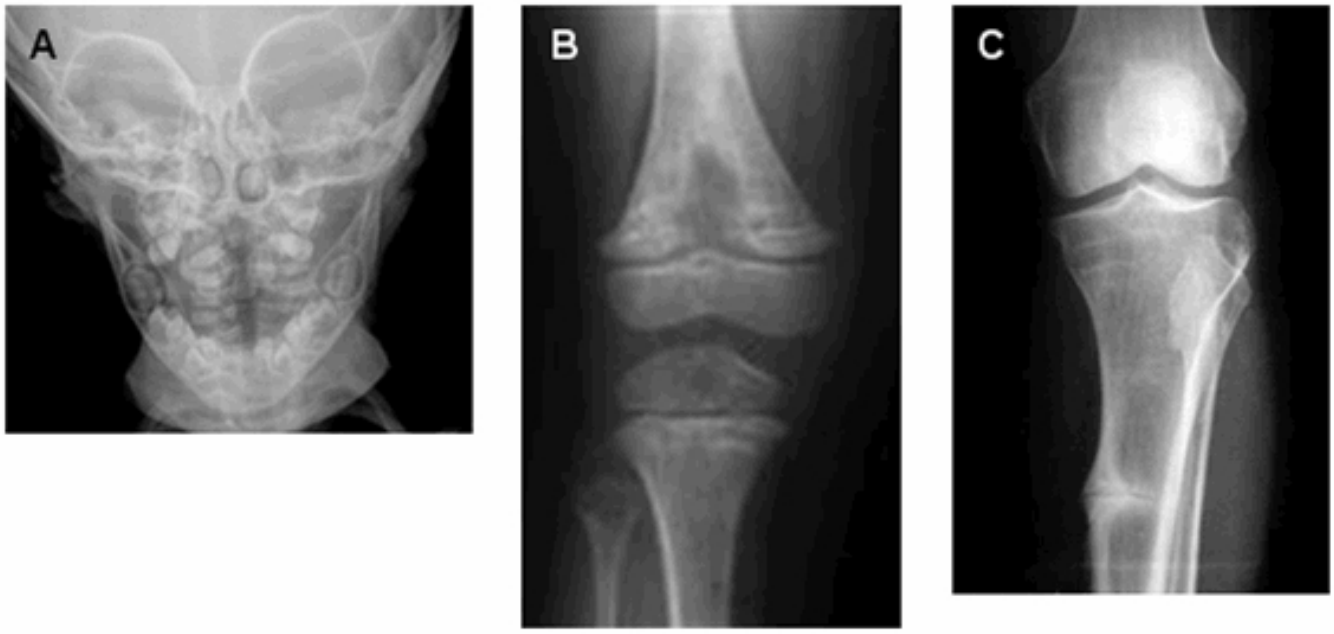

Figure 1. Radiographic signs of hypophosphatasia
A. Alveolar bone loss surrounding molars, childhood hypophosphatasia
B. Hypolucent "tongue," mid-metaphysis, childhood hypophosphatasia
C. Looser zone (pseudofracture), adult hypophosphatasia