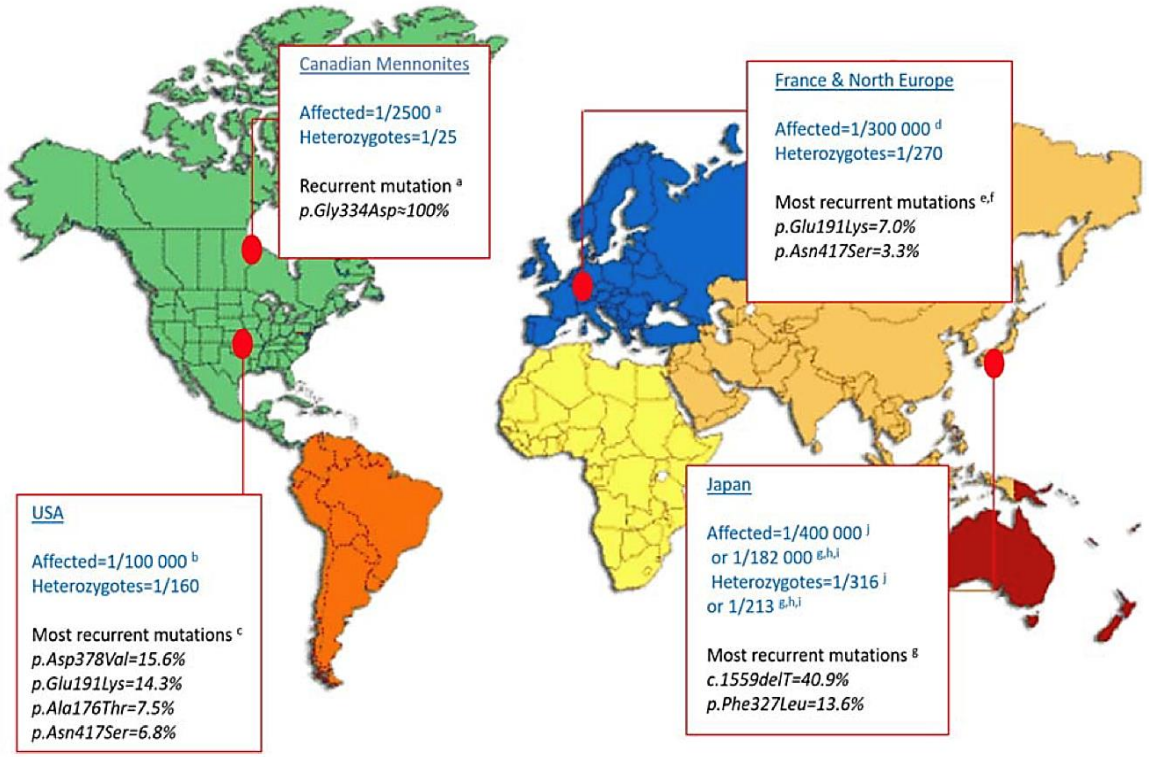
Hypophosphatasia (HPP)

Hypophosphatasia (HPP)

- Rare and heterogeneous inherited disorder of bone and mineral metabolism
- Caused by loss-of-function mutations in *ALPL* gene, encoding TNSALP → generalized reduction of ALP activity
- AD or AR inheritance
- >381 *ALPL* mutations identified
- Highly variable clinical expression
  - Several forms of the disease ranging from lethal to mild
  - Depending on type of mutation and inheritance mechanism
  - Genotype/phenotype correlation is not very consistent → different phenotypic presentations within the same family

Osteoporos Int 2020;31(8):1445-1460.

Epidemiology



Distributed worldwide with very variable prevalence

Severe form

- Global prevalence ≤1/100,000 except Canadian Mennonites

Milder forms

- Difficult to estimate (variety of clinical presentation and frequent undiagnosed)
- According to genetic model, prevalence of dominant “mild” HPP in the European population is about 1/6370

Metabolism 2018;82:142-155, Osteoporos Int 2020;31(8):1445-1460

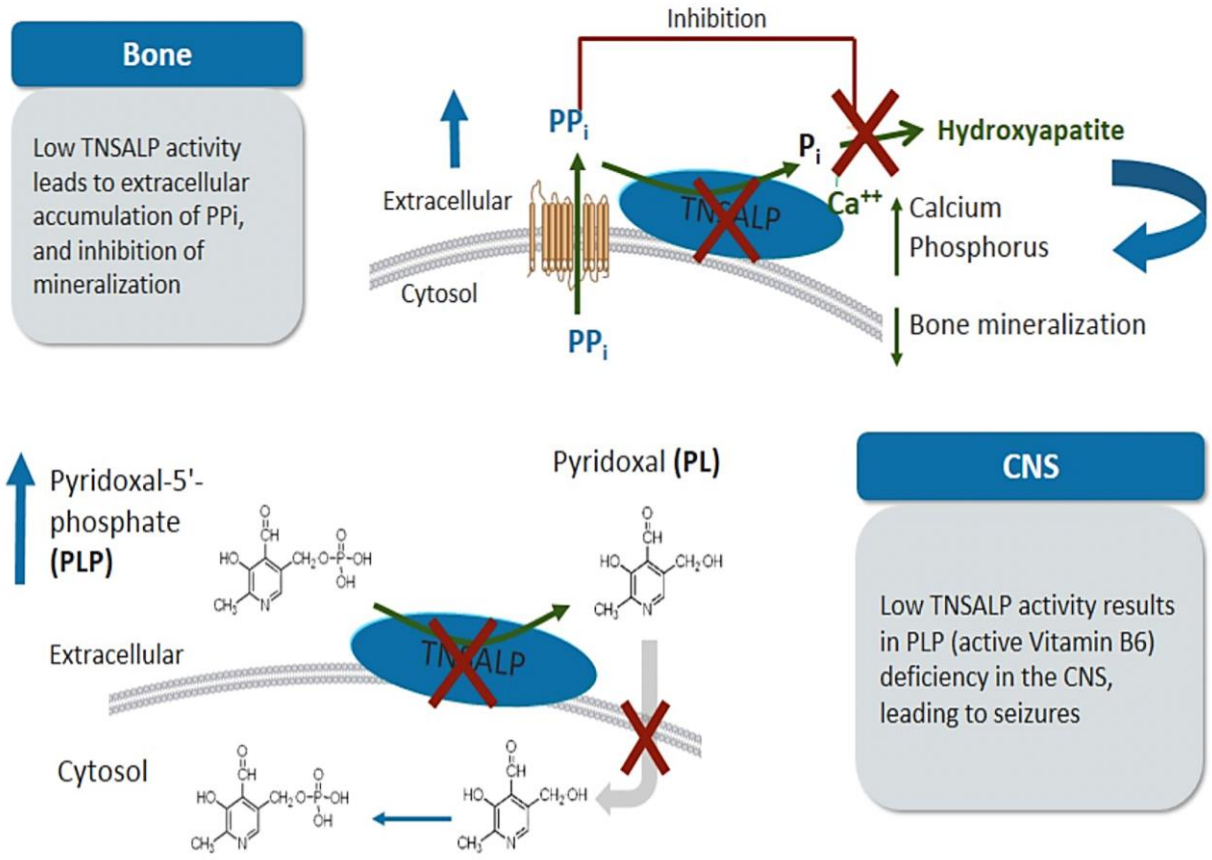
Alkaline phosphatase (ALP)

- ALP is a membrane-bound phosphomonoesterase that catalyzes dephosphorylation reactions of inorganic pyrophosphate (PPi) and other molecules
- It is expressed in all tissues
- 4 isoenzymes

ALP isoenzyme	Gene	Chromosome location
Tissue-nonspecific alkaline phosphatase (TNSALP or TNAP)	*ALPL*	1p36.1-p34
Intestinal alkaline phosphatase (IALP)	*ALPI*	2q34-37
Placental alkaline phosphatase (PLALP)	*ALPP*	2q34-37
Germ cell alkaline phosphatase (GCALP)	*ALPG (ALPPL2)*	2q34-37

Osteoporos Int 2020;31(8):1445-1460

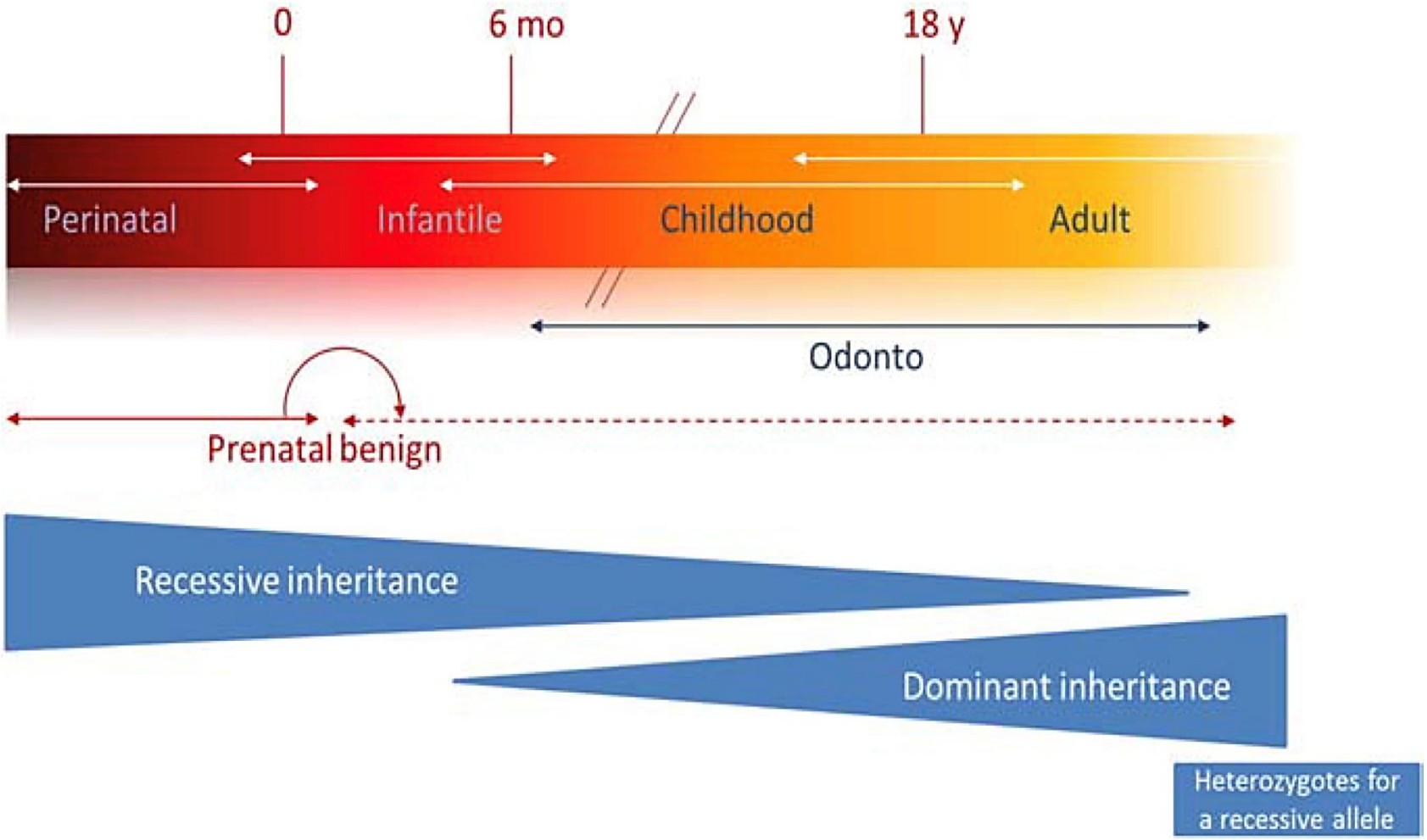
TNSALP



- **Accounts for approximately 95% of total serum ALP activity**
- **Abundant in bone, liver, and kidney, but also expressed in growth plates, cartilage, teeth, and brain**
- **PPi and PLP are main physiological substrates**
- **PLP is an essential cofactor in several biochemical processes including synthesis of major neurotransmitters**

J Nippon Med Sch 2010;77(1):4-12, Osteoporos Int 2020;31(8):1445-1460

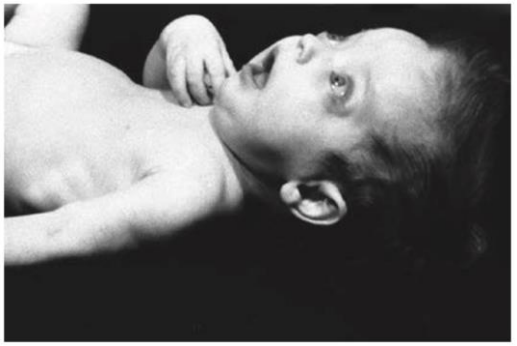
Classification



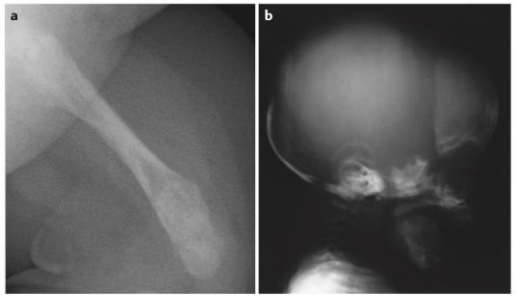
Metabolism 2018;82:142-155

Clinical presentation

Form	Inheritance	Clinical course	Features
Perinatal lethal	AR	- Most severe form - Stillbirth or death within days/weeks after birth	- Severe hypomineralization - Derangements in Ca, P metabolism - Osteochondral spurs in forearms, legs - Severe lung hypoplasia (chest deformities, rib fractures) - Seizures
Prenatal (or perinatal benign)	AR/AD	- Benign evolution (but long-term course unknown)	- Limb shortening and bowing of long bones observed in utero - Spontaneous improvement of skeletal defects after birth
Infantile	AR	- Present before 6 months of age - Poor prognosis during the first year	- Severe hypomineralization (rachitic ribs) - Premature craniosynostosis, swallowing disorders, irritability, seizures - Severe muscular hypotonia - Hypercalcemia, hypercalciuria, nephrocalcinosis



Infantile HPP with prominent anterior fontanel, proptotic eyes, scaphoid chest and rachitic changes

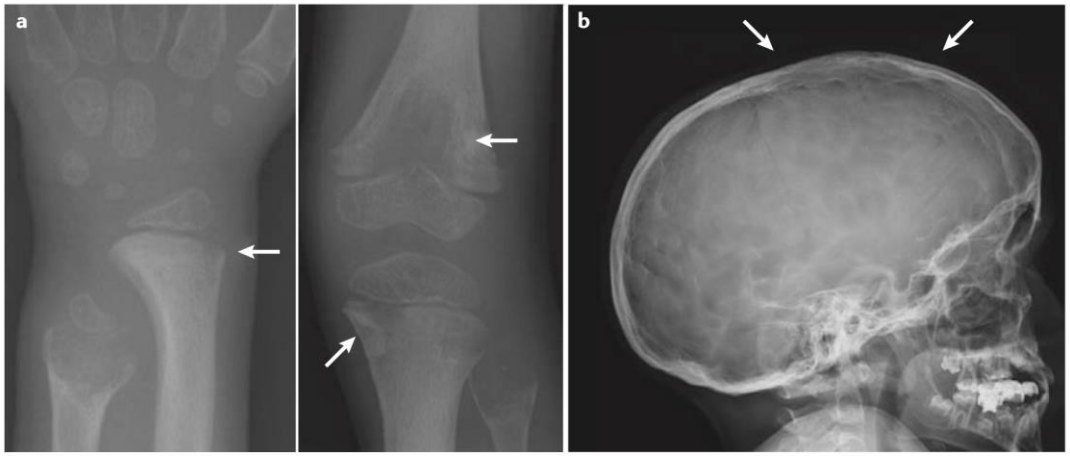


Hypomineralized and distorted proximal and distal metadiaphyses, skull hypo mineralization

Osteoporos Int 2015;26(12):2743-57, Nat Rev Endocrinol 2016;12(4):233-46

Clinical presentation

Form	Inheritance	Clinical course	Features
Childhood HPP	AR/AD	- Present after 6 months to 18 years of age	- Rickets-like signs of hypomineralization - Short stature, failure to thrive - Delayed walking, repeated fractures, waddling gait due to bone deformities - Chronic bone pain (lower extremities) - Premature loss of deciduous teeth (before age 5), dental caries



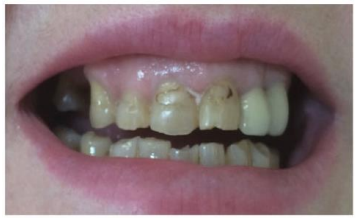
- **'Tongue' of radiolucency (arrows)**
- **Hypomineralization of metaphyses of distal ulna and proximal fibula**

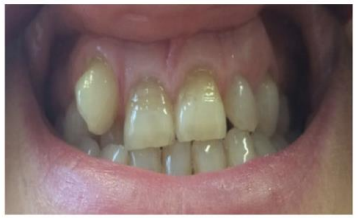
- **Elongated (dolichocephalic) skull with 'beaten-copper' appearance**

Osteoporos Int 2015;26(12):2743-57, Nat Rev Endocrinol 2016;12(4):233-46

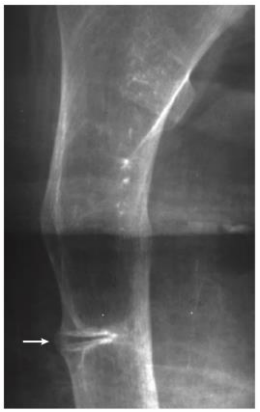
Clinical presentation

Form	Inheritance	Clinical course	Features
Adult HPP	AR/AD	- >18 years - Typically present during middle age	- Stress fractures of metatarsals, pseudofractures - Fragility fractures, osteomalacia, osteoporosis - Loss of permanent teeth at 40–60 years of age - Chondrocalcinosis, calcific periarthritis - History of delayed fracture healing, rickets, early deciduous teeth loss in childhood - Renal abnormalities, reduced GFR, nephrocalcinosis, kidney stones - Psychiatric symptoms (insomnia, restlessness, anxiety, depression)
OdontoHPP	AR/AD	- Any age	- Not associated with bone, articular, or muscular problems - Premature loss of deciduous and/or permanent teeth - Severe dental caries





Adult HPP patients
Lt image: dental abnormalities with loss of secondary teeth
Rt image: enamel thinning



Adult HPP with pseudofracture at Rt subtrochanteric femur

Osteoporos Int 2015;26(12):2743-57, Nat Rev Endocrinol 2016;12(4):233-46

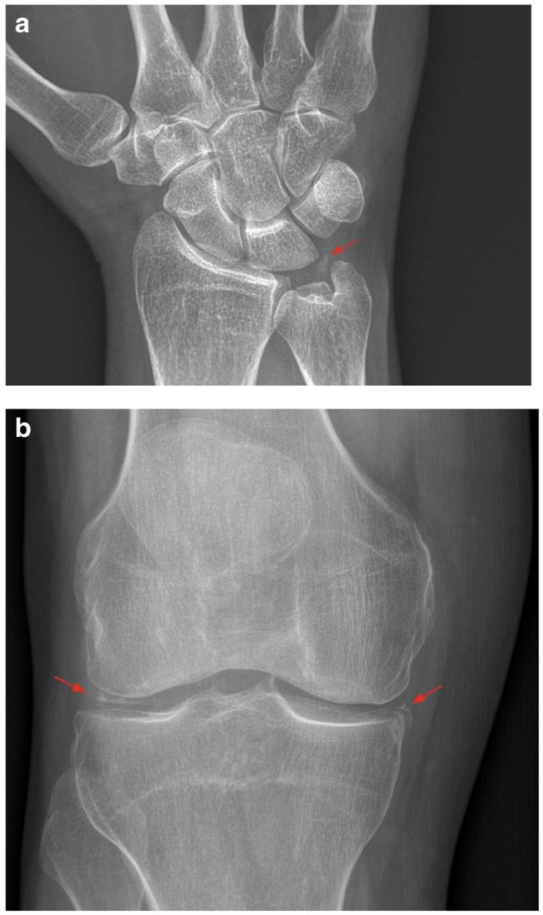
Hypophosphatasia in adults

- **Clinical spectrum of the disease is extraordinarily wide**
- **Fractures**
  - Non traumatic and recurrent fractures as a consequence of defective bone mineralization
  - Typical clinical manifestation: foot pain (stress fractures of metatarsals, 21-23%) with delay healing and nonunion
  - Thigh pain related to AFF
    - Initiate in lateral cortex of subtrochanteric diaphysis
    - Mean age 45.9 years (30-62) at first AFF
    - Risk factors: abnormal bone geometry, hypovitaminosis D (80% of case), BPs (46.7%)
  - Fracture risk evaluation in HPP cannot be based on BMD and T-scores

Osteoporos Int 2020;31(8):1445-1460

Hypophosphatasia in adults

- **Joint and periarticular diseases**
  - Extracellular PPi has a key role in crystal deposition
  - Chondrocalcinosis
    - CPPD can be sign that reveals HPP
    - CPPD is responsible for acute arthritis and osteoarthritis may occur earlier than expected
    - Risk of CPPD was higher in both females and males (4.5 and 3.8 fold) as compared with controls
    - Mainly localized at knees, pubic symphysis, hips, and wrists



Osteoporos Int 2020;31(8):1445-1460

Hypophosphatasia in adults

- **Joint and periarticular diseases**
  - Painful periarticular calcifications, most often in shoulders, elbows, wrists, hips, or Achilles tendons
  - Enthesopathies (risk 2.7-fold in females and 3.1-fold in males vs controls)
  - Diffuse idiopathic skeletal hyperostosis (risk 19.3-fold in females and 8.4-fold in males) as compared with controls
  - Enthesopathies, producing a spur on a tendon (e.g., Achilles), iliac crest, and/or ossification of vertebral ligaments, can be associated with pain, not relieved by rest

Osteoporos Int 2020;31(8):1445-1460

Hypophosphatasia in adults

- Early tooth loss, enamel thinning, abnormal tooth shape and color, and severe caries
- Nephrocalcinosis and nephrolithiasis
- Asymptomatic hypercalcemia (13%) and hyperphosphatemia (18-50%)
- Chronic muscle pain and weakness associated with reduced mobility and physical activity

Osteoporos Int 2020;31(8):1445-1460

Dahir *et al. Orphanet Journal of Rare Diseases* (2022) 17:277
https://doi.org/10.1186/s13023-022-02393-8

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Clinical profiles of treated and untreated adults with hypophosphatasia in the Global HPP Registry

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Table 1 Baseline demographics and clinical characteristics of HPP in adults (aged ≥ 18 years)

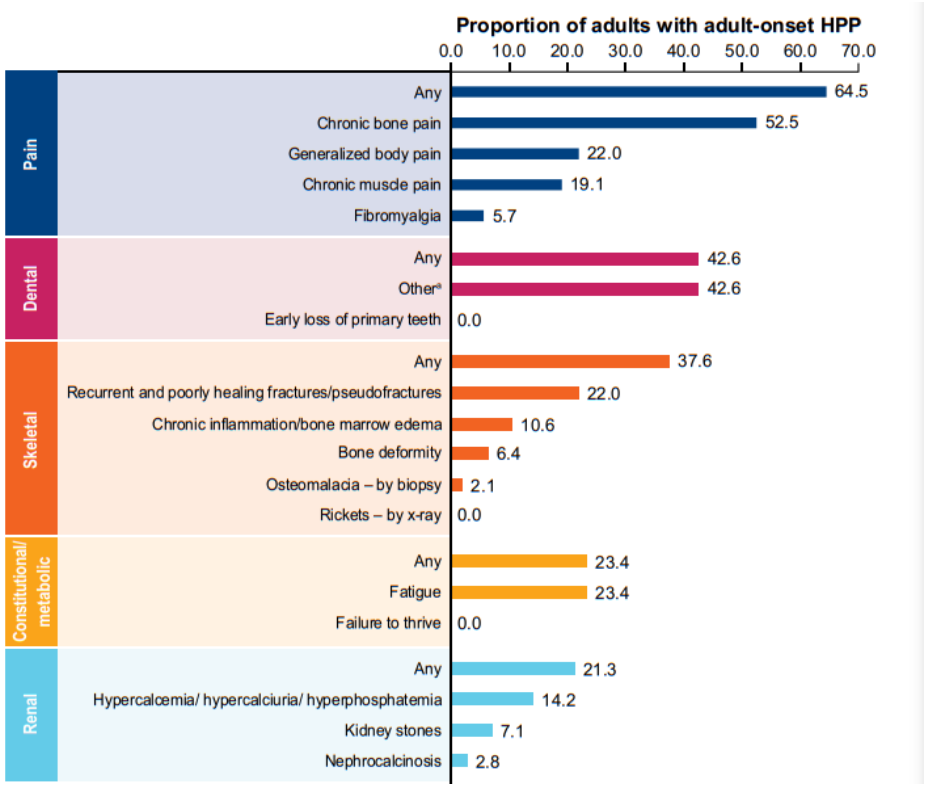
Characteristic	Adults (overall)[a] N = 398	Pediatric-onset HPP n = 213	Adult-onset HPP n = 141
Sex, n (%)			
Male	109 (27.4)	68 (31.9%)	34 (24.1)
Female	289 (72.6)	145 (68.1%)	107 (75.9)
Age at baseline, years			
Mean (SD)	47.5 (14.9)	44.8 (15.1)	51.4 (13.9)
Median (minimum, maximum)	48.1 (18.3, 81.2)	43.8 (18.3, 77.9)	51.9 (19.5, 79.8)
Age at first HPP manifestation, years			
n	275	161	114
Mean (SD)	22.1 (20.9)	8.6 (11.5)	41.2 (15.6)
Median (minimum, maximum)	14.4 (0.0, 75.3)	5.0 (0.0, 72.0)	39.0 (18.0, 75.3)
Age at HPP diagnosis, years			
n	349	184	131
Mean (SD)	41.3 (19.3)	35.2 (21.0)	48.9 (13.9)
Median (minimum, maximum)	42.3 (0.0, 78.9)	36.0 (0.0, 77.0)	49.0 (18.7, 76.6)
Received ERT, n (%)	119 (29.9%)	114 (53.5%)	2 (1.4%)
Baseline ALP, (U/L)[b]			
n	344	176	128
Mean (SD)	26.4 (13.8)	25.1 (15.0)	27.5 (12.8)
Median (minimum, maximum)	24.0 (2.0, 98.0)	22.5 (2.0, 98.0)	25.0 (7.0, 98.0)

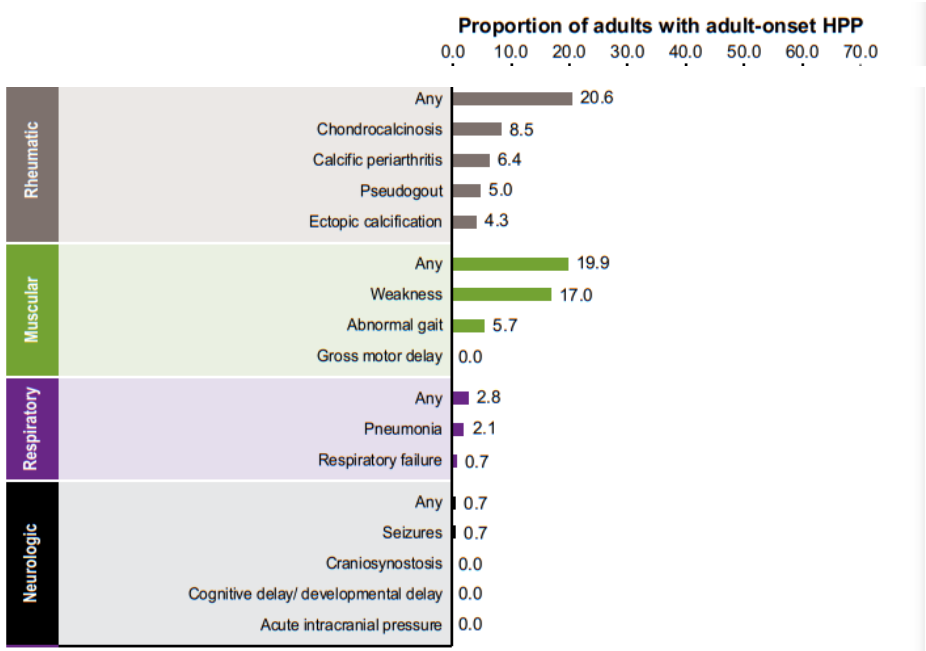
ALP Alkaline phosphatase, *ERT* enzyme replacement therapy, *HPP* hypophosphatasia, *SD* standard deviation

[a] Includes 44 patients with missing or unknown age of onset

[b] Measures may have been obtained during adulthood (age ≥ 18 years) or childhood (age < 18 years)

Clinical manifestation of adult-onset HPP (n=141)





Dental: Includes loss of permanent teeth, loose teeth, poor dentition, hypodontia, dental implants, dental bridges, and dentures. HPP, hypophosphatasia

Hypophosphatasia: Diagnosis

- Persistently low serum ALP for age and sex, elevation of substrates (PLP, PEA, PPi) with suggestive clinical signs and symptoms

- Exclude other causes of low ALP

- Some conditions (such as severe cholestatic diseases or recent fractures) can increase serum ALP levels, hiding the diagnosis of HPP

Osteoporos Int 2020;31(8):1445-1460

Hypophosphatasia: Diagnosis

- Genetic test (ALPL gene), in case of doubt or to confirm diagnosis
- X-rays, CT, MRI, bone scintigraphy to detect metatarsal stress fractures/atypical femur fractures
- X-rays or musculoskeletal ultrasound of wrist and knee to reveal CPPD (chondrocalcinosis)
- Kidney ultrasound to reveal nephrocalcinosis or kidney stones

Osteoporos Int 2020;31(8):1445-1460

Elevation of TNAP substrates

Serum PLP (pyridoxal 5’-phosphate)

- Active metabolite and major circulating form of vitamin B6
- Most sensitive and specific biochemical marker
- Usually reflect the severity of the disease
- Withhold vitamin B6-containing supplements 1 week prior to prevent false positive result

PEA (phosphoethanolamine) in blood or urine

- Less reliable marker than PLP
- Can be unremarkable in mild HPP
- Elevated in other metabolic bone diseases
- Level varies with age, diet, and circadian rhythm

Urinary PPi (inorganic pyrophosphate)

- Sensitive marker
- Currently perform in research laboratories only

Bone 2017;102:15-25, Osteoporos Int 2020;31(8):1445-1460

Bone turnover markers

- BTMs have been scarcely analyzed in HPP
  - Series of 42 individuals with persistently low ALP, 50% with a TNSALP pathogenic variant
  - Both serum PINP and CTX were lower in patients with hypophosphatasemia than in controls
  - No significant differences in the BTM levels between patients with and without *ALPL* mutation

Table 1 Main characteristics and bone turnover markers in cases and controls (mean ± SD)

	Low ALP cases ($n = 42$)	Controls ($n = 45$)	p value
Age (year)	48 ± 14	47 ± 18	ns
Sex	10 M, 32 F	10 M, 35 F	ns
Height (cm)	163 ± 9	163 ± 9	ns
Weight (kg)	70 ± 17	66 ± 14	ns
P1NP (ng/ml)	31.4 ± 13.7	48.9 ± 24.4	0.0002
Crosslaps (ng/ml)	0.21 ± 0.17	0.34 ± 0.22	0.0015

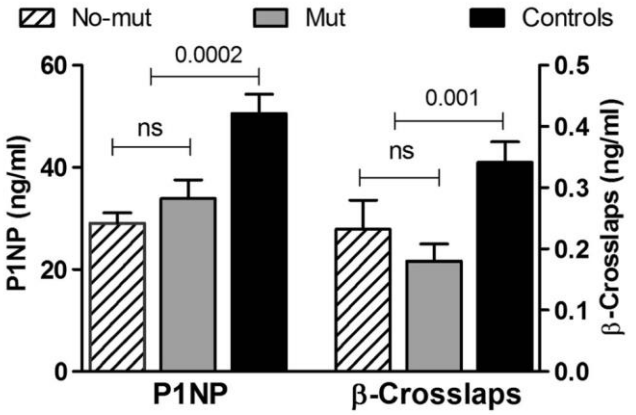


Fig. 1 Bone turnover markers in individuals with low ALP levels, without (dashed bars) or with mutations (gray solid bars) of the ALPL gene, in comparison with those in controls (black solid bars)

Osteoporos Int 2018;29:2147-50, Osteoporos Int 2020;31(8):1445-1460.

Treatment of HPP in adults

- Mainly supportive care: chronic pain, fracture, acute arthritis, osteoarthrosis, etc.
- Chronic pain must be assessed and treated carefully; NSAIDs are effective in acute arthritis.
- According to the severity of the disease, low-impact physical exercises are recommended.
- Any activity with a significant risk of trauma must be avoided.
- Attention must be paid to dental problems, including prosthetic rehabilitation.

Curr Opin Rheumatol 2016, 28:448–451, Osteoporos Int 2020;31(8):1445-1460

Treatment of HPP in adults

- Calcium and vitamin D deficiency must be prevented to avoid any secondary hyperparathyroidism
    - Avoid over supplement: may result in hypercalcemia, hypercalciuria, and formation of kidney stones

- No established treatment for bone fragility related to HPP in adults.
    - **Antiresorptive drugs are contraindicated** as they can worsen the underlying osteomalacia
    - Anabolic agents: PTH(1-34) or PTH(1-84) <case reports>: inconsistent results, suggest that the response to the treatment may depend on the specific gene mutation?

Curr Opin Rheumatol 2016, 28:448–451, Osteoporos Int 2020;31(8):1445-1460

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STRENSIQ safely and effectively. See full prescribing information for STRENSIQ.

STRENSIQ® (asfotase alfa) injection, for subcutaneous use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Dosing and Administration (2.3, 2.4)	6/2020
Warnings and Precautions (5.4)	6/2020

INDICATIONS AND USAGE

STRENSIQ is a tissue nonspecific alkaline phosphatase indicated for the treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP). (1)

DOSAGE AND ADMINISTRATION

Perinatal/Infantile-Onset HPP (2.1)

- Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. Injection site reactions may limit the tolerability of the six times per week regimen.
- The dose may be increased to 3 mg/kg three times per week for insufficient efficacy.

Juvenile-Onset HPP (2.2)

- Recommended dosage regimen is 2 mg/kg administered subcutaneously three times per week, or 1 mg/kg administered six times per week. Injection site reactions may limit the tolerability of the six times per week regimen.

Preparation and Weight-Based Dosing (2.3):

- *Caution:* Do not use the 80 mg/0.8 mL vial in pediatric patients weighing less than 40 kg because the systemic asfotase alfa exposure achieved with the 80 mg/0.8 mL vial (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients.
- See full prescribing information for tables of weight-based dosing by treatment regimen.

Administration (2.4):

- For subcutaneous injection only.
- Rotate injection sites. Do not administer to areas that are reddened, inflamed or swollen.

DOSAGE FORMS AND STRENGTHS

Injection: 18 mg/0.45 mL, 28 mg/0.7 mL, 40 mg/mL, or 80 mg/0.8 mL solution in single-dose vials. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor and if a severe reaction occurs, discontinue treatment and initiate appropriate medical treatment. (5.1)
- Lipodystrophy: Localized reactions were reported after several months of treatment; follow proper injection technique and rotate injection sites. (5.2)
- Ectopic Calcifications (eye and kidneys): Monitor using ophthalmologic examinations and renal ultrasounds at baseline and periodically during treatment. (5.3)
- Possible Immune-Mediated Clinical Effects: Evaluate patients for antibody formation if clinically indicated. (5.4)

ADVERSE REACTIONS

Most common adverse reactions (≥ 10%) are injection site reactions, lipodystrophy, ectopic calcifications and hypersensitivity reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drug Interference with Laboratory Tests: Alkaline Phosphatase (ALP) is used as a detection reagent in many laboratory tests and the presence of asfotase alfa in clinical laboratory samples could result in erroneous test results. Inform laboratory personnel and discuss use of an alternative testing platform for patients on treatment. (7.1)
- Serum Alkaline Phosphatase: Serum ALP measurements are expected to be elevated during treatment and may be unreliable for clinical decision making. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Enzyme replacement therapy

- Asfotase alfa (Strensiq®) – a recombinant bone-targeted human TNSALP
- Approved in many countries for treatment of perinatal/infantile and pediatric-onset HPP
- Skeletal, respiratory, and functional improvement → milestone in the treatment of severe forms of HPP

<u>In adult onset HPP</u>

- Limited data
- Optimal dose, dose adjustments, duration of therapy are unknown
- Adverse effects of long-term therapy have not been defined
- Treatment decisions should be individualized according to all available clinical information, including patient preference

J Bone Miner Res 2017;32(10):1977-80, Osteoporos Int 2020;31(8):1445-1460.

PERSPECTIVE

JBMR®

Hypophosphatasia in Adults: Clinical Assessment and Treatment Considerations

Jay R Shapiro [1] and E Michael Lewiecki [2]

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[2]New Mexico Clinical Research and Osteoporosis Center, Albuquerque, NM, USA

Treatment of adults with HPP be considered when

- History of childhood involvement (before age 18), such as early loss of primary or secondary teeth, craniosynostosis, gait disturbance, developmental delays, skeletal deformity, bone pain or fractures, or
- No documentation of childhood symptoms, and one or more of the following criteria:
    1. Musculoskeletal pain requiring prescription pain medications, especially chronic opioids
    2. Disabling polyarthropathy or chondrocalcinosis
    3. Major low-trauma fracture attributable to HPP
    4. Delayed or incomplete fracture healing or fracture non-union
    5. Repeated episodes of orthopedic surgery for complications of HPP, especially for non-union and delayed union fractures
    6. Disabling functional impairment
    7. Low BMD by DXA (T-score –2.5 or Z-score –2.0) with fractures
    8. Radiological evidence of nephrocalcinosis

J Bone Miner Res 2017;32(10):1977-80

Full Length Article

Five-year efficacy and safety of asfotase alfa therapy for adults and adolescents with hypophosphatasia☆

Priya S. Kishnani[a,*], Cheryl Rockman-Greenberg[b], Frank Rauch[c], M. Tariq Bhatti[d], Scott Moseley[e], Andrew E. Denker[e], Eric Watsky[e,1], Michael P. Whyte[f,g]

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[f] Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children, St. Louis, MO, USA
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ARTICLE INFO

Keywords:
Absorptiometry
Alkaline phosphatase
Ambulation
Biopsy
Enzyme replacement therapy
Inorganic pyrophosphate
Metabolic bone disease
Motor skills
Muscle strength
Osteomalacia
Physiologic calcification
Pyridoxal 5′-phosphate
Vitamin B6

ABSTRACT

Hypophosphatasia (HPP) features low tissue-nonspecific alkaline phosphatase (TNSALP) isoenzyme activity resulting in extracellular accumulation of its substrates including pyridoxal 5′-phosphate (PLP), the principal circulating form of vitamin B6, and inorganic pyrophosphate (PPi), a potent inhibitor of mineralization. Asfotase alfa is an enzyme replacement therapy developed to treat HPP. This multinational, randomized, open-label study (NCT01163149; EudraCT 2010-019850-42) evaluated the efficacy and safety of asfotase alfa in adults and adolescents 13–66 years of age with HPP. The study comprised a 6-month primary treatment period and a 4.5-year extension phase. In the primary treatment period, 19 patients were randomized to receive asfotase alfa 0.3 mg/kg/d subcutaneously (SC; n = 7), asfotase alfa 0.5 mg/kg/d SC (n = 6), or no treatment (control; n = 6) for 6 months. In the extension phase, patients received asfotase alfa (0.5 mg/kg/d for 6 mo–1 y, then 1 mg/kg/d 6 d/wk). During the primary treatment period, changes from Baseline to Month 6 in plasma PLP and PPi concentrations (coprimary efficacy measure) were greater in the combined asfotase alfa group compared with the control group, reaching statistical significance for PLP ($P = 0.0285$) but not for PPi ($P = 0.0715$). However, for the total cohort, the within subject changes in both PLP and PPi after 6 months and over 5 years of treatment with asfotase alfa were significant ($P < 0.05$). Secondary efficacy measures included transiliac crest histomorphometry, dual-energy X-ray absorptiometry (DXA), and the 6-Minute Walk Test (6MWT). A significant decrease from Baseline in mineralization lag time was observed in the combined asfotase alfa group at Year 1. There were no significant differences between treated and control patients in DXA mean bone mineral density results at 6 months; Z-scores and T-scores were within the expected range for age at Baseline and remained so over 5 years of treatment. On the 6MWT, median (min, max) distance walked increased from 355 (10, 620; n = 19) meters before treatment to 450 (280, 707; n = 13) meters at 5 years ($P < 0.05$). Results for the exploratory outcome measures suggested improvements in gross motor function, muscle strength, and patient-

Anti-sclerostin monoclonal antibody

- BPS-804 (setrusumab) administered for 16 weeks in 8 patients with adult HPP, mean age 47.8
- Increased bone formation markers and BMD
- More data are needed on the use of romosozumab in HPP, especially when it is discontinued

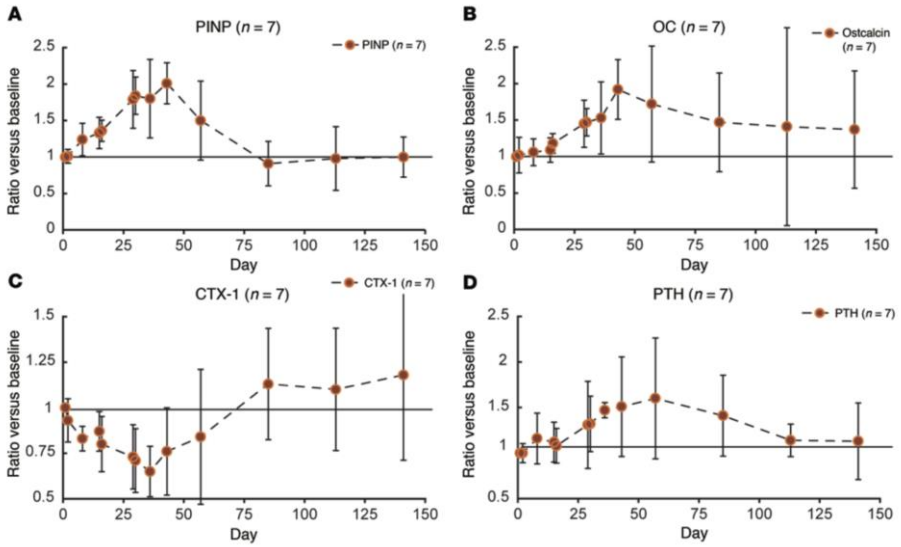

Table 2. Lumbar spine BMD

Patient no.	LS-BMD (mg/cm²)/z-score			Change from baseline (%)	
	Baseline	Day 85	EoS	Day 85	EoS
1	980/−1.0	1,033/−0.5	1,053/−0.3	5.4	7.4
2	991/−1.1	NP[A]	NP[A]	–	–
3	903/−1.6	924/−1.4	927/−1.4	2.3	2.7
4	991/−1.6	1,075/−0.8	1,055/−0.9	8.5	6.5
5	917/−2.4	955/−1.9	975/−1.8	4.1	6.3
6	1,087/0.1	1,080/0.1	1,119/0.4	−0.6	2.9
7	1,019/−0.8	1,011/−0.8	1,025/−0.7	−0.8	0.6
9	1,512/4.5	1,548/4.8	1,527/4.6	2.4	1.0
Mean				3.0	3.9

J Clin Invest 2017;127(6):2148-58.
Osteoporos Int 2020;31(8):1445-1460.

- Clinical presentations of secondary osteoporosis or other causes of low BMD vary from asymptomatic or nonspecific to severe diseases
- Careful history and examination provide important clues towards the etiology
- Laboratory testing should be considered for all postmenopausal women with osteoporosis (or low BMD, before treatment)

When to suspect HPP

- Defective bone mineralization: nontraumatic/recurrent fractures, stress fractures, delayed fracture healing
- Defective tooth mineralization: premature tooth loss, enamel hypoplasia, severe dental caries
- Laboratory: persistently low serum ALP after exclusion of other causes, increased levels of ALP substrates
- Radiology/ultrasound: chondrocalcinosis, enthesopathies, calcific periarthritis

Diagnosis

- Persistently low serum ALP for age and sex, elevation of substrates (PLP, PEA, PPi) with suggestive clinical signs and symptoms
- Genetic test (ALPL gene), in case of doubt or to confirm diagnosis

Common errors

- *Lack of attention to low ALP values*
- *Start antiresorptive treatment for osteoporosis without evaluation of ALP levels*

Management

- *** Symptomatic treatment – Pain and inflammation control (NSAIDs)
- Optimal Ca/vitamin D supplementation
- Enzyme replacement therapy (asfotase alfa) in pediatric-onset HPP, if clinically indicated
- For fracture fixation, use load-sharing implants, if possible

What should not be given

- Oversupplements of Ca/vitamin D
- Antiresorptive drugs (BPs, denosumab)
- Plates and screws for fracture fixation