# A lifelong Burden of Hypophosphatasia (HPP) in children & adolescents

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# Objectives

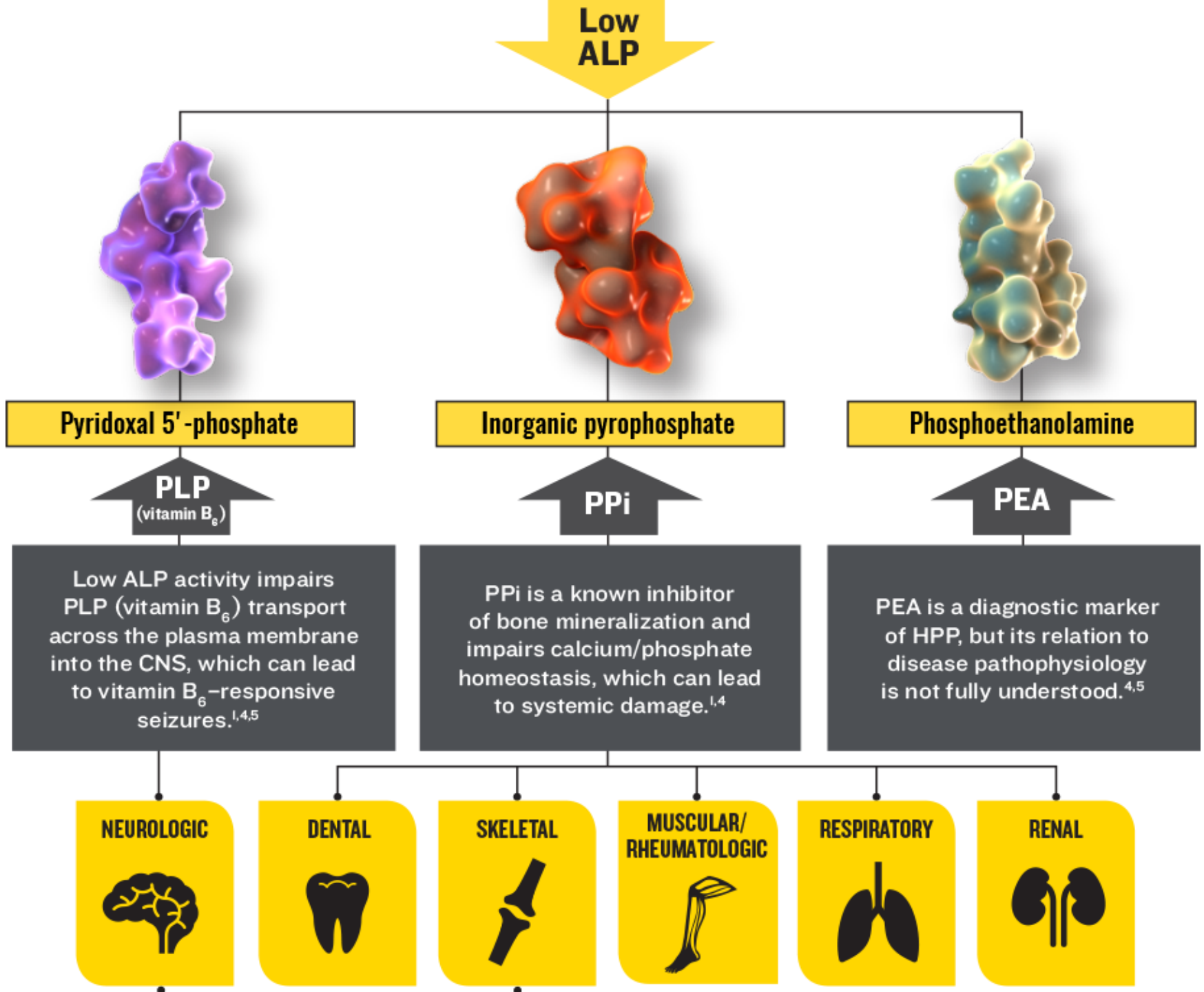
## Overall consequences of HPP include:

- Impact on respiratory system.
- Impact on neurological system.
- Dental consequences.
- Skeletal manifestations.
- Ectopic calcifications in kidneys, joints & eyes.
- Functional impairment.
- Decreased quality of life.
- Summary.

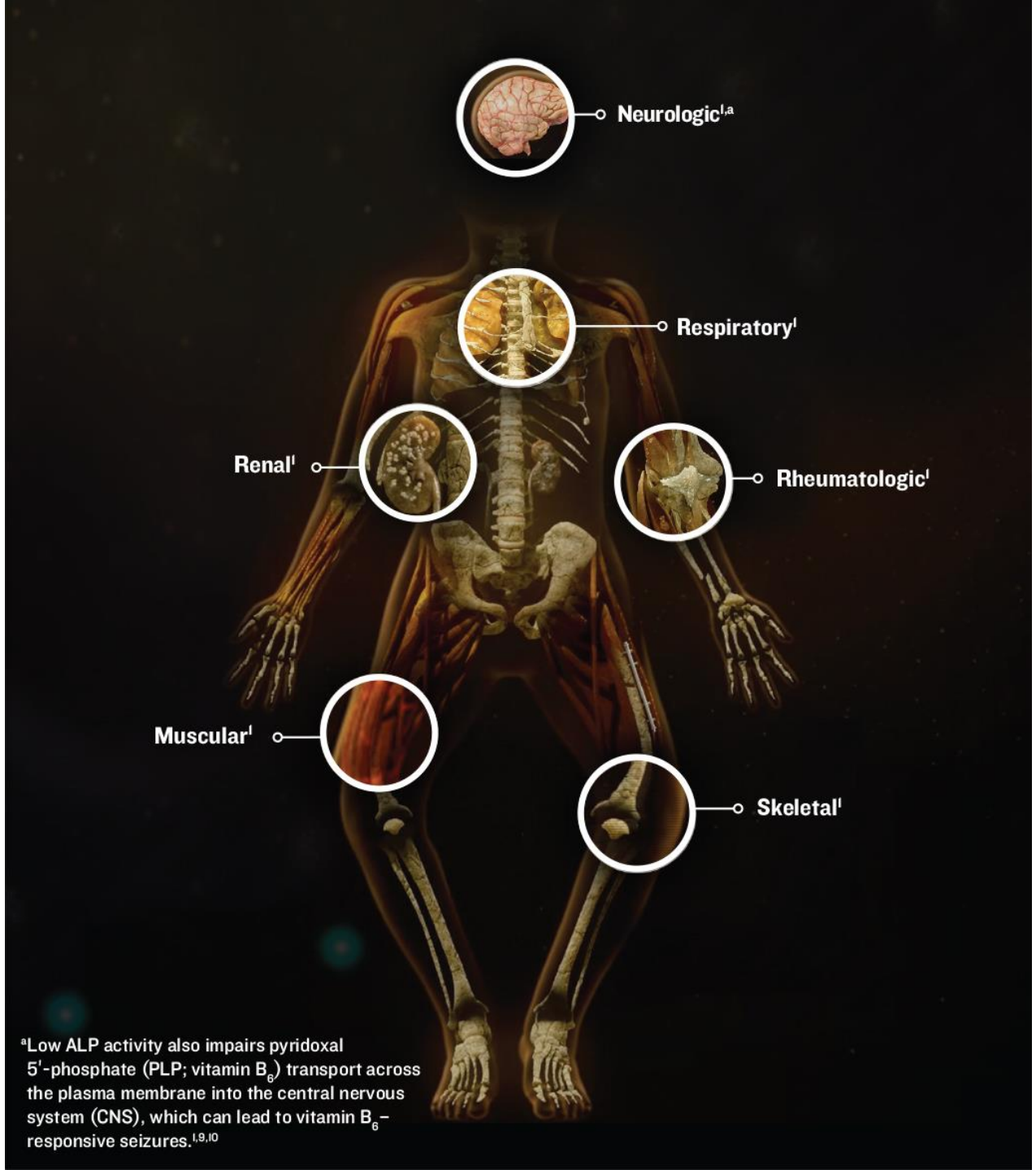
# Introduction

- Hypophosphatasia (HPP) is a life-threatening, progressive, systemic, inherited metabolic disorder.
- Caused by loss-of-function mutations in the ALPL gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP).
- (TNSALP) deficiency in osteoblasts & chondrocytes impairs bone mineralization, leading to rickets or osteomalacia.

Clinical symptoms are heterogeneous, ranging from a rapidly fatal, perinatal variant, with profound skeletal hypo-mineralization, respiratory compromise or vitamin B6 dependent seizures to a milder, progressive osteomalacia later in life.


Low ALP
Pyridoxal 5'-phosphate
Inorganic pyrophosphate
Phosphoethanolamine
PLP (vitamin $B_6$)
PPi
PEA
Low ALP activity impairs PLP (vitamin $B_6$) transport across the plasma membrane into the CNS, which can lead to vitamin $B_6$–responsive seizures.[1,4,5]
PPi is a known inhibitor of bone mineralization and impairs calcium/phosphate homeostasis, which can lead to systemic damage.[1,4]
PEA is a diagnostic marker of HPP, but its relation to disease pathophysiology is not fully understood.[4,5]
NEUROLOGIC
DENTAL
SKELETAL
MUSCULAR/ RHEUMATOLOGIC
RESPIRATORY
RENAL

# HPP is a Lifelong Disease with Multi Systemic Consequences

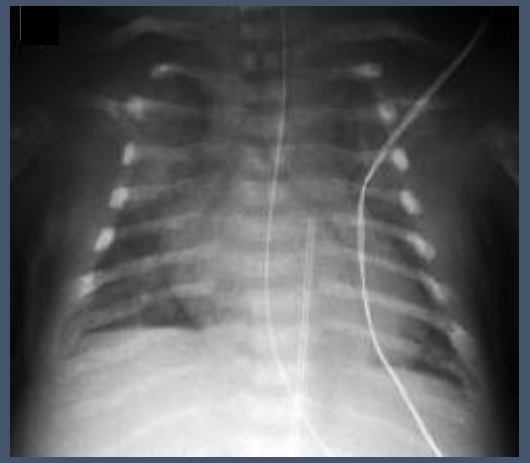



[a]Low ALP activity also impairs pyridoxal 5′-phosphate (PLP; vitamin $B_6$) transport across the plasma membrane into the central nervous system (CNS), which can lead to vitamin $B_6$–responsive seizures.[1,9,10]

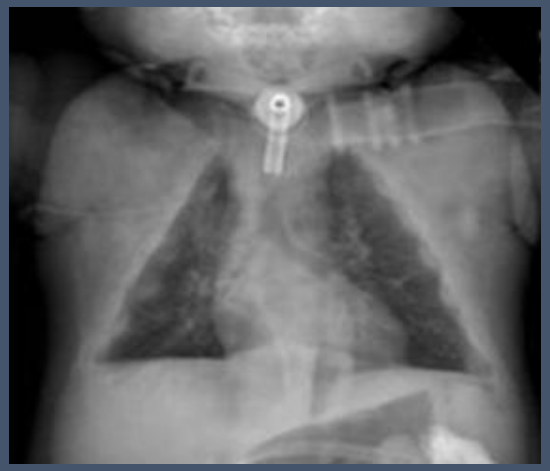
# Pulmonary Consequences

# Pulmonary Manifestations of HPP

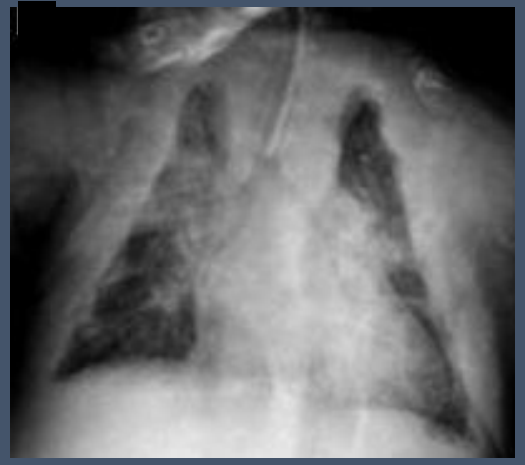
Severe rib cage hypomineralization leading to chest deformity and decreased thoracic volume can occur in newborn and infant patients with HPP[1-4]:



Bell-shaped chest deformity in a patient aged 12 days[3,a]



Undermineralized ribs and bell-shaped chest deformity in a patient aged 33 months[3,a]



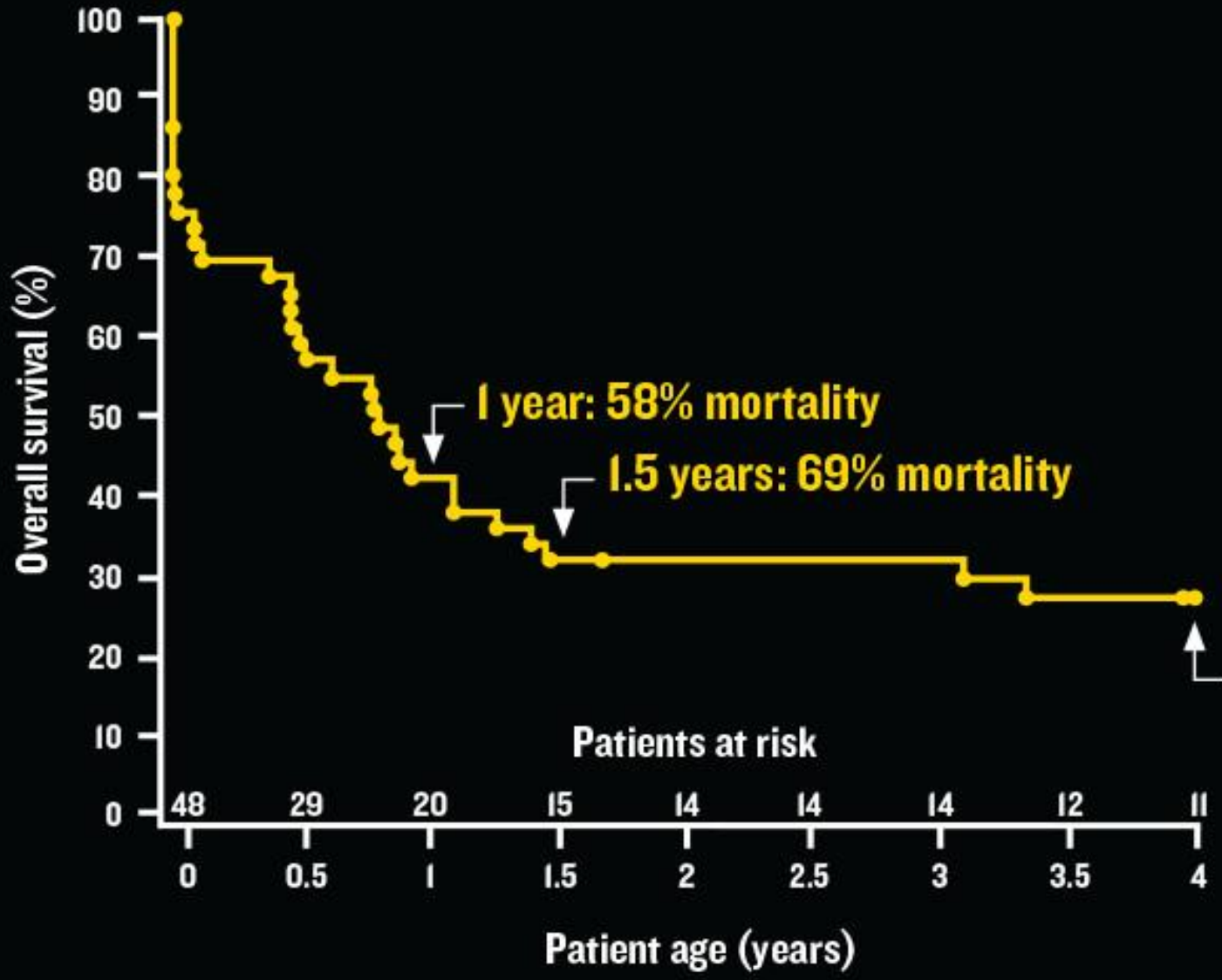
Deformities and poor mineralization in a patient aged 32 months[3,a]

Respiratory complications are the most common cause of death in patients with HPP[5]

HPP, hypophosphatasia.

[a]Images are from different patients. Images reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

**1.** Linglart and Biosse-Duplan. *Curr Osteoporos Rep.* 2016;14:95-105. **2.** Rockman-Greenberg. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. **3.** Whyte et al. *N Engl J Med.* 2012;366:904-913. **4.** Silver et al. *Pediatr Pathol.* 1988;8:483-493. **5.** Whyte et al. *J Pediatr*. 2019;pii: S0022-3476(19)30139-8 [Epub].


100
90
80
70
60
50
40
30
20
10
0
Overall survival (%)
1 year: 58% mortality
1.5 years: 69% mortality
4 years: 73% mortality
Patients at risk
48
29
20
15
14
14
14
12
11
0
0.5
1
1.5
2
2.5
3
3.5
4
Patient age (years)


73%

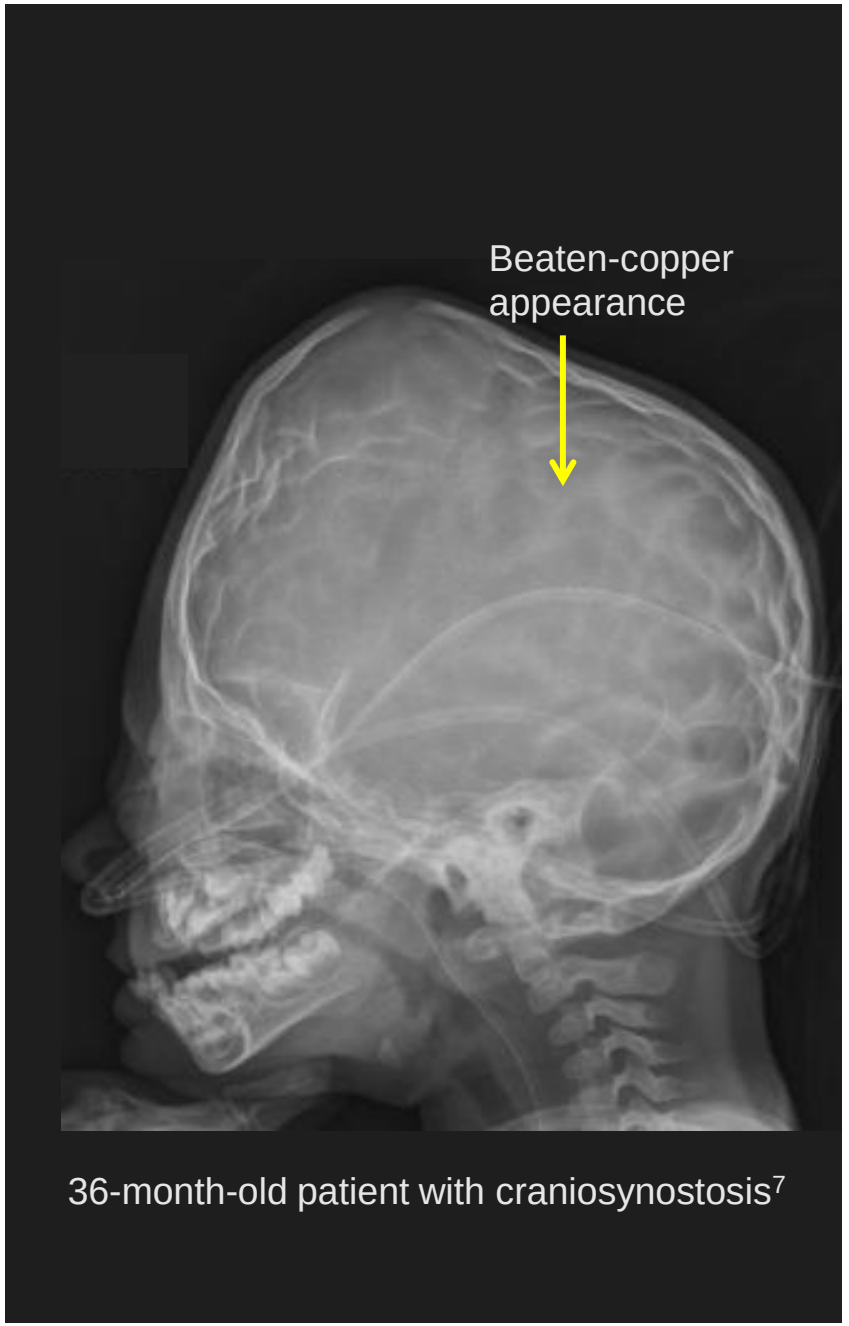
mortality

# Neurological Consequences

# Neurologic manifestations occur in patients with HPP because of low vitamin $B_6$ and complications from craniosynostosis

## Neonates and infants with HPP can experience:

- Vitamin $B_6$–responsive seizures[1,2]
  - These seizures are a fatal prognostic indicator[1]
- Intracranial hypertension and hemorrhage[3]
- Encephalopathy[3]
- Conductive deafness[4-6]
- Brainstem or cerebral cortex damage[4]
- Craniosynostosis[3]




36-month-old patient with craniosynostosis[7]

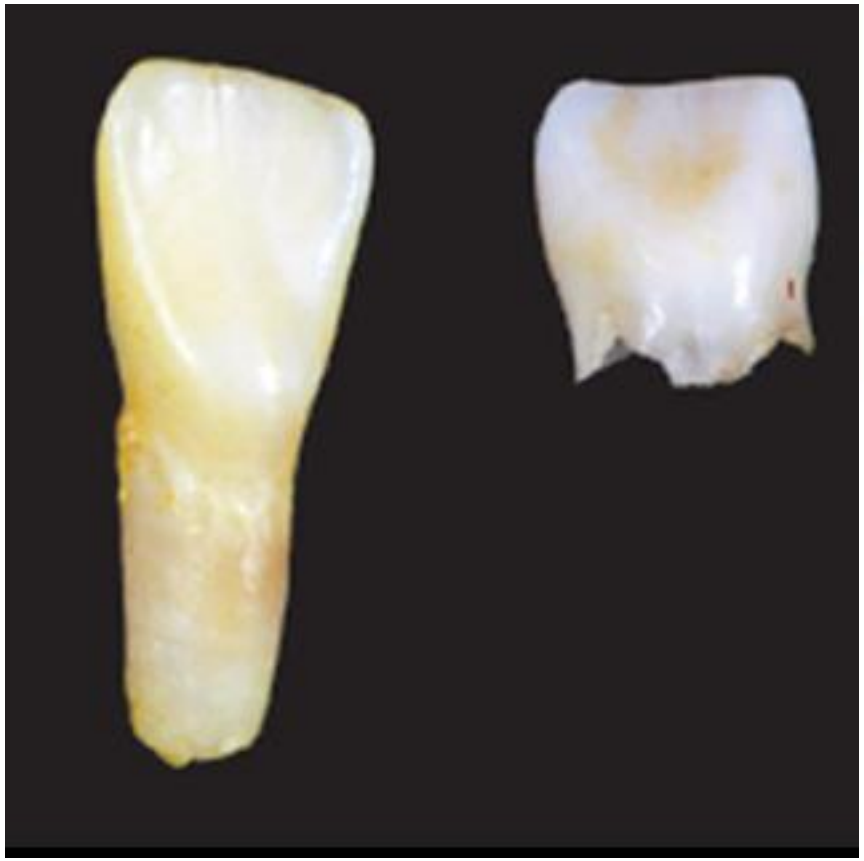
HPP, hypophosphatasia.
Image reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.
**1.** Baumgartner-Sigl et al. *Bone*. 2007;40:1655-1661. **2.** Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **3.** Collmann et al. *Childs Nerv Syst*. 2009;25:217-223. **4.** Taketani et al. *Arch Dis Child.* 2014;99:211-215. **5.** Kitaoka et al. *Clin Endocrinol*. 2017;87:10-19. **6.** Whyte et al. *Lancet Diabetes Endocrinol.* 2019;7:93-105. **7.** Whyte et al. *N Engl J Med*. 2012;366:904-913.

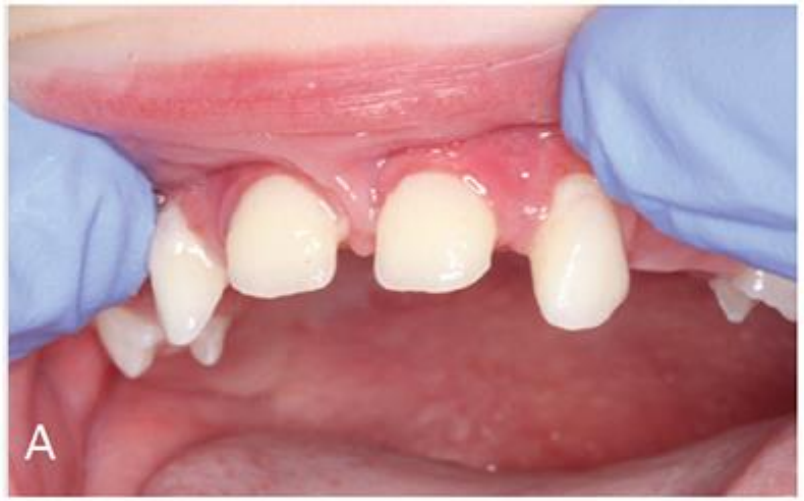
# Dental Consequences

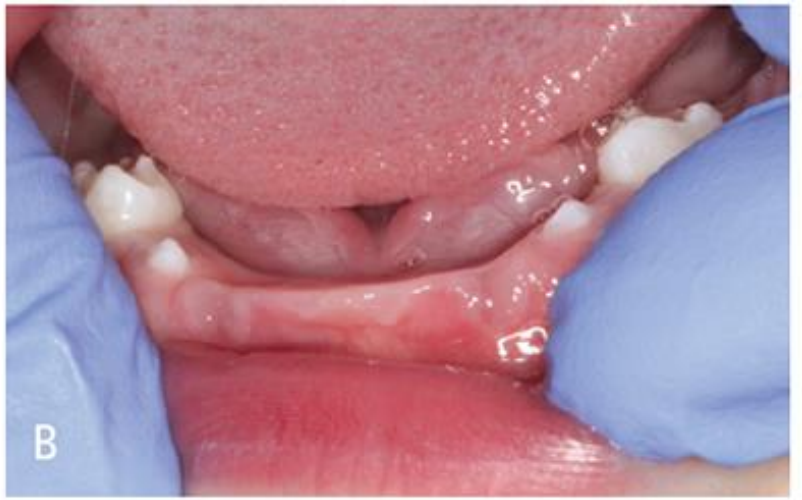
Dental manifestations are a hallmark symptom of HPP.

Children may experience premature tooth loss (before aged 5 years) with the root intact.

Adults may experience poor dentition or early loss of permanent teeth




A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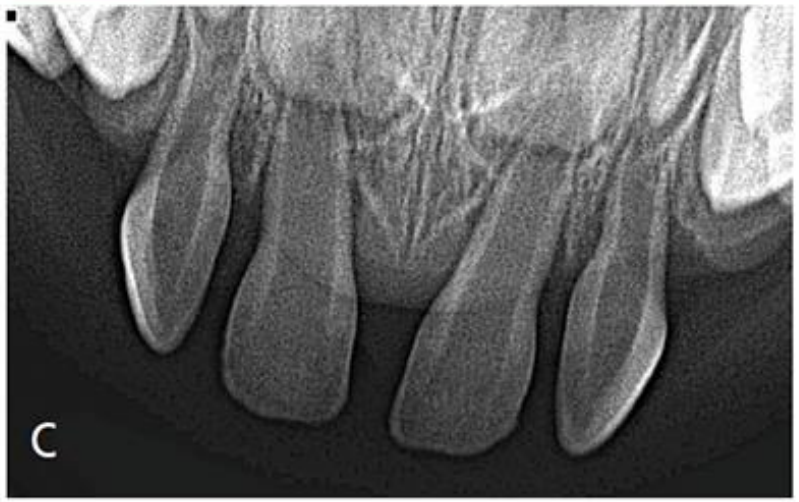
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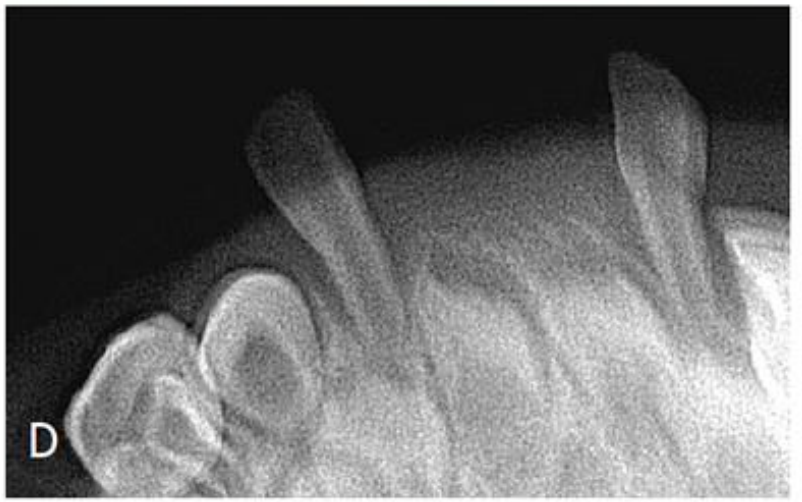
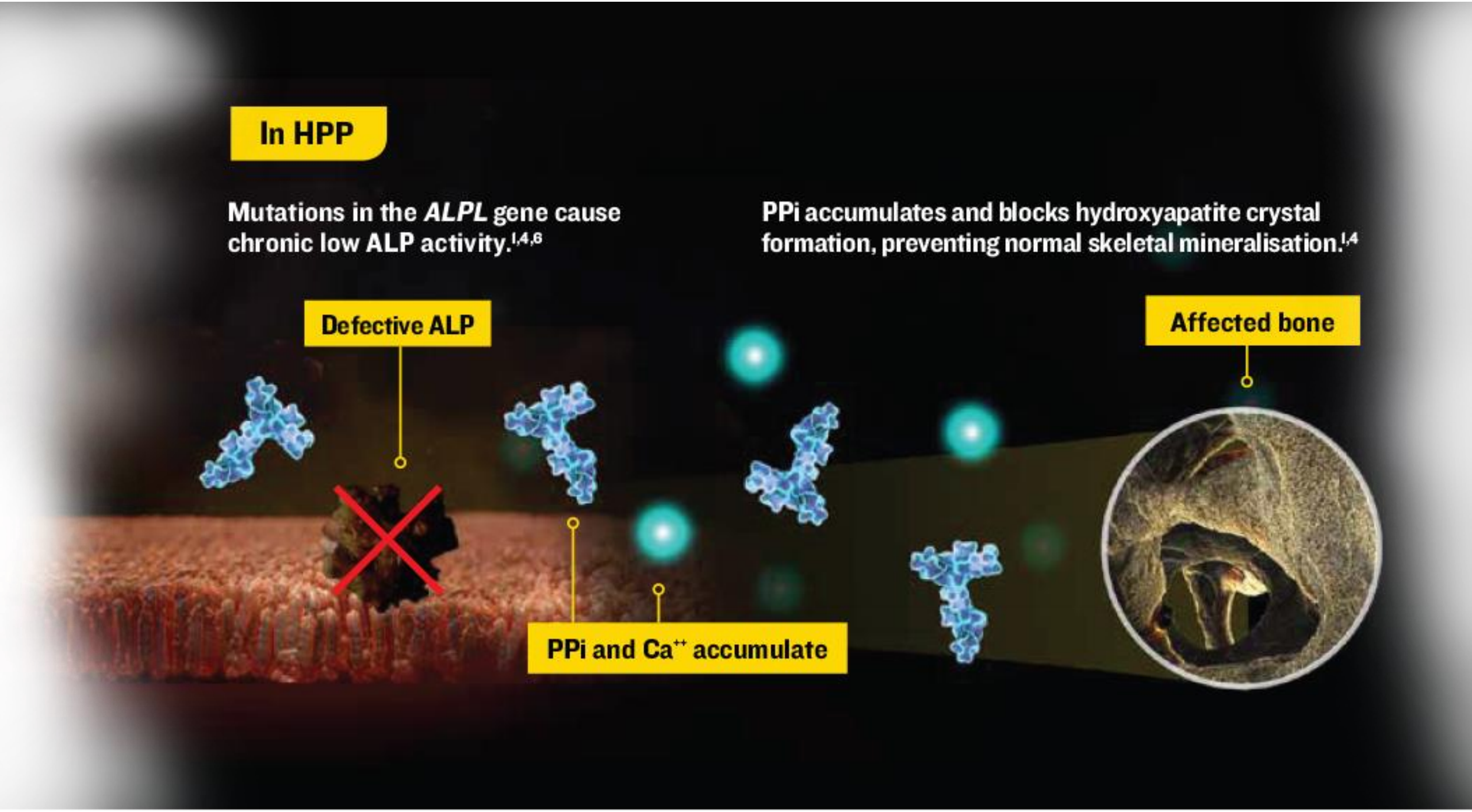
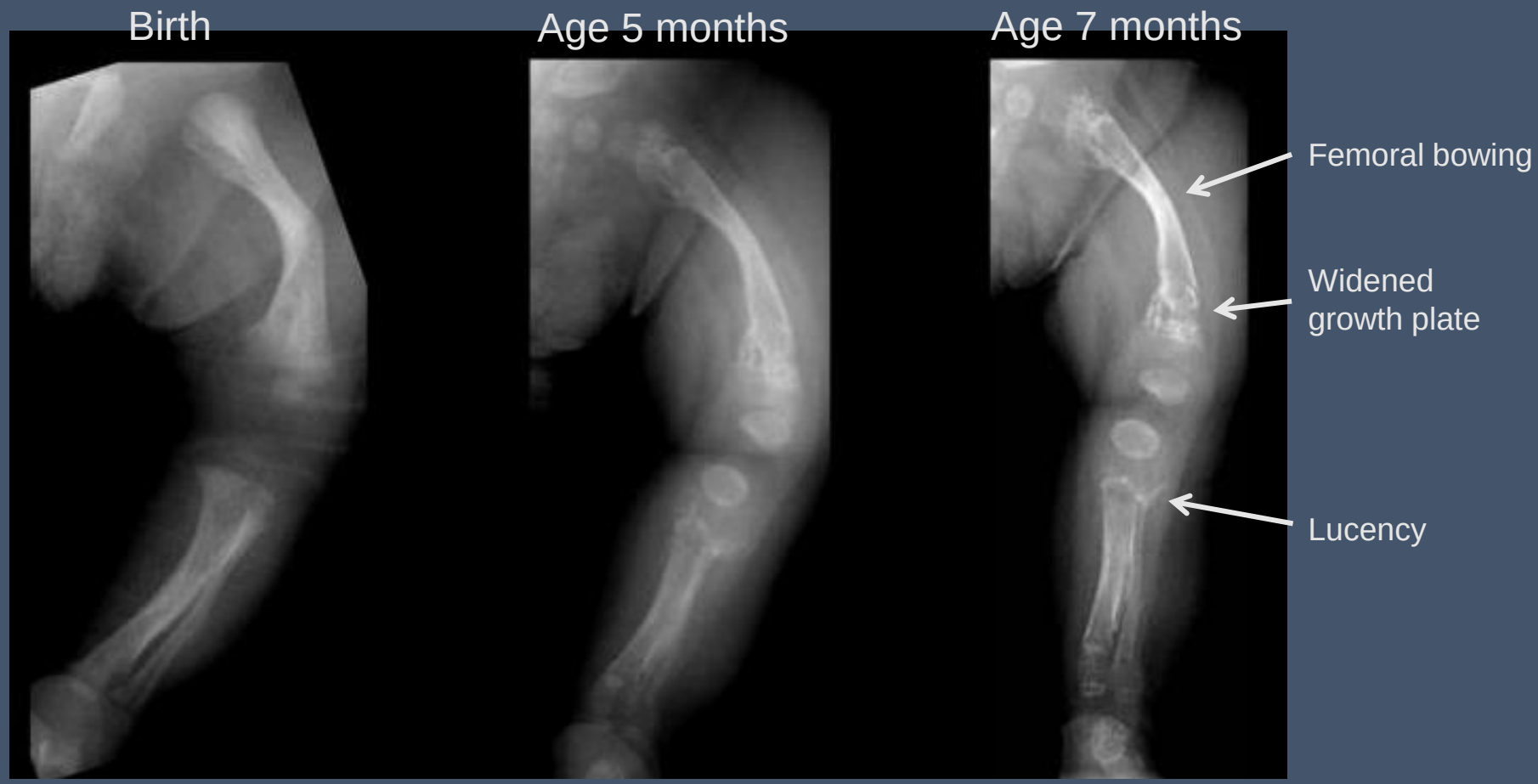

D

# Skeletal Consequences


In HPP
Mutations in the *ALPL* gene cause chronic low ALP activity.[1,4,6]
PPi accumulates and blocks hydroxyapatite crystal formation, preventing normal skeletal mineralisation.[1,4]
Defective ALP
Affected bone
PPi and Ca++ accumulate

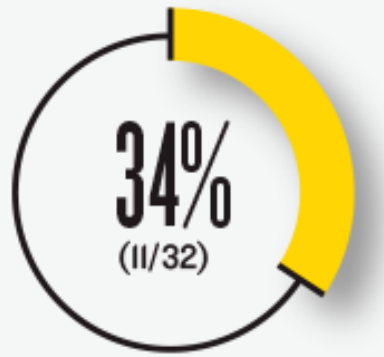
# Progressive Skeletal Bowing & Demineralization



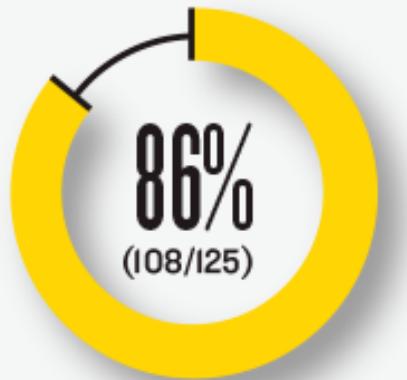

Images reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

## PREVALENCE OF FRACTURES IN PATIENTS OF DIFFERENT AGES WITH HPP


Infants and young children (≤5 years)[4,b]




Children and adolescents (5 to 15 years)[16,c]




Adults[11,d]

# Ectopic Calcifications

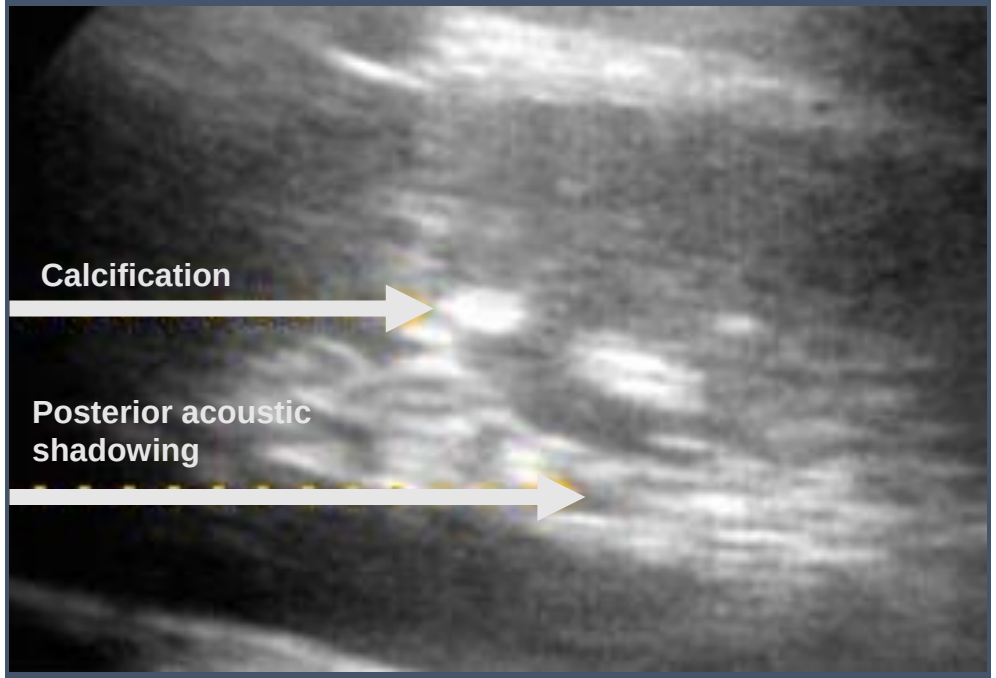
# Joint Calcifications
# Nephrocalcinosis

# Nephrocalcinosis result from Impaired Calcium & Phosphate Homeostasis

- Accumulation of serum calcium can overload the renal resorptive mechanisms, resulting in calcium deposition in the kidneys[1,2]
- Hypercalcemia is relatively common in infantile HPP but is less common in childhood and adult forms of HPP[3]
- Hypercalcemia is associated with[1,4,5]:
  - **Nephrocalcinosis**
  - Apnea
  - Anorexia
  - Vomiting
  - Polydipsia
  - Polyuria
  - Dehydration
  - Constipation
  - Hypotonia

**Nephrocalcinosis may be severe and result in kidney failure[2,7]**

## Kidney ultrasound




In a chart review of patients ≤5 years of age with HPP, 52% (16/31) of patients had nephrocalcinosis[6,a]

HPP, hypophosphatasia.

[a]Data from a noninterventional, retrospective chart review study designed to understand the natural history of 48 patients with perinatal- and infantile-onset HPP ≤5 years of age.[6] Image reproduced from Barvencik et al. *Osteoporos Int*. 2011;22:2667-2675. With permission from Springer Nature.

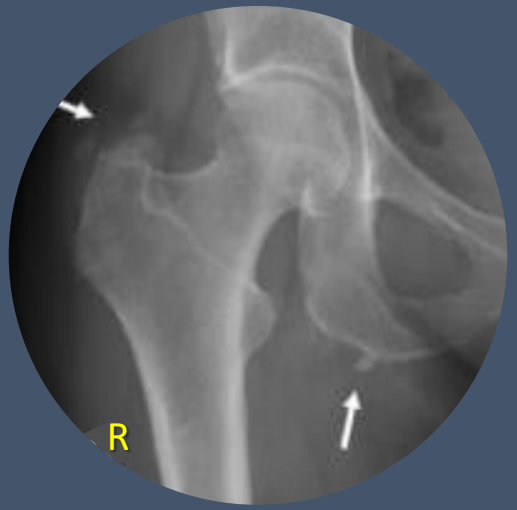
**1.** Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **2.** Sumner et al. *Clin Nephrol*. 1984;22:317-319. **3.** Ramage et al. *J Clin Pathol*. 1996;49:682-684. **4.** Whyte. In*: Genetics of Bone Biology and Skeletal Disease*. 2013:337-360. **5.** Whyte. *Ann N Y Acad Sci.* 2010;1192:190-200. **6.** Whyte et al. *J Pediatr.* 2019;pii: S0022-3476(19)30139-8 [Epub]. **7.** Eade et al. *Ann Rheum Dis*. 1981;40:164-170.

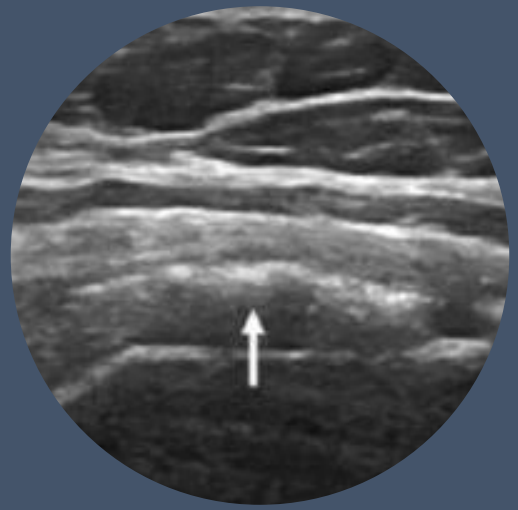
# Burden of Ectopic Calcifications in Joints

CPPD crystal deposition in patients with HPP can result in:

CPPD disease[1,2] • Calcific tendinitis[3] • Joint swelling[4] • Pseudogout[1,2] • Chondrocalcinosis[1,2,5,6] • Calcific periarthritis[1,2,6] • Arthropathy[5]

Calcium deposition (arrows) adjacent to the greater trochanter of the right femur and likely within the right gluteal tendon insertion and hamstring tendon origins[3]



Calcium (arrow) within the right gluteus medius tendon at its insertion on the greater trochanter, with minimal posterior acoustic shadowing[3]

These conditions may cause chronic muscle and joint pain[1,3]

CPPD, calcium pyrophosphate dihydrate; HPP, hypophosphatasia.
Images reproduced from Guanabens et al. *J Bone Miner Res*. 2014;29:929-934. With permission from American Society for Bone and Mineral Research.

1. Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Chuck et al. *Ann Rheum Dis.* 1989;48:571-576. 3. Guanabens et al. *J Bone Miner Res*. 2014;29:929-934. 4. Linglart and Biosse-Duplan. *Curr Osteoporos Rep.* 2016;14:95-105. 5. Whyte et al. *Am J Med.* 1982;72:631-641. 6. McKiernan et al. *J Bone Miner Res.* 2014;29:1651-1660.

# The Manifestations of HPP Leads to Functional Impairment

**The manifestations of HPP that can lead to mobility issues can include:**

- Pain
- Loss of physical function
- Muscle weakness
- Recurrent fractures leading to repeated surgeries
- Unusual gait and impaired mobility

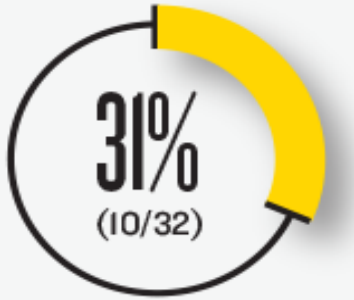
HPP, hypophosphatasia.

Weber et al. *Metabolism*. 2016;65:1522-1530.

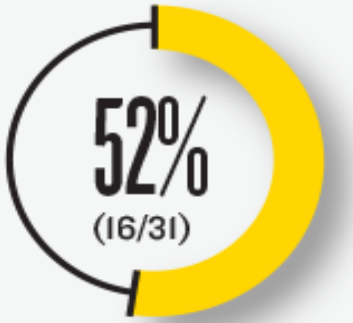
# Decreased Quality of Life

# CHILDREN WITH HYPOPHOSPHATASIA EXPERIENCE A RANGE OF DEVASTATING CONSEQUENCES.[1,10,18]

In natural history studies:




31% of patients with hypophosphatasia experienced craniosynostosis[9,c]

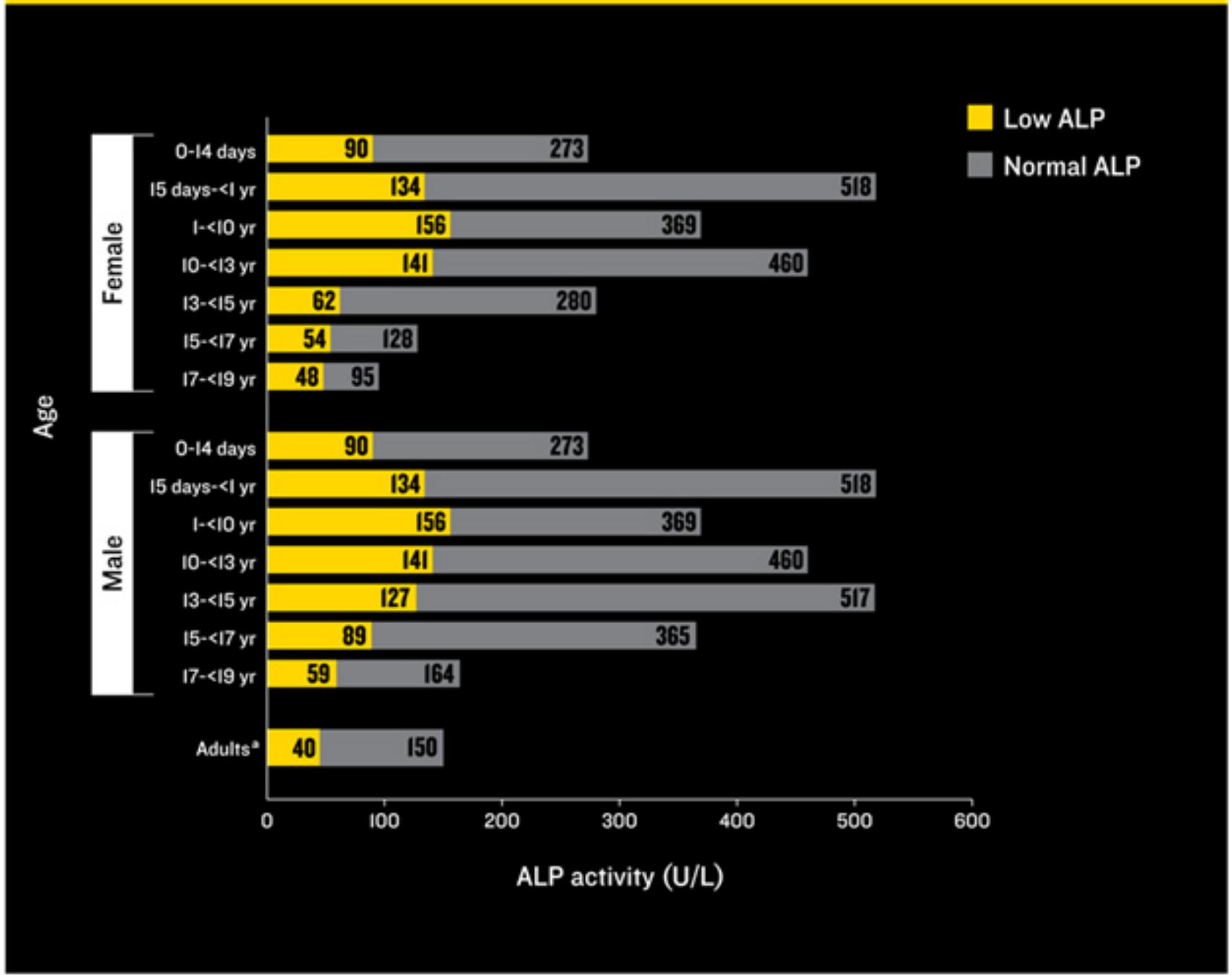



52% of patients experienced nephrocalcinosis[19,b]


89% of patients experienced delayed motor development[19,b]


42% of patients with delayed motor development experienced delayed walking[19,b]

## AGE- AND GENDER-ADJUSTED ALP REFERENCE INTERVALS (U/L) [8,10]



# Summary

- HPP is a rare, inherited metabolic disorder with lifelong, systemic clinical manifestations.
- The burden of HPP is characterized by a variety of painful, disabling symptoms that can occur at any age.
- Skeletal and non skeletal manifestations can lead to mortality in babies and infants and dental problems, poorly healing/nonhealing fractures, bone deformities, muscle and joint weakness, pain, and possible renal failure in surviving children and adults.
- These manifestations can result in impairment of daily activities and decreased quality of life.
- Timely and accurate diagnosis of HPP is critical because misdiagnosis can lead to ineffective management that can potentially worsen the burden of symptoms.
- A multidisciplinary team is necessary for the optimal management of patient symptoms.

# Thank You