Recognizing the Clinical Consequences of Low Alkaline Phosphatase (ALP)

Diagnosing Hypophosphatasia (HPP)

Patient image is hypothetical.

08/2021 US/UNB-H/0211

ALEXION®
AstraZeneca Rare Disease

Today's Objectives

EXPLORE

the connection between low levels of alkaline phosphatase (ALP) and one or more clinical signs and symptoms of hypophosphatasia (HPP)

UNDERSTAND

the highly variable nature of HPP presentation and how it can affect the different systems of the body

RECOGNIZE

the signs, symptoms, and burden of HPP, as well as the importance of a timely diagnosis

HPP Has a High Burden of Disease for Both Adult and Pediatric Patients

Ellen

Click here

Choose a Patient to Learn About

Ronny

Click here

HPP, hypophosphatasia.
Hypothetical patients.

Case Study: Identifying and Diagnosing HPP

This is Ellen…

A 49-year-old woman referred to an endocrinologist for pain and fatigue.

Hypothetical patient.

History of presenting illness

Positive for: knee pain/other joint involvement, ankle pain without swelling; general fatigue and depressed mood for years that worsened ~1 year ago

Negative for: swelling, redness, rash, fever, chills, nausea, headaches, or difficulty sleeping

Medical History	Premature loss of a tooth with root intact at 15 months, nontraumatic fractures (ages 11 and 17; does not recall instigating injury), ALP value reported as 118 U/L* on lab results at age 11, normal menses
Social history	Single mom, lives with 2 daughters, denies tobacco or alcohol use
Family history	Fibromyalgia (mother)
Medications	Over-the-counter pain medication as needed

Lab results show low ALP but is not noted as a concern by the physician

Labs (abnormal values flagged)	
Calcium, mg/dL	9.6
Phosphorus, mg/dL	3.3
Vitamin D, 25-Hydroxy, ng/mL	42
ALP, IU/L	**33 (L)†**
PTH, ng/L	12

Check with your lab for their appropriate age- and sex-adjusted reference range.

*Age- and sex-adjusted normal range for 11-year-old female, 141-460 U/L †Age- and sex-adjusted normal range for adults, 40-120 U/L.[1-6]
ALP, alkaline phosphatase; HPP, hypophosphatasia; PTH, parathyroid hormone.
Hypothetical patient case.

1. Colantonio DA. *Clin Chem*. 2012;58(5):854-868. 2. Adeli K. *Clin Chem.* 2015;61(8):1049-1062. 3. Schumann G. *Clin Chem Lab Med*. 2011;49(9):1439-1446. 4. Quest Diagnostics. Accessed April 12, 2021. https://testdirectory.questdiagnostics.com/test/test-detail/234/alkaline-phosphatase?cc=MASTER. 5. Labcorp. Accessed April 12, 2021. https://www.labcorp.com/tests/001107/alkaline-phosphatas 6. ARUP Laboratories. Accessed April 12, 2021. https://ltd.aruplab.com/Tests/Pub/0021020

Persistently Low ALP Differentiates HPP From Other Conditions[1]

- Persistently low values may be defined as at least 2 values below normal within 6 months[2]
- ALP <40 U/L is considered LOW for adults[3-7*]

ALP Levels†

PRECIPITOUSLY LOW	TRANSIENTLY LOW	PERSISTENTLY LOW
• Multiple myeloma or other cancers • Cardiac bypass surgery • Major trauma or surgery • Chemotherapy • Transfusion (often massive) • Starvation • Sepsis/multi-organ/hepatic failure	• Osteogenesis imperfecta type II • Profound hypothyroidism • Cushing disease • Bisphosphonate therapy • Adynamic renal osteodystrophy • Milk-alkali syndrome • Vitamin D intoxication • Wilson disease • Celiac disease	• Hypophosphatasia • Cleidocranial dysplasia • Mseleni joint disease

***Limitations:** An ALP level of below 40 U/L is not conclusive for diagnosis of HPP. Patient should be evaluated for other symptoms of HPP and differential diagnoses should be ruled out. Check with your lab for their appropriate age- and sex-adjusted reference range. The connection between alkaline phosphatase and PEA has not been fully established. Inorganic pyrophosphate (PPi) is also a substrate associated with HPP; however, tests for PPi are not commercially available.

† Not an exhaustive list of conditions associated with low levels of ALP.

ALP, alkaline phosphatase; HPP, hypophosphatasia; PEA, phosphoethanolamine.

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ALP Is a Key Enzyme Needed for Hydroxyapatite Crystal Formation

Under normal circumstances

ALP dephosphorylates PPi, releasing Pi.

Pi binds to calcium (Ca^{2+}) to form hydroxyapatite crystals that mineralize bone.

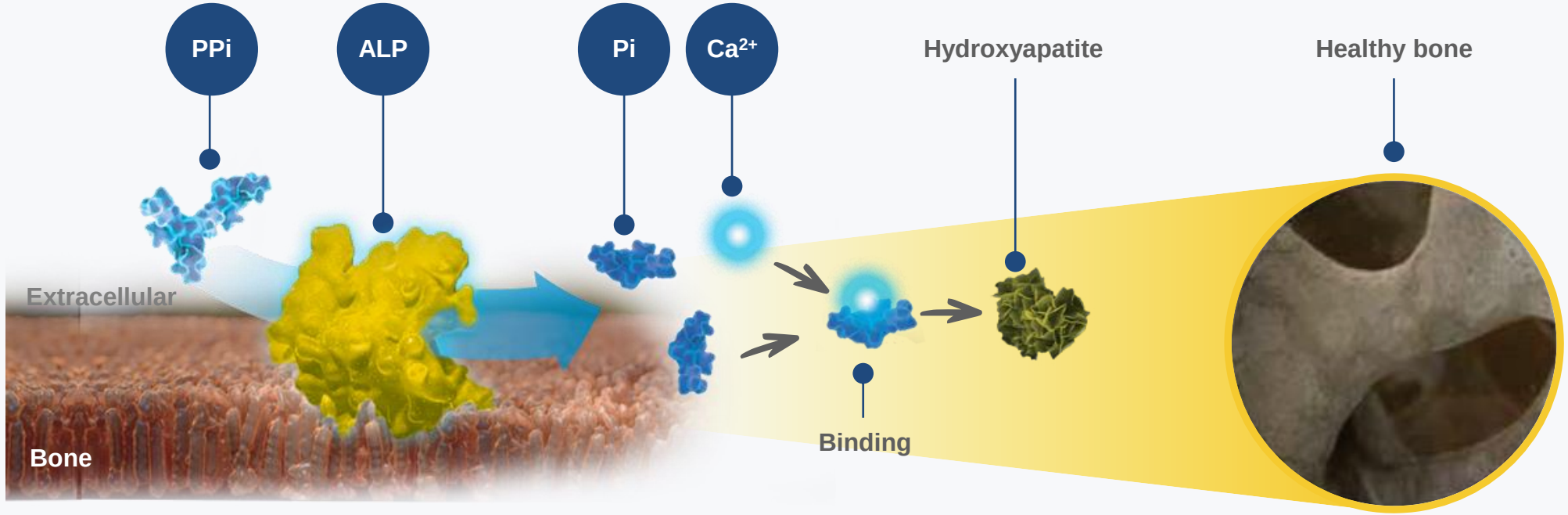


Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes.

ALP, alkaline phosphatase; Ca^{2+}, calcium; Pi, inorganic phosphate; PPi, inorganic pyrophosphate.

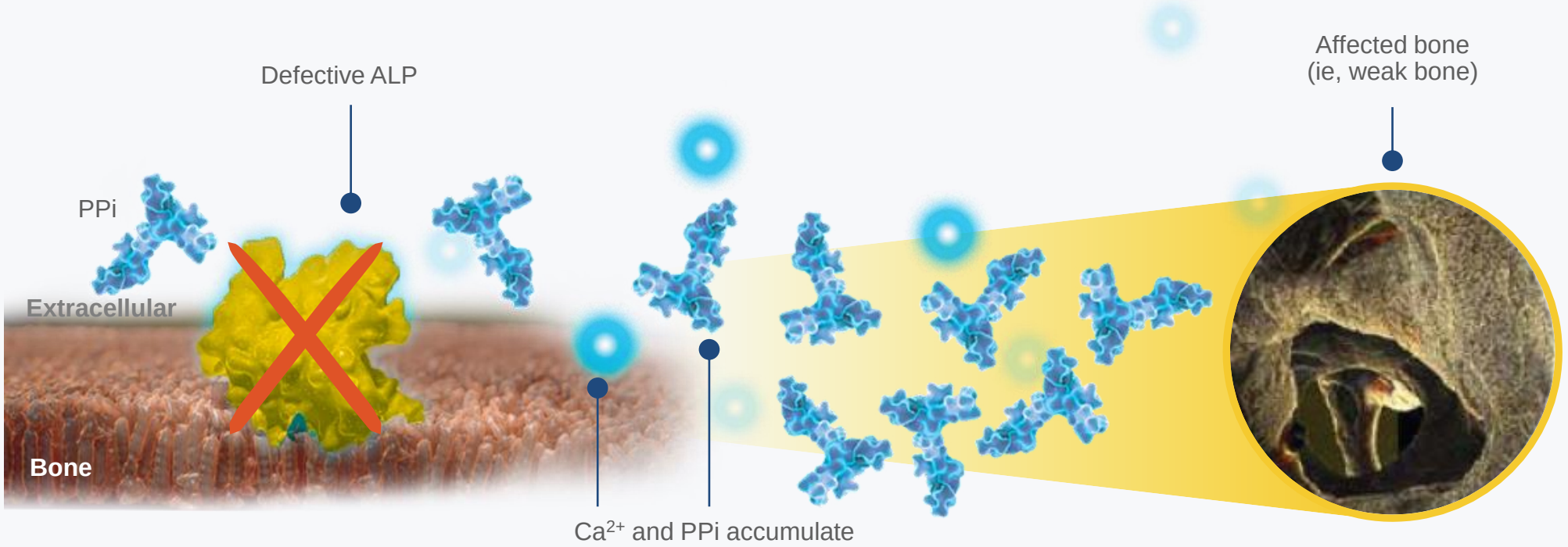
Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388.

In HPP, ALP Is Deficient[1,2]

With HPP

Mutations in the *ALPL* gene cause low ALP activity.

PPi accumulates and prevents hydroxyapatite crystal formation and bone mineralization.



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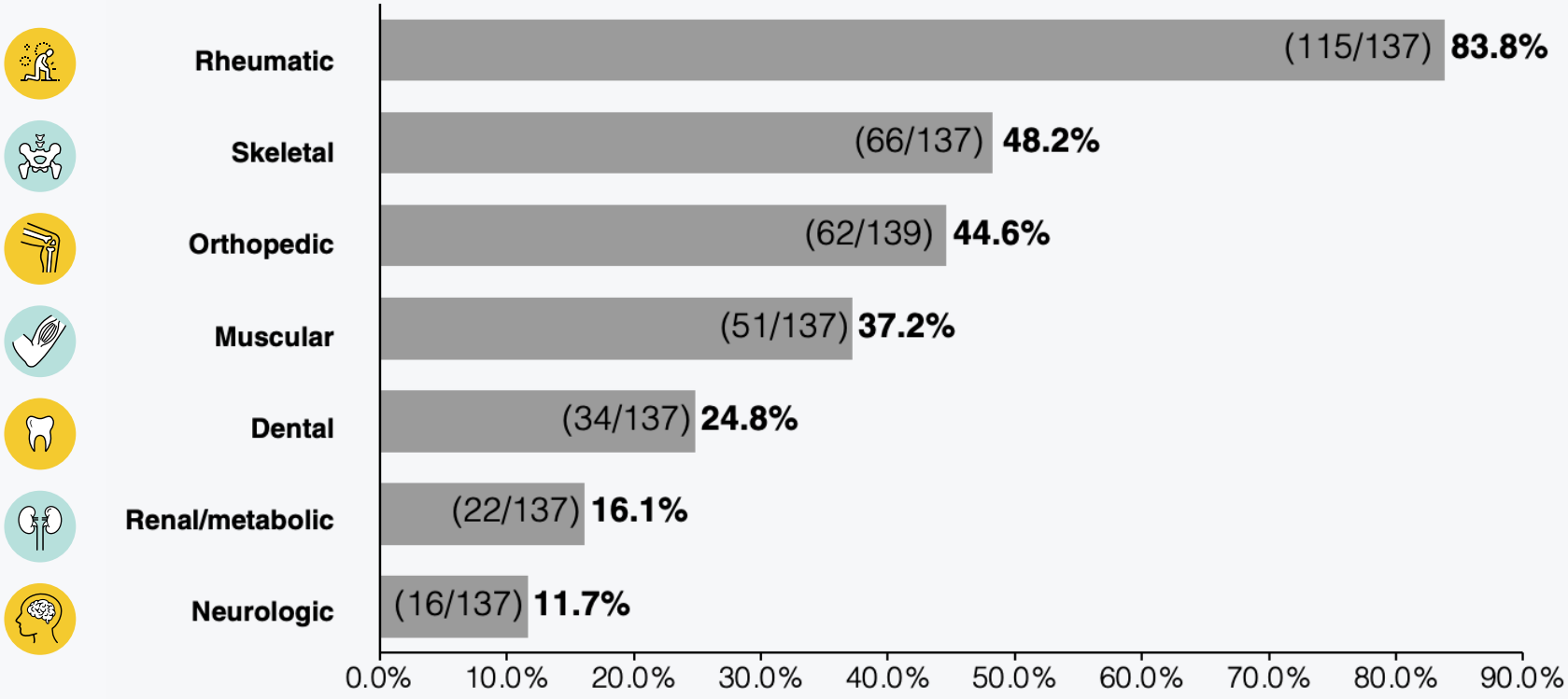
HPP Is Characterized by a Range of Signs and Symptoms

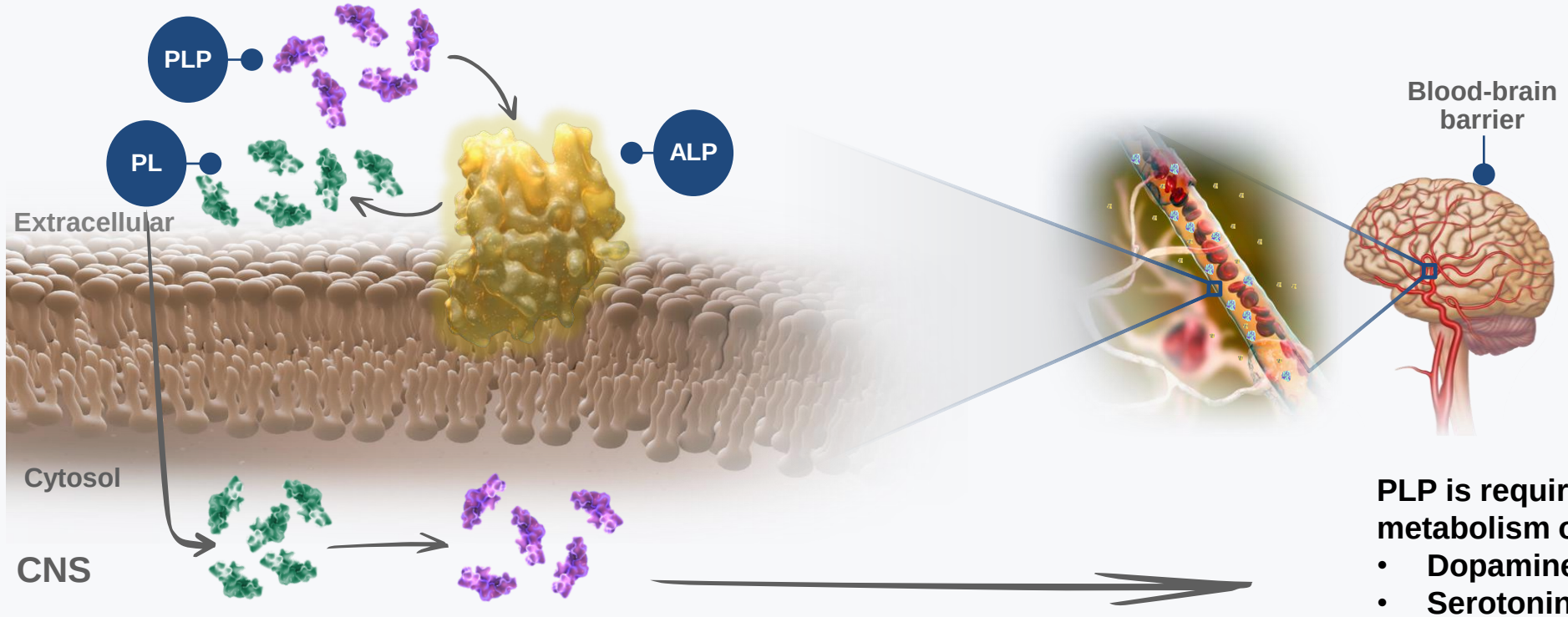


Observational, multinational, prospective Global HPP Registry study conducted in adults (n=148; ≥ 18 years) from January 2015 - September 2017

HPP, hypophosphatasia.
Högler W. *BMC Musculoskelet Disord*. 2019;20(1):80.

Low ALP Activity May Lead to Neurological Symptoms in HPP[1-4]

Under normal circumstances



PLP is required for metabolism of[2,3]:

- **Dopamine**
- **Serotonin**
- **GABA**

Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes.

ALP, alkaline phosphatase; CNS, central nervous system; GABA, gamma-aminobutyric acid; HPP, hypophosphatasia; PL, pyridoxal; PLP, pyridoxal 5'-phosphate.

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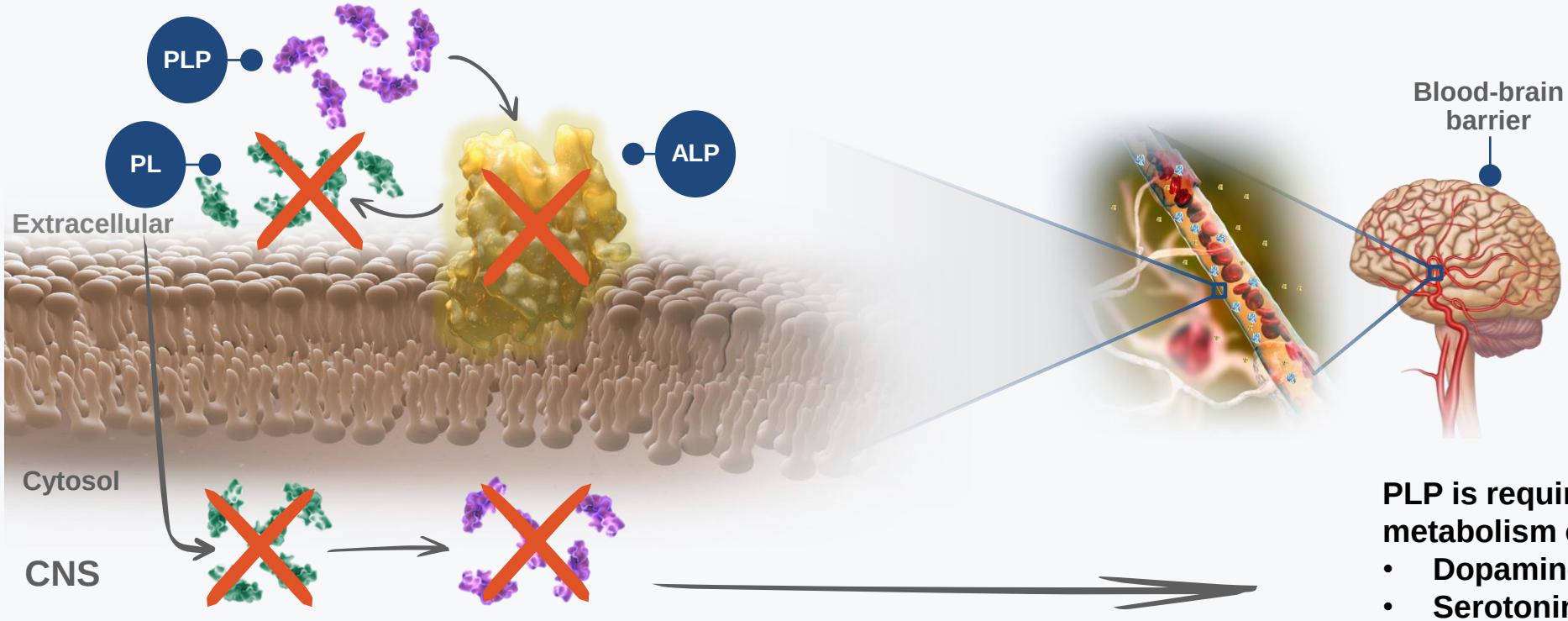
Low ALP Activity May Lead to Neurological Symptoms in HPP[1-4]

In HPP



PLP (ie, active form of vitamin B6) deficiency in the CNS results in deficient GABA activity

PLP is required for metabolism of[2,3]:

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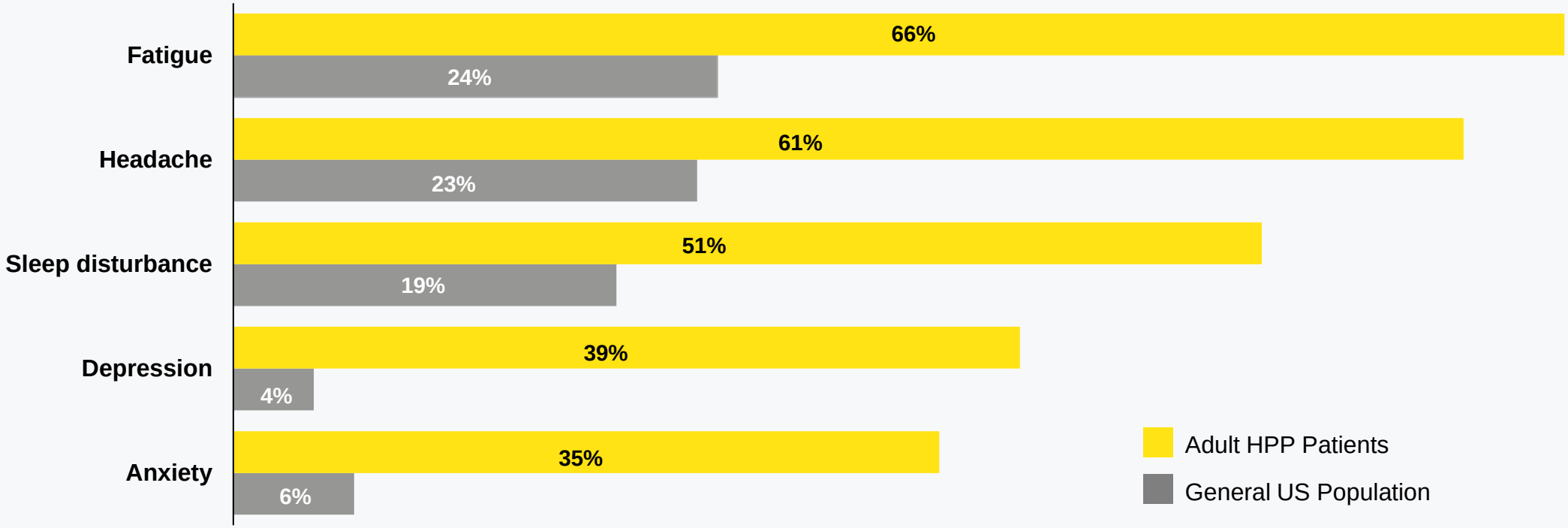
Neurological Symptoms May Occur in Adult Patients Living With HPP

- Along with skeletal and dental symptoms, adult patients with HPP have a higher prevalence of neurological symptoms compared to the general US population

A retrospective chart review studied the prevalence of common neurological symptoms with HPP

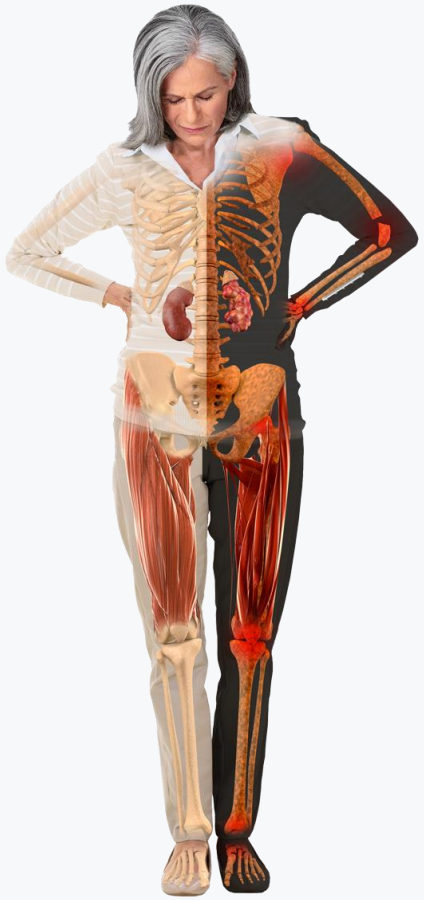
Prevalence of neurological symptoms in adults with HPP (N=82) compared to the general US population



HPP, hypophosphatasia.

Colazo JM. *Osteoporos Int*. 2019;30(2):469-480.

HPP Is a Multisystemic Disorder[1]



HPP is a heterogeneous disease. Signs and symptoms can include[1]

Dental[1-5]	• Premature tooth loss • Abnormal dentition • Periodontal disease
Skeletal[1,6-10]	• Rickets/osteomalacia • Skeletal deformities (eg, short stature, bowed legs, etc) • Frequent fractures (nontraumatic and nonhealing)
Muscular/ rheumatologic[1,11-13]	• Muscle weakness/pain • CPPD/pseudogout/chondrocalcinosis • Bone/joint pain
Renal[1,14-17]	Hypercalcemia/hypercalciuria leading to • Nephrocalcinosis • Renal damage
Neurologic[18]	• Fatigue • Sleep disturbance • Mood disorders

Click for example X-Ray

Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes. Source: Gettyimages. Patient image is hypothetical.

CPPD, calcium pyrophosphate dihydrate crystal deposition disease; HPP, hypophosphatasia.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Reibel A. *Orphanet J Rare Dis.* 2009;4:6. 3. Whyte MP. *Am J Med.* 1982;72(4):631-641. 4. Foster BL. *J Dent Res*. 2014;93(7):7S-19S. 5. Watanabe H. *J Periodontol.* 1993;64(3):174-180. 6. Whyte MP. *N Engl J Med*. 2012;366(10):904-913. 7. Beck C. *Rheumatol Int.* 2011;31(10):1315-1320. 8. Coe JD. *Bone Joint Surg Am.* 1986;68(7):981-990. 9. Gagnon C. *J Clin Endocrinol Metab.* 2010;95(3):1007-1012. 10. Schalin-Jäntti C. *J Clin Endocrinol Metab.* 2010;95(12):5174-5179. 11. Seshia SS. *Arch Dis Child.* 1990;65(1):130-131. 12. Data on file. New Haven, CT: Alexion Pharmaceuticals. 13. Chuck AJ. *Ann Rheum Dis*. 1989;48(7):571-576. 14. Mohn A. *Acta Paediatr*. 2011;100(7):e43-e46. 15. Whyte MP. *Genetics Bon Biol and Skel Dis*. 2013:337-360. 16. Eade AWT. *Ann Rheum Dis*. 1981;40(2):164-170. 17. Whyte MP. *Clin Endocrinol Metab*. 2013;98(12):4606-4612. 18. Colazo JM. *Osteoporos Int*. 2019;30(2):469-480.

ALEXION® AstraZeneca Rare Disease

Adult Patients With HPP May Experience Unpredictable, Devastating, and Life-Limiting Consequences[1]

The Global HPP Registry results highlighted the challenges associated with HPP for many adults living with HPP, regardless of age of onset[2]*

PAIN

- Adults with HPP **frequently experience pain[2]**
- Some patients may require pain medication, **including opioids[2]**

DIMINISHED QUALITY OF LIFE

- **Physical and mental functioning is affected[2]**
- Quality-of-life ratings are **worse than in the general population[2]**

DISABILITY

- May require the use of assistive devices, such as **crutches[2]**
- In an HPP Outcomes Study Telephone (HOST) interview in adults, **walking and climbing/descending stairs were most problematic** for patients with HPP (n=36)[3]

*The study included 304 adults with a confirmed diagnosis of HPP from a total of 57 participating study sites in 14 countries.
HPP, hypophosphatasia.
1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Seefried L. *J Bone Miner Res*. 2020;35(11):2171-2178. 3. Weber TJ. *Metabolism.* 2016;65(10):1522-1530.

Low ALP Can Differentiate HPP From Other Metabolic Disorders[1]

	ALP	Calcium	Phosphate	Vitamin D	Parathyroid hormone
HPP	↓	↑ or Normal	↑ or Normal	Normal	↓ or Normal
X-linked hypophosphatemic rickets	↑	Normal	↓	↓ or Normal	Normal
Nutritional rickets	↑	↓	↓	↓	↑
Osteogenesis imperfecta	Normal to transiently ↓	Normal	Normal	↓ or Normal	Normal

ALP, alkaline phosphatase; HPP, hypophosphatasia.

1. Bloch-Zupan A. *Int J Paediatr Dent*. 2016;26(6):426-438.

Early Diagnosis of HPP Is Important to Prevent Further Complications[1]

- HPP is often misdiagnosed because it resembles other musculoskeletal diseases in clinical presentations and imaging[2]
- Misdiagnosis can lead to mismanagement and the use of ineffective or potentially harmful therapies that add further complications[1,3]

Misdiagnosis	Treatment	Potential Impact on Patients With HPP
Osteoporosis*	Bisphosphonates	Can increase risk of atypical femoral fractures in adults[1,3]
	Recombinant human parathyroid hormone	Does not address the underlying cause of HPP[2]
Nutritional rickets	Vitamin D and calcium	Can lead to hypercalcemia and hypercalciuria with nephrocalcinosis[1]
CPPD/Pseudogout or Fibromyalgia[4]	Analgesics[5]	Does not address the underlying cause of HPP[6]
XLH	High-dose vitamin D,[7,8] phosphate	Can exacerbate hypercalcemia and hypercalciuria[2]

In most cases, HPP can be diagnosed based on low levels of ALP activity, clinical presentation, and radiologic findings[2]

*Other treatments for osteoporosis (eg, denosumab) may have adverse effects in adults with HPP.[9]

ALP, alkaline phosphatase; CPPD, Calcium pyrophosphate dihydrate crystal deposition disease; HPP, hypophosphatasia; XLH, X-linked hypophosphatemia.

1. Weber TJ. *Metabolism*. 2016;65(10):1522-1530. 2. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 3. Sutton RA. *J Bone and Miner Res*. 2012;27(5):987-994. 4. Braunstein N. *Bone Rep.* 2015;4:1-4. 5. Mahagna H. *Int J Clin Pract*. 2016;70(2):163-170. 6. Guañabens N. *J Bone Miner Res*. 2014;29(4):929-934. 7. Shore RM. Rickets: Part I. *Pediatr Radiol*. 2013;43(2):140-151. 8. Shore RM. Rickets: Part II. *Pediatr Radiol.* 2013;43(2):152-172. 9. Shapiro JR. *J Bone and Miner Res*. 2017;32(10):1977-1980.

Any of These Key Signs and Symptoms Plus Persistently Low ALP Is Sufficient to Diagnose HPP[1-3]

Not all signs and symptoms need to be present for a patient to be diagnosed with HPP[1]

Skeletal[1,3-5]

Bone/joint pain, fractures, rickets, osteomalacia, pseudofractures, osteopenia, skeletal deformities

Development/ Growth[1,3]

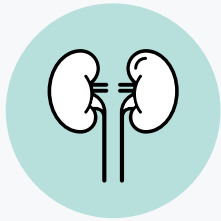
Short stature, bowing, missed milestones in childhood

Respiratory[1,3,6-8]

Rachitic chest, pneumonia, pulmonary insufficiency

Neurologic[9]

Fatigue, headache, sleep disturbances, mood disorder, seizures



Renal[1,4,10]

Hypercalcemia, hypercalciuria, nephrocalcinosis

Muscular[1]

Muscle pain or weakness, waddling gait, difficulty walking

Dental[1]

Premature tooth loss, abnormal dentition, periodontal disease

Persistently Low ALP (<40 U/L) for adults[11-15]*

Diagnose HPP

***Limitations:** An ALP level of below 40 U/L is not conclusive for diagnosis of HPP. Patient should be evaluated for other symptoms of HPP and differential diagnoses should be ruled out. Check with your lab for their appropriate age- and sex-adjusted reference range.

ALP, alkaline phosphatase; HPP, hypophosphatasia.
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To go back

Key Learnings From Ellen's Story

Patient image is hypothetical.

Low ALP is the biochemical hallmark of HPP and can differentiate HPP from other conditions[1,2]

HPP is characterized by a range of multisystemic signs and symptoms, including neurological complications[3]

HPP is associated with a high burden of disease and reduced quality of life in adults[4]

HPP should be considered in patients with key signs/symptoms and persistently low ALP (<40 U/L)[1,5-9*] in adults

***Limitations:** An ALP level of below 40 U/L is not conclusive for diagnosis of HPP. Patient should be evaluated for other symptoms of HPP and differential diagnoses should be ruled out. Check with your lab for their appropriate age- and sex-adjusted reference range.

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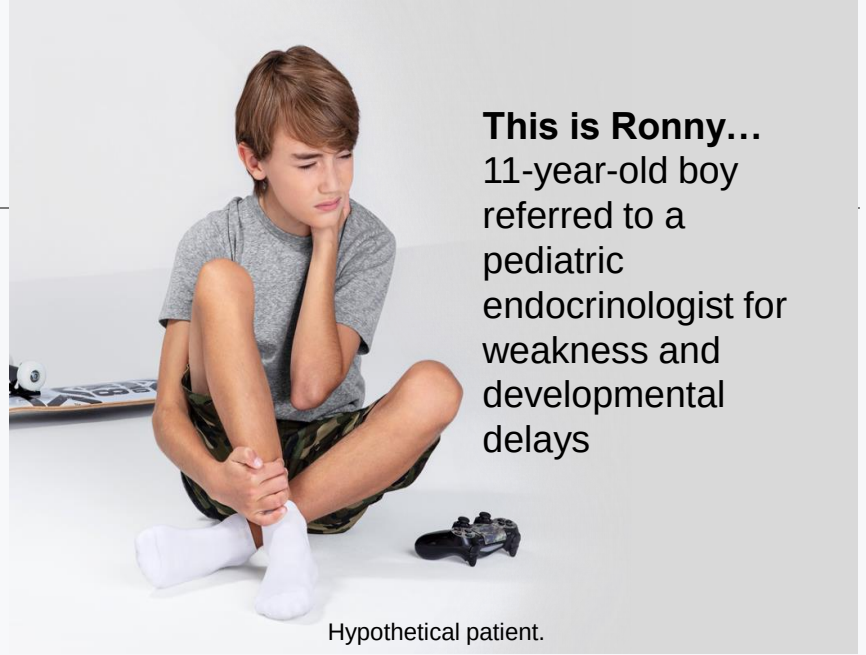
Case Study: Identifying and Diagnosing HPP



This is Ronny…
11-year-old boy referred to a pediatric endocrinologist for weakness and developmental delays

Hypothetical patient.

History of presenting illness

- Falling behind peers in growth and experiencing delayed motor development
- Short stature, mild bowing of the legs, and a slight waddling gait
- Complains of feeling weak and tired, and experiences anxiety at school while interacting with his peers

Medical history	History of dental abscesses; delayed walking; missed multiple motor milestones
Social history	Has been behind peers in motor milestones and stature; struggles keeping up with peers in physical activities
Family history	Type 2 diabetes and hypertension (father)
Medications	None

Lab results show low ALP but is not noted as a concern by the physician

Labs (abnormal values flagged)	
Calcium, mg/dL	10.0
Phosphorus, mg/dL	4.1
Vitamin D, 25-Hydroxy, ng/mL	56
ALP, IU/L	**111***
PTH, ng/L	25

Check with your lab for their appropriate age- and sex-adjusted reference range.

*Age- and sex- adjusted normal range, 141-460 U/L.[1-5]
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ALP Levels†

PRECIPITOUSLY LOW	TRANSIENTLY LOW	PERSISTENTLY LOW
• Multiple myeloma or other cancers	• Osteogenesis imperfecta type II	• Hypophosphatasia
• Cardiac bypass surgery	• Profound hypothyroidism	• Cleidocranial dysplasia
• Major trauma or surgery	• Cushing disease	• Mseleni joint disease
• Chemotherapy	• Bisphosphonate therapy	
• Transfusion (often massive)	• Adynamic renal osteodystrophy	
• Starvation	• Milk-alkali syndrome	
• Sepsis/multi-organ/hepatic failure	• Vitamin D intoxication	
	• Wilson disease	
	• Celiac disease	

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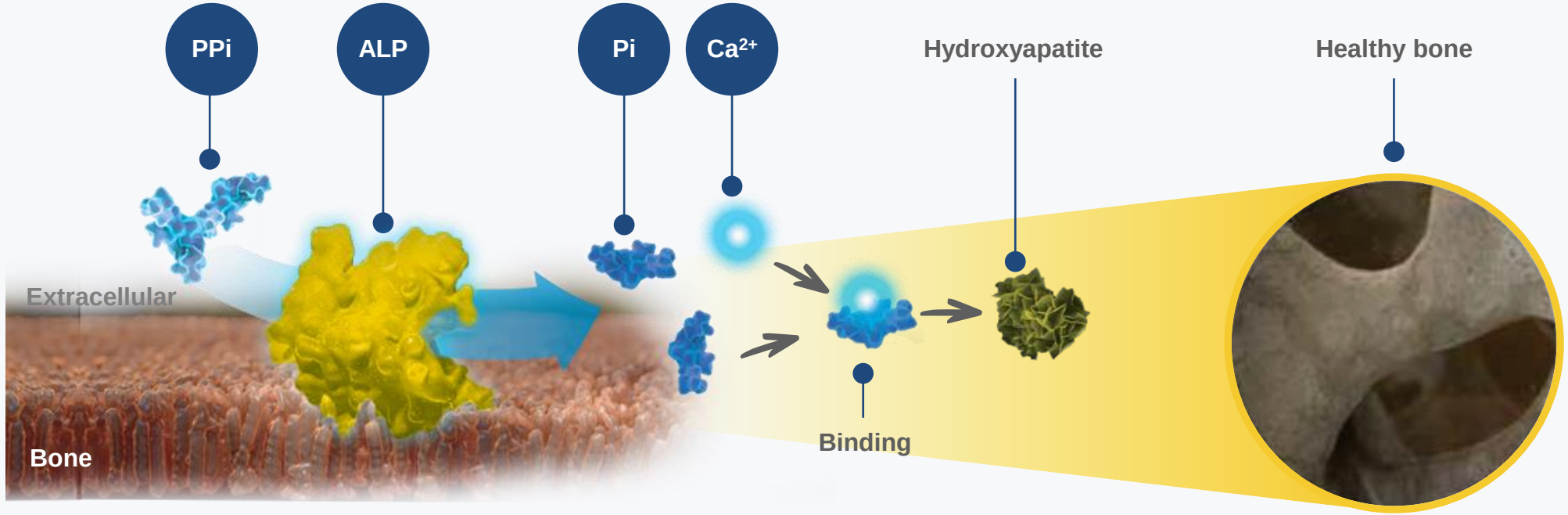

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Mutations in the *ALPL* gene cause low ALP activity.

PPi accumulates and prevents hydroxyapatite crystal formation and bone mineralization.

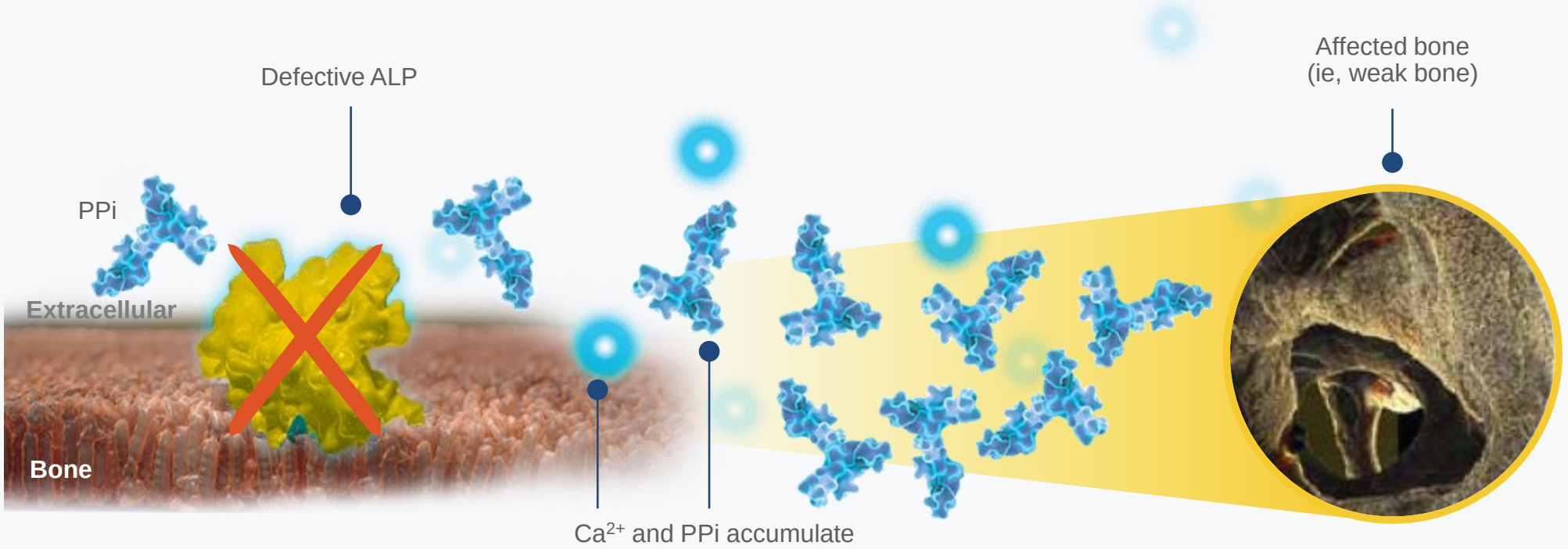


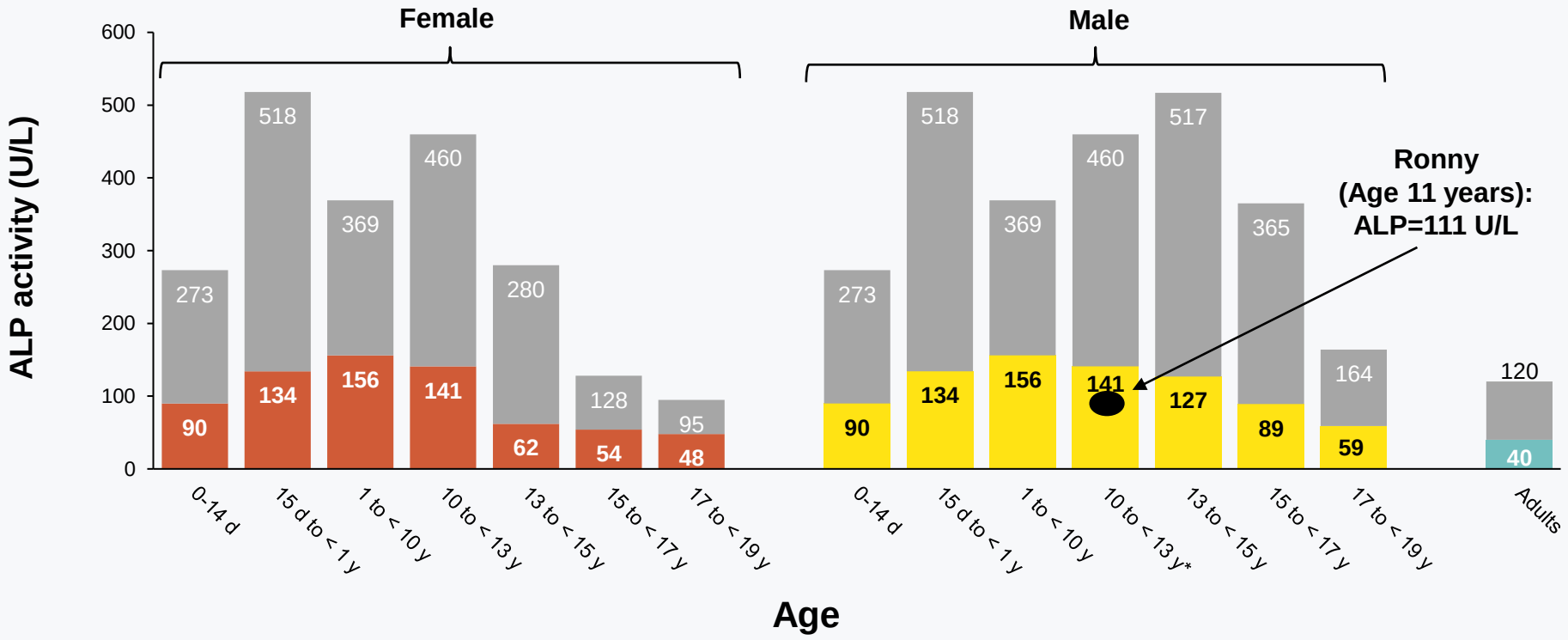
Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes.

ALP, alkaline phosphatase; Ca^{2+}, calcium; HPP, hypophosphatasia; PPi, inorganic pyrophosphate.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Whyte M. Hypophosphatasia. In: *Genetics of Bone Biology and Skeletal Disease.* Elsevier Inc; 2013:337-360.

Age- and Sex-Adjusted ALP Reference Intervals Must Be Used to Correctly Diagnose HPP, Especially in Childhood[1,2]

Age- and Sex-Adjusted ALP Reference Ranges (U/L)[2-7*]



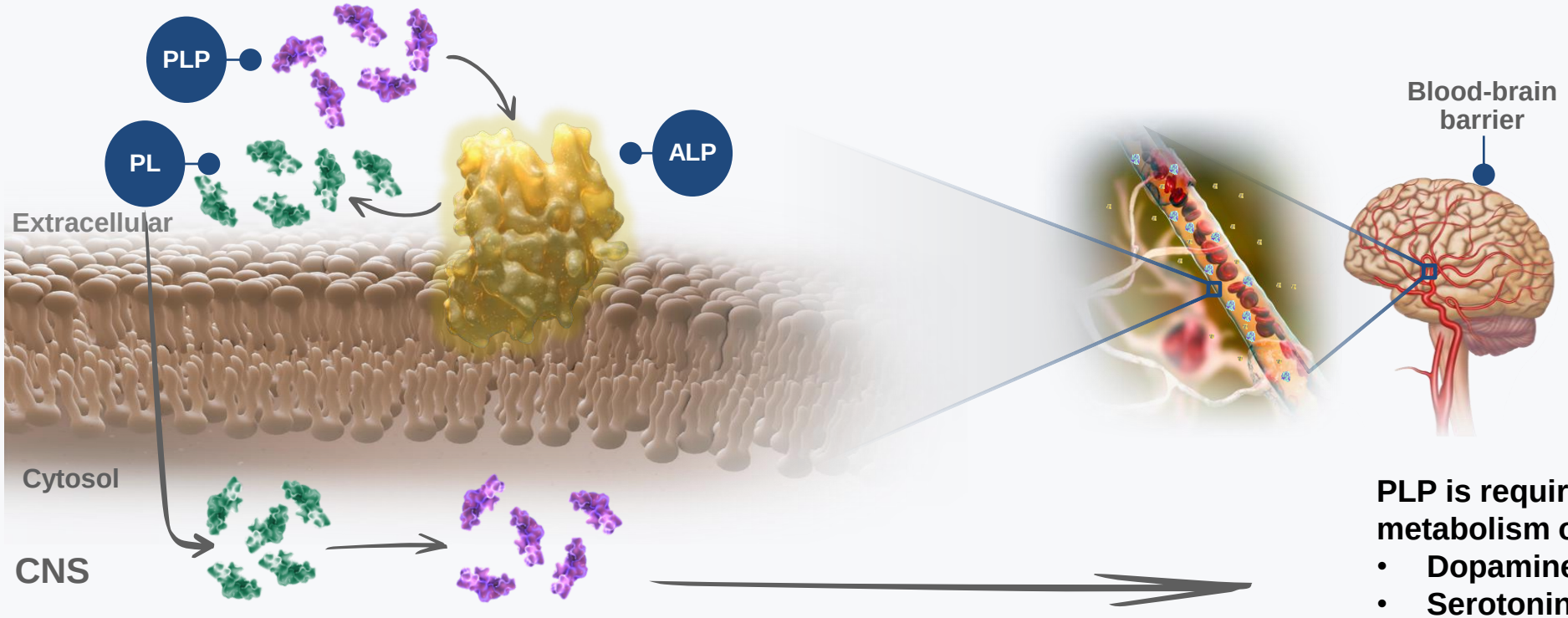
NOTE: Graph adapted from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project (Colantonio, et al. 2012). CALIPER samples from 1072 male and 1116 female participants (newborn to 18 years) were used to calculate age- and sex-specific reference intervals. No variation in ALP based on ethnic differences was observed.

*Age- and sex-adjusted normal range, 40-120 U/L.[3-7]
Limitations: Check with your lab for their appropriate age- and sex-adjusted reference range.
ALP, alkaline phosphatase; HPP, hypophosphatasia.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. 2. Colantonio DA. *Clin Chemistry*. 2012;58(5):854-868. 3. Adeli K. *Clin Chem*. 2015;61(8):1049-1062. 4. Schumann G. *Clin Chem Lab Med*. 2011;49(9):1439-1446. 5. Quest Diagnostics. Alkaline phosphatase. Accessed April 12, 2021. https://testdirectory.questdiagnostics.com/test/test-detail/234/alkaline-phosphatase?cc=MASTER 6. Labcorp. Alkaline phosphatase. Accessed April 12, 2021. https://www.labcorp.com/tests/001107/alkaline-phosphatase 7. ARUP Laboratories. Alkaline phosphatase isoenzymes, serum or plasma. Accessed April 12, 2021. https://ltd.aruplab.com/Tests/Pub/0021020

Low ALP Activity May Lead to Neurological Symptoms in HPP[1-4]

Under normal circumstances



PLP is required for metabolism of[2,3]:

- **Dopamine**
- **Serotonin**
- **GABA**

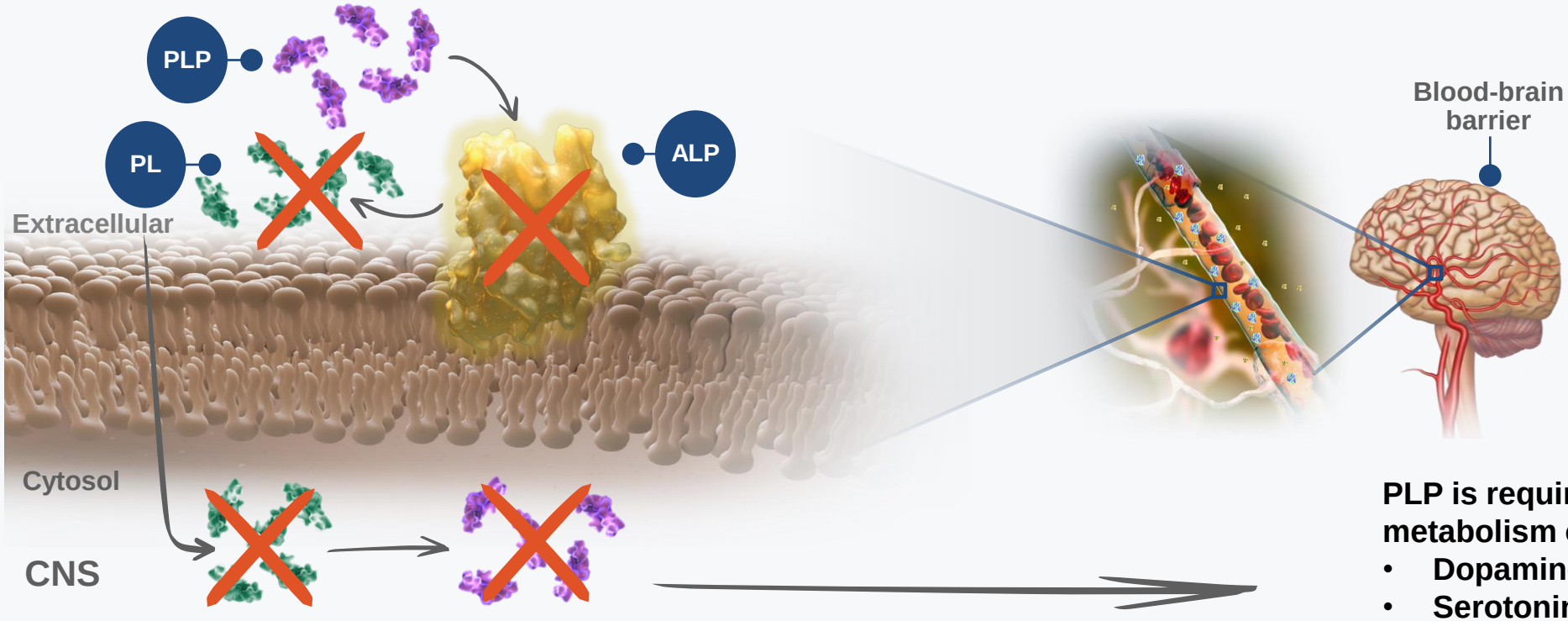
Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes.

ALP, alkaline phosphatase; CNS, central nervous system; GABA, gamma-aminobutyric acid; HPP, hypophosphatasia; PL, pyridoxal; PLP, pyridoxal 5'-phosphate.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Taketani T. *Subcell Biochem*. 2015;76:309-322. 3. Surtees R. *Future Neurol*. 2006;1(5):615-620. 4. Colazo JM. *Osteoporos Int*. 2019;30(2):469-480.

Low ALP Activity May Lead to Neurological Symptoms in HPP[1-4]

In HPP



PLP (ie, active form of vitamin B6) deficiency in the CNS results in deficient GABA activity

PLP is required for metabolism of[2,3]:

- **Dopamine**
- **Serotonin**
- **GABA**

Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes.

ALP, alkaline phosphatase; CNS, central nervous system; GABA, gamma-aminobutyric acid. HPP, hypophosphatasia; PL, pyridoxal; PLP, pyridoxal 5'-phosphate.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Taketani T. *Subcell Biochem*. 2015;76:309-322. 3. Surtees R. *Future Neurol*. 2006;1(5):615-620. 4. Colazo JM. *Osteoporos Int*. 2019;30(2):469-480.

HPP Is a Multisystemic Disorder[1]

HPP is a heterogeneous disease. Signs and symptoms can include[1]

Dental[1-5]	• Premature tooth loss • Abnormal dentition • Periodontal disease
Skeletal[1,6-10]	• Rickets/osteomalacia • Skeletal deformities (eg, short stature, bowed legs, etc) • Frequent fractures (nontraumatic and nonhealing)
Muscular/ rheumatologic[1,11-13]	• Muscle weakness/pain • CPPD/pseudogout/chondrocalcinosis • Bone/joint pain
Renal[1,14-17]	Hypercalcemia/hypercalciuria leading to • Nephrocalcinosis • Renal damage
Neurologic[18]	• Fatigue • Sleep disturbance • Mood disorders

Click for example X-Ray

Image created for Alexion Pharmaceuticals, Inc. for illustrative purposes. Source: Gettyimages. Patient image is hypothetical.

CPPD, calcium pyrophosphate dihydrate crystal deposition disease; HPP, hypophosphatasia.

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Reibel A. *Orphanet J Rare Dis.* 2009;4:6. 3. Whyte MP. *Am J Med.* 1982;72(4):631-641. 4. Foster BL. *J Dent Res*. 2014;93(7):7S-19S. 5. Watanabe H. *J Periodontol.* 1993;64(3):174-180. 6. Whyte MP. *N Engl J Med*. 2012;366(10):904-913. 7. Beck C. *Rheumatol Int.* 2011;31(10):1315-1320. 8. Coe JD. *Bone Joint Surg Am.* 1986;68(7):981-990. 9. Gagnon C. *J Clin Endocrinol Metab.* 2010;95(3):1007-1012. 10. Schalin-Jäntti C. *J Clin Endocrinol Metab.* 2010;95(12):5174-5179. 11. Seshia SS. *Arch Dis Child.* 1990;65(1):130-131. 12. Data on file. New Haven, CT: Alexion Pharmaceuticals. 13. Chuck AJ. *Ann Rheum Dis*. 1989;48(7):571-576. 14. Mohn A. *Acta Paediatr*. 2011;100(7):e43-e46. 15. Whyte MP. *Genetics Bon Biol and Skel Dis*. 2013:337-360. 16. Eade AWT. *Ann Rheum Dis*. 1981;40(2):164-170. 17. Whyte MP. *Clin Endocrinol Metab*. 2013;98(12):4606-4612. 18. Colazo JM. *Osteoporos Int*. 2019;30(2):469-480.

ALEXION® AstraZeneca Rare Disease

Pediatric Patients With HPP May Experience Unpredictable, Devastating, and Life-Limiting Consequences[1]

In one study, parent ratings of their children's overall quality of life indicated clinically meaningful impairment in[2]*:

PAIN, SLEEP, AND MOOD

- For some children (7/24), pain associated with skeletal and muscle symptoms **interfered with their typical daily activities[2]**
- More than half of the children (17/30) were classified as **poor sleepers[2]**
- Children with HPP (13/30) showed greater symptomatology than healthy children on the **Depression scale[2]**

QUALITY OF LIFE

- **Reductions in quality of life** were consistent with a major chronic health condition (15/30)[2]
- In nearly all cases, sleep, pain, and mood issues were accompanied by **reduced quality of life[2]**

*The study consisted of parents/caregivers of 30 eligible children with HPP under the age of 18 years.[2]
HPP, hypophosphatasia.
1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Pierpont E. *Orphanet J Rare Dis.* 2021;16(1):80.

Low ALP Can Differentiate HPP From Other Metabolic Disorders[1]

	ALP	Calcium	Phosphate	Vitamin D	Parathyroid hormone
HPP	↓	↑ or Normal	↑ or Normal	Normal	↓ or Normal
X-linked hypophosphatemic rickets	↑	Normal	↓	↓ or Normal	Normal
Nutritional rickets	↑	↓	↓	↓	↑
Osteogenesis imperfecta	Normal to transiently ↓	Normal	Normal	↓ or Normal	Normal

ALP, alkaline phosphatase; HPP, hypophosphatasia.

1. Bloch-Zupan. *Int J Paediatr Dent*. 2016;26(6):426-438.

Early Diagnosis of HPP Is Important to Prevent Further Complications[1]

- HPP is often misdiagnosed because it resembles other musculoskeletal diseases in clinical presentations and imaging[2]
- Misdiagnosis can lead to mismanagement and the use of ineffective or potentially harmful therapies that add further complications[1,3]

Misdiagnosis	Treatment	Potential Impact on Patients With HPP
Osteoporosis*	Bisphosphonates	Can increase risk of atypical femoral fractures in adults[1,3]
	Recombinant human parathyroid hormone	Does not address the underlying cause of HPP[2]
Nutritional rickets	Vitamin D and calcium	Can lead to hypercalcemia and hypercalciuria with nephrocalcinosis[1]
CPPD/Pseudogout or Fibromyalgia[4]	Analgesics[5]	Does not address the underlying cause of HPP[6]
XLH	High-dose vitamin D,[7,8] phosphate	Can exacerbate hypercalcemia and hypercalciuria[2]

In most cases, HPP can be diagnosed based on low levels of ALP activity, clinical presentation, and radiologic findings[2]

*Other treatments for osteoporosis (eg, denosumab) may have adverse effects in adults with HPP.[9]

ALP, alkaline phosphatase; CPPD, Calcium pyrophosphate dihydrate crystal deposition disease; HPP, hypophosphatasia; XLH, X-linked hypophosphatemia.

1. Weber TJ. *Metabolism*. 2016;65(10):1522-1530. 2. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 3. Sutton RA. *J Bone and Miner Res*. 2012;27(5):987-994. 4. Braunstein N. *Bone Rep.* 2015;4:1-4. 5. Mahagna H. *Int J Clin Pract*. 2016;70(2):163-170. 6. Guañabens N. *J Bone Miner Res*. 2014;29(4):929-934. 7. Shore RM. Rickets: Part I. *Pediatr Radiol*. 2013;43(2):140-151. 8. Shore RM. Rickets: Part II. *Pediatr Radiol.* 2013;43(2):152-172. 9. Shapiro JR. *J Bone and Miner Res*. 2017;32(10):1977-1980.

Any of These Key Signs and Symptoms Plus Persistently Low ALP Is Sufficient to Diagnose HPP[1-3]

Not all signs and symptoms need to be present for a patient to be diagnosed with HPP[1]

Skeletal[1,3-5]

Bone/joint pain, fractures, rickets, osteomalacia, pseudofractures, osteopenia, skeletal deformities

Development/ Growth[1,3]

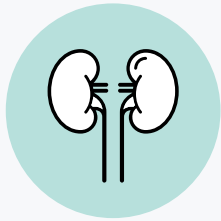
Missed milestones, failure to thrive, bowing, short stature

Respiratory[1,3,6-8]

Rachitic chest, pneumonia, pulmonary insufficiency

Neurologic[9]

Fatigue, headache, sleep disturbances, mood disorder, seizures



Renal[1,4,10]

Hypercalcemia, hypercalciuria, nephrocalcinosis

Muscular[1]

Muscle pain or weakness, waddling gait, difficulty walking

Dental[1]

Premature tooth loss, abnormal dentition, periodontal disease

Persistently Low ALP (age- and sex-adjusted)[11-15]

Diagnose HPP

ALP, alkaline phosphatase; HPP, hypophosphatasia.
1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. 2. Mornet E. *GeneReviews®*. Accessed April 14, 2021. 3. Whyte MP. *Princ Bone Biol*. 2008:1573-1598. 4. Whyte MP. *Genetics Bon Biol and Skel Dis*. 2013:337-360. 5. Zankl A. *Am J Med Genet Part A*. 2008;146A(9):1200-1204. 6. Baumgartner-Sigl S. *Bone*. 2007;40(6):1655-1661. 7. Balasubramaniam S. *J Inherit Metab Dis*. 2010;33(3):25-33. 8. Silver MM. *Pediatr Pathol*. 1988;8(5):483-493. 9. Colazo JM. *Osteoporos Int*. 2019;30(2):469-480. 10. Fallon MD. *Medicine*. 1984;63(1):12-24. 11. Adeli K. *Clin Chem*. 2015;61(8):1049-1062. 12. Schumann G. *Clin Chem Lab Med*. 2011;49(9):1439-1446. 13. Quest Diagnostics. Alkaline phosphatase. Accessed April 12, 2021. https://testdirectory.questdiagnostics.com/test/test-detail/234/alkaline-phosphatase?cc=MASTER 14. Labcorp. Alkaline phosphatase. Accessed April 12, 2021. https://www.labcorp.com/tests/001107/alkaline-phosphatase 15. ARUP Laboratories. Alkaline phosphatase isoenzymes, serum or plasma. Accessed April 12, 2021. https://ltd.aruplab.com/Tests/Pub/0021020

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Key Learnings From Ronny's Story


Patient image is hypothetical.

HPP is associated with a wide range of multisystemic complications[1]

HPP leads to a high disease burden and reduced quality of life in many children[2,3]

While HPP is an inherited disorder, diagnosis is based on low ALP and clinical signs and symptoms[3,5]

HPP should be considered in patients with key signs/symptoms and persistently low ALP (age- and sex-adjusted)[3,4]

ALP, alkaline phosphatase; HPP, hypophosphatasia.

1. Högler W. *BMC Musculoskelet Disord*. 2019;20(1):80. 2. Pierpont E. *Orphanet J Rare Dis*. 2021;16(1):80. 3. Rockman-Greenberg C. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. 4. Colantonio DA. *Clin Chem*. 2012;58(5):854-868. 5. Khan AA. *Osteoporos Int.* 2019;30(9):1713-1722.

Thank you!

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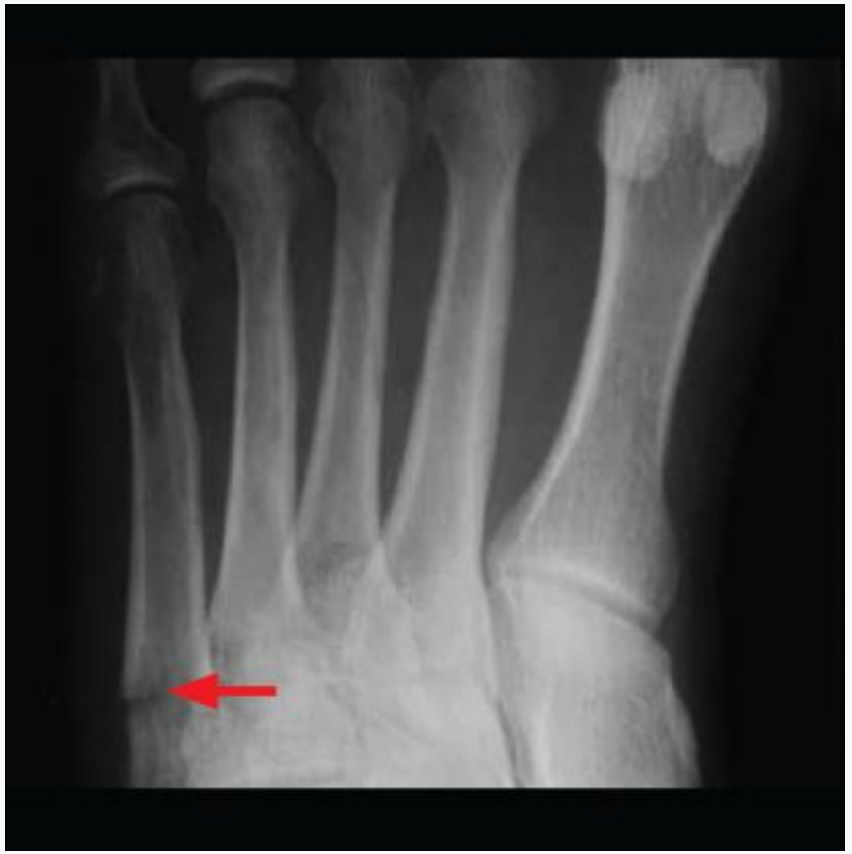
Appendix

Adult HPP – Left Foot



Radiograph: Recurrent, poorly healing, metatarsal stress fractures (arrow)

Age: 56 years old

HPP, hypophosphatasia.
Reproduced with permission from Whyte MP. Hypophosphatasia. In: Bilezikian JP. *Principles of Bone Biology*. 3rd ed. Cambridge, Massachusetts: Academic Press; 2008:1573-1598.

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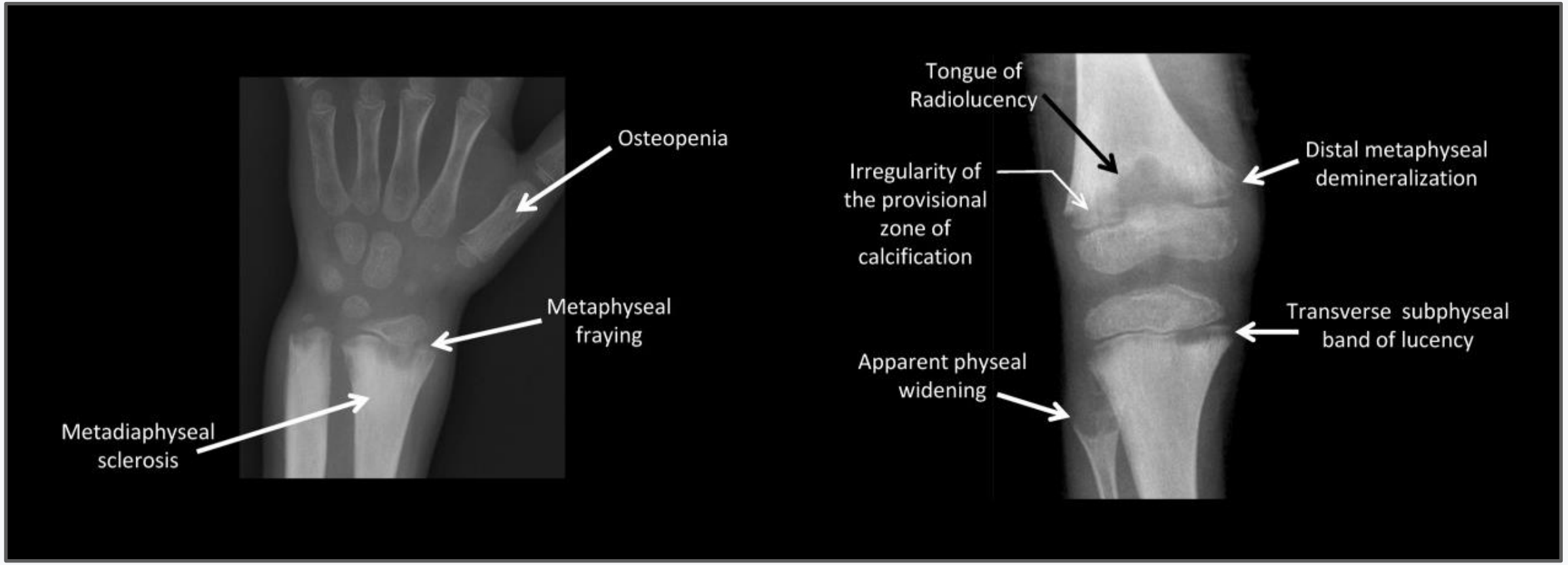
Pediatric HPP – Wrist and Knee



Age: 6 years old

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HPP, hypophosphatasia.
Reproduced with permission from Whyte MP. *JCI Insight*. 2016;1(9):e85971.