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OVERCOMING COMMON CHALLENGES ENCOUNTERED IN THE DIAGNOSIS OF RARE BONE DISEASE

AN INDEPENDENT SYMPOSIUM

23rd May 2022

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- The pharmaceutical companies that compose the consortium are **committed to** joining forces to **raise awareness of rare bone disease** through medical education, with the intention of **improving outcomes in rare bone diseases and quality of life for people living with them**

- **Please note:** The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

EXPERT FACULTY

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Richard Keen

London, United Kingdom

Maria Luisa Brandi

Florence, Italy

Lothar Seefried

Würzburg, Germany

AGENDA

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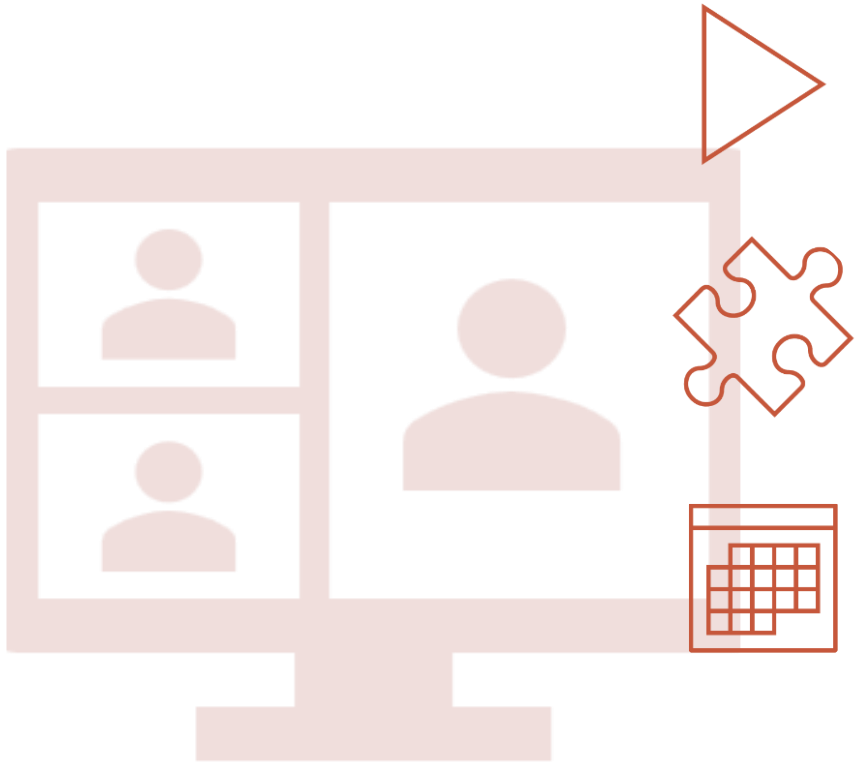
Common challenges encountered in the diagnosis of rare bone disease:



Challenges in fibrodysplasia ossificans progressiva

Richard Keen (UK)

Challenges in FGF23-related hypophosphataemic rickets/osteomalacia

Maria Luisa Brandi (Italy)

Challenges in hypophosphatasia

Lothar Seefried (Germany)

CHALLENGES IN FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

Professor Richard Keen

Royal National Orthopaedic Hospital, London, UK

richard.keen1@nhs.net

Royal National Orthopaedic Hospital NHS
NHS Trust

DISCLOSURES

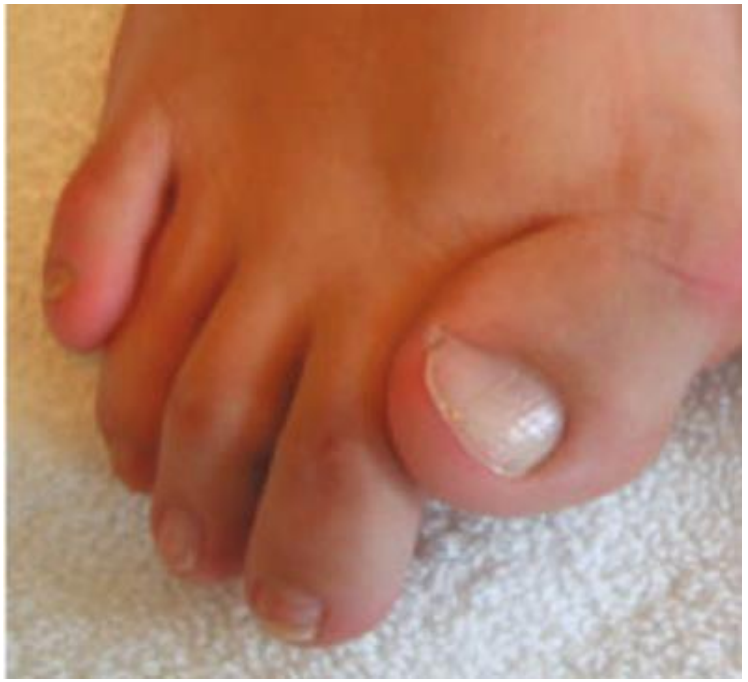
- **Research grants & educational grants:**
  - Ipsen, Kyowa Kirin, Mereo BioPharma, Regeneron Pharmaceuticals
- **Speakers Fees:**
  - Amgen, UCB
- **Consultancies:**
  - Alexion Pharmaceuticals, Ipsen, Kyowa Kirin
- **Other**
  - Brittle Bone Society Scientific Advisory Board, International Clinical Council on FOP, Royal Osteoporosis Society Bone Academy

What is Fibrodysplasia Ossificans Progressiva?

- Fibrodysplasia ossificans progressiva (FOP) (OMIM #135100) is a rare, severely disabling disease characterised by malformed big toes and progressive heterotopic ossification (HO) in muscles, tendons, and ligaments; it is often associated with painful, recurrent episodes of soft tissue swelling (flare-ups)
- The apparent prevalence of registered and confirmed FOP patients varies substantially from approximately 0.65 per million in North America, 0.47 per million in Western Europe, and 0.27 per million in Latin America, to 0.05 per million in Africa and nearly 0.04 per million in the Asia-Pacific region[1]
- Prevalence estimates are hampered by the ultra-rarity of FOP, heterogeneity of the disease, and access to medical services with appropriate diagnostic services

1. Liljesthrom M, et al. J Rare Dis Res Treat 2020; 5(2):31-6

Malformation of Big Toes



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"hallux valgus" | Options | View Results as: Gene Map Table | Clinical Synopsis | Display: Highlights

Search: '"hallux valgus" '
Results: 55 entries. Show 100 | Download As | « First | ‹ Previous | Next › | Last »

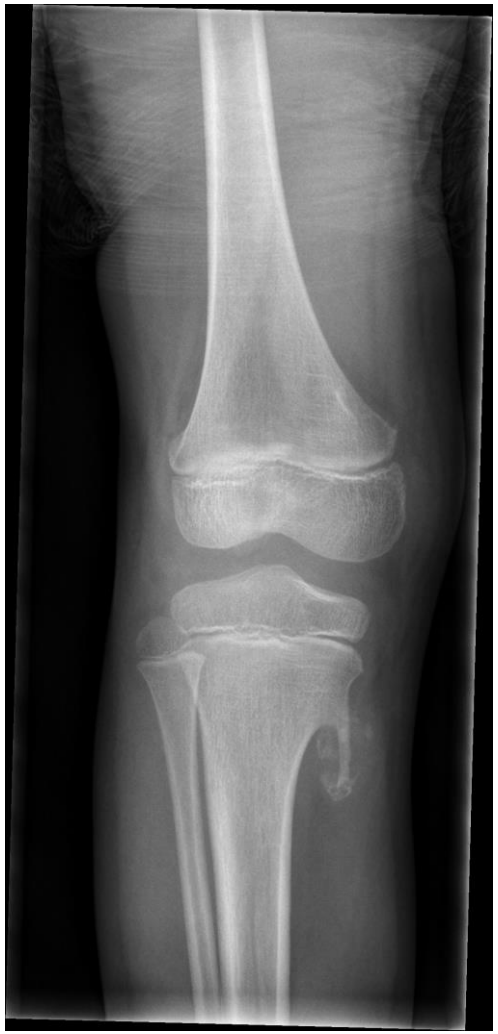
1: # 617180. CHITAYAT SYNDROME; CHYTS
Cytogenetic location: 19q13.2
Matching terms: "hallux valgus"
► Phenotype-Gene Relationships ► Links

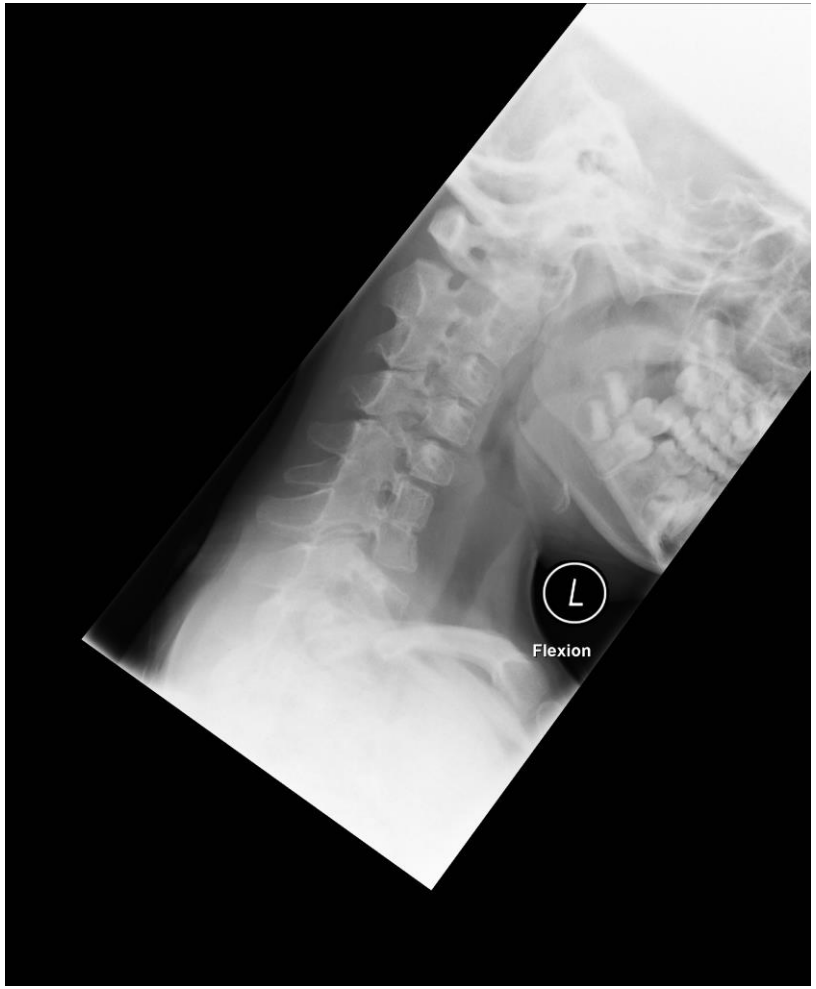
2: * 601622. TWIST FAMILY bHLH TRANSCRIPTION FACTOR 1; TWIST1
Cytogenetic location: 7p21.1, Genomic coordinates (GRCh38): 7:19,113,046-19,117,635
Matching terms: "hallux valgus"
► Gene-Phenotype Relationships ► ICD+ ► Links

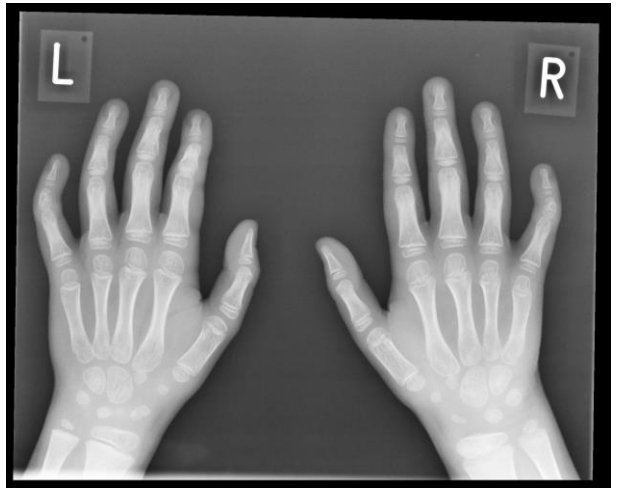
3: 211910. CAMPTODACTYLY SYNDROME, GUADALAJARA, TYPE I; GCS1
Matching terms: "hallux valgus"
► ICD+ ► Links

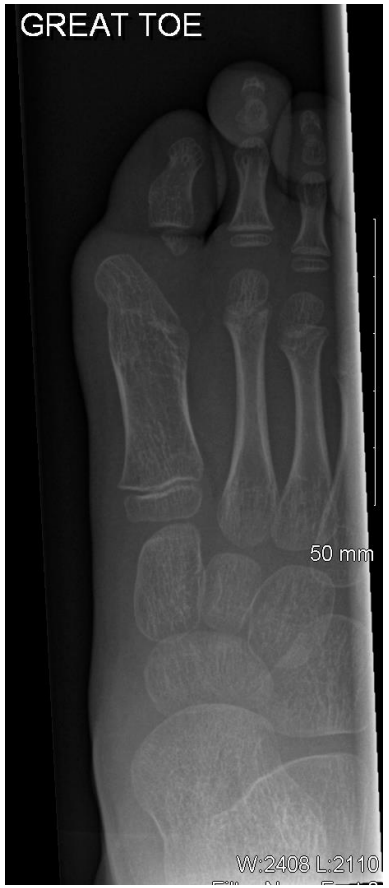
4: # 101400. SAETHRE-CHOTZEN SYNDROME; SCS
SAETHRE-CHOTZEN SYNDROME WITH EYELID ANOMALIES, INCLUDED
Cytogenetic locations: 7p21.1, 10q26.13

Radiological Features









Keen, R. Personal communication

Genetic Diagnosis

- The diagnosis of FOP is clinical, but requires genetic confirmation

- FOP is caused by heterozygous activating mutations in activin A receptor, type I/activin-like kinase 2 (ACVR1/ALK2), which is a bone morphogenetic protein (BMP) type I receptor

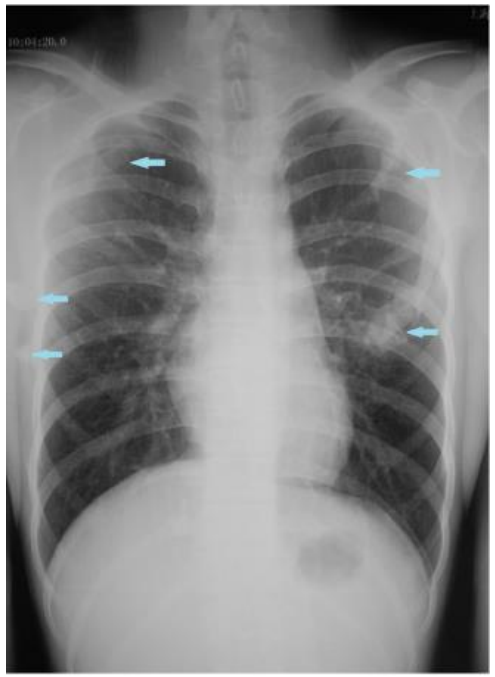
- The most authoritative indicator is the detection of the *ACVR1* gene mutation
  - ~97% of cases have the classic c.617G>A mutation resulting in the substitution of arginine by histidine at codon 206 (p.R206H)

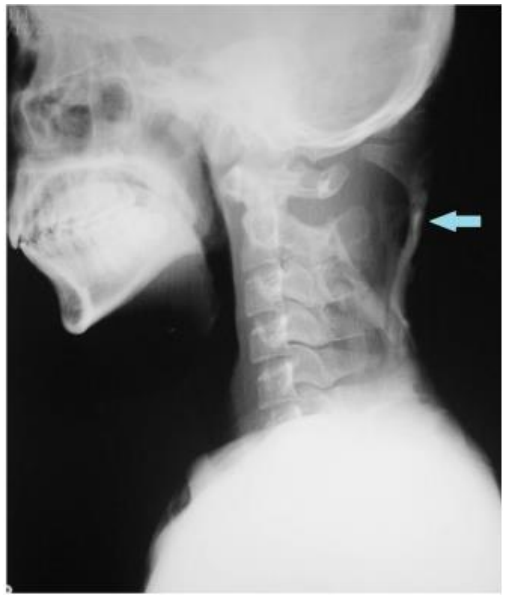
FOP, fibrodysplasia ossificans progressive

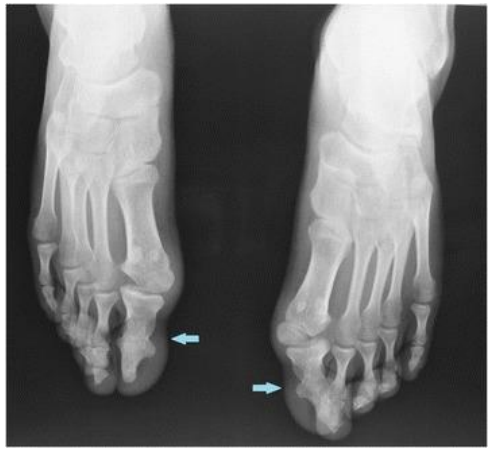
Kaplan FS, et al. Hum Mutat. 2009;30(3):379–390;
Whyte MP, et al. J Bone Miner Res. 2012; 27 (3): 729-37

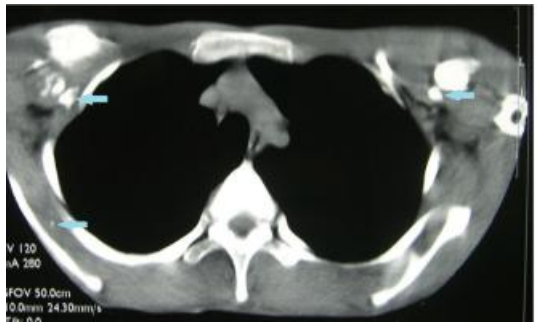
Patient Case – Genetic Confirmation

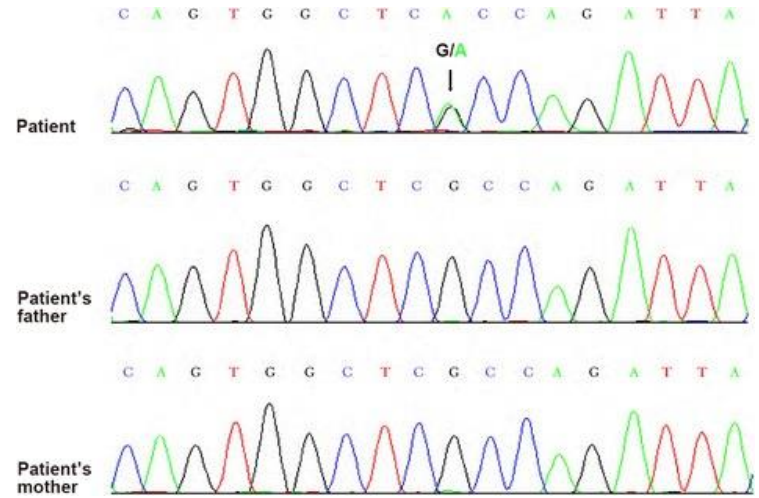
- Boy 16 yrs who had suffered from pain and swelling in the biopsy site for two months
- Initial tender stiffness of shoulders and back developed at age 9
- Physical exam presented serious stiffness and multiple bony masses in the body, with his bilateral halluces characterized by hallux valgus deformity and macrodactyly
- Imaging examinations showed widespread HO
- Normal lab results except for alkaline phosphatase
- de novo heterozygous mutation (c.617G > A; p.R206H) was found in the ACVR1/ALK2 using gene sequencing
- FOP diagnosis confirmed











ER, emergency room

Tian S, et al. BMC Med Genet 2018; 19: 30

Royal National Orthopaedic Hospital NHS
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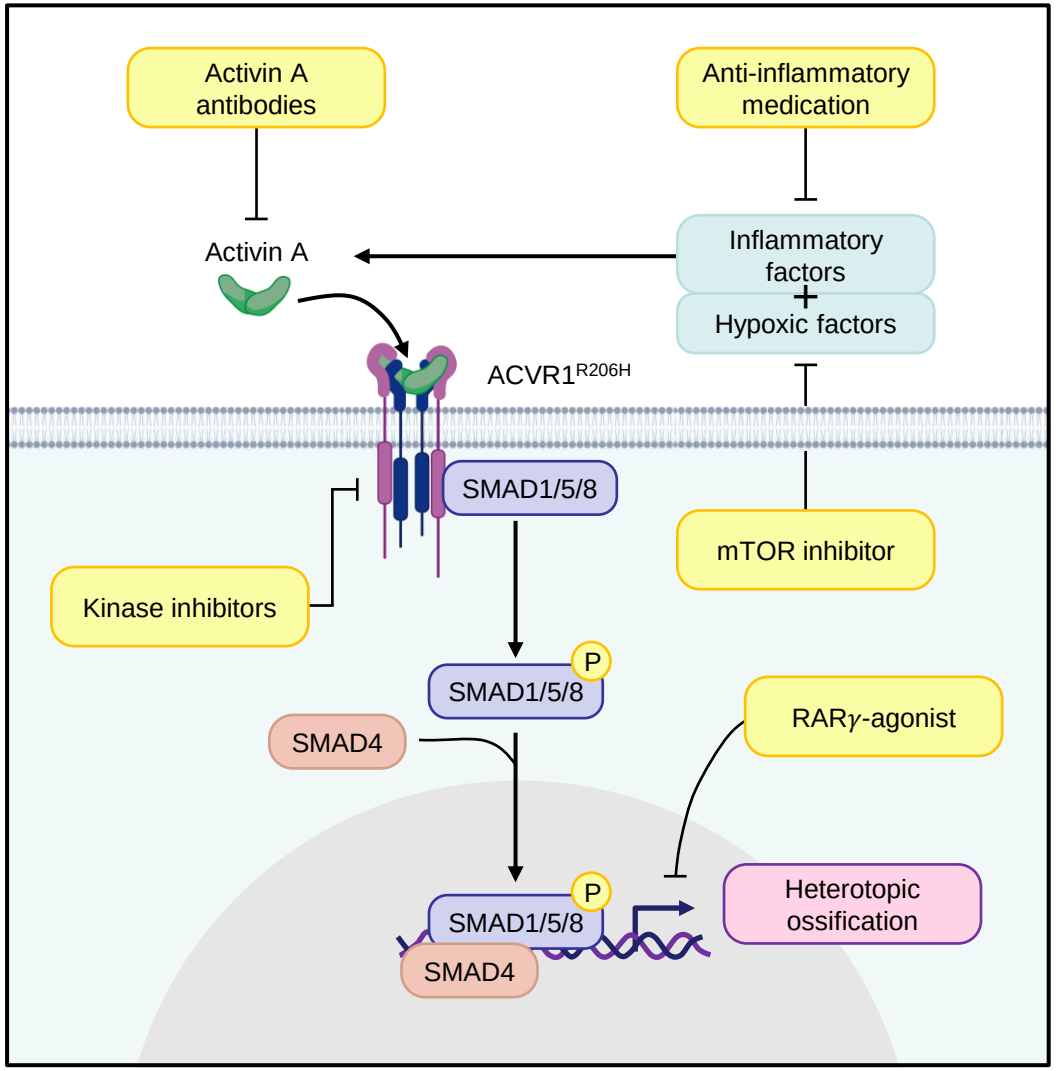
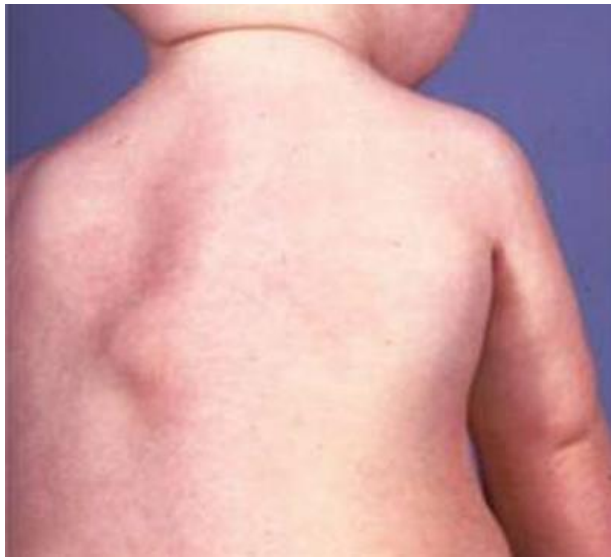
Pathological Pathway leading to Heterotopic Ossification



Adapted from: Smilde B, et al. Orthop Res Rev. 2022;14:113-120

Royal National Orthopaedic Hospital NHS Trust

Symptom Onset



Pignolo *et al. Orphanet Journal of Rare Diseases* (2019) 14:98
https://doi.org/10.1186/s13023-019-1068-7

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes

Robert J. Pignolo[1*], Geneviève Baujat[2], Matthew A. Brown[3], Carmen De Cunto[4], Maja DiRocco[5], Edward C. Hsiao[6], Richard Keen[7], Mona Al Mukaddam[8], Kim-Hanh Le Quan Sang[2], Amy Wilson[9], Barbara White[9], Donna R. Grogan[9] and Frederick S. Kaplan[10*]

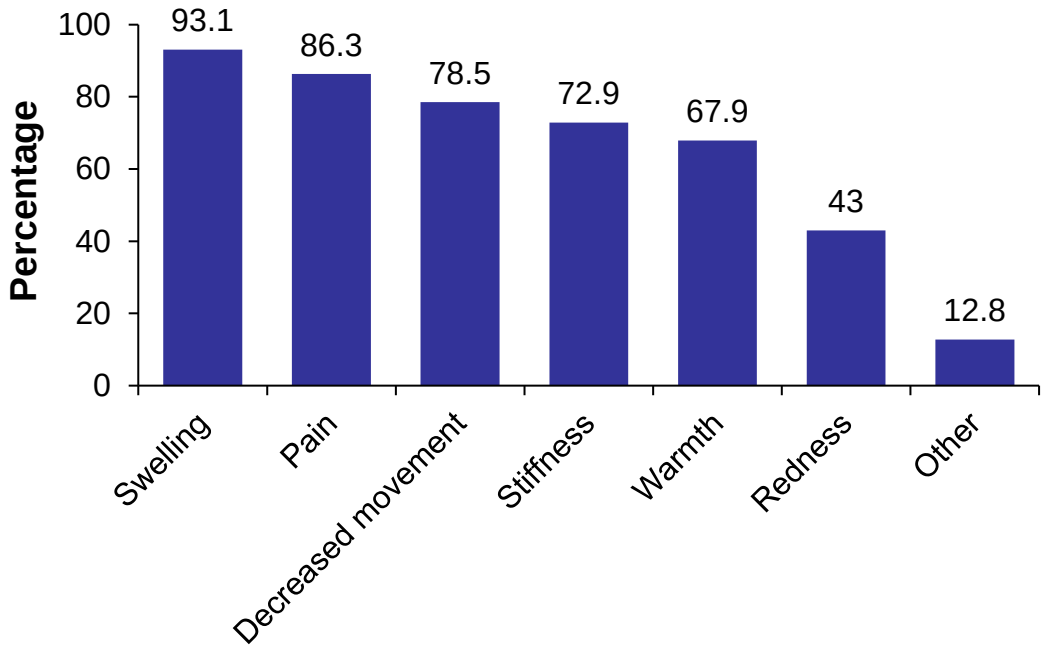
Demographic and baseline disease by age category

	<8 years (N=17)	8 to <15 years (N=36)	15 to <25 years (N=27)	≥25 to ≤65 years (N=27)	Total (N=114)
Males, n (%)	9 (52.9)	24 (66.7)	16 (47.1)	13 (48.1)	62 (54.4)
Age (years)					
Mean ± SD	5.9 ± 1.1	11.4 ± 2.1	18.9 ± 3.1	31.7 ± 6.7	17.6 ± 9.7
Median (min, max)	6.0 (4, 7)	11.0 (8, 14)	18.5 (15, 24)	30.0 (25, 56)	15.0 (4, 56)
Age at 1st flare-up					
Mean ± SD	2.9 ± 2.1	4.4 ± 3.6	5.6 ± 4.8	7.1 ± 5.0	5.2 ± 4.4
Median (min, max)	2.0 (1, 6)	4.0 (0, 13)	3.5 (0, 17)	5.0 (0, 20)	4.0 (0, 20)

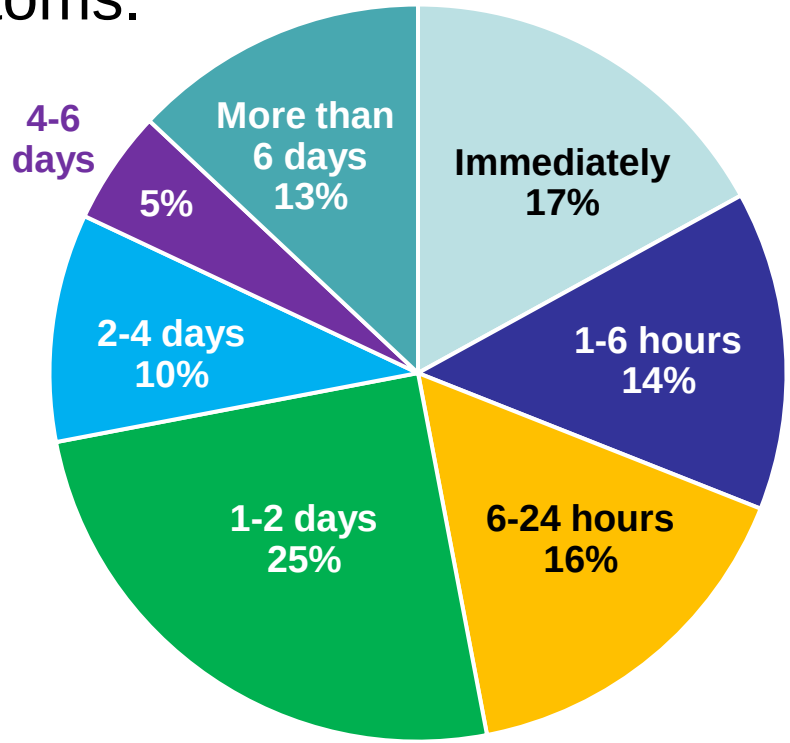
SD, standard deviation
Pignolo R, et al. Orphanet J Rare Dis. 2019;14:98

Recognition of Disease Flare-Ups

The majority of patients report swelling, pain, decreased movement, warmth, and redness as prominent symptoms of a flare-up.



Most patients reported confirmation of a flare-up within two days of onset of symptoms.

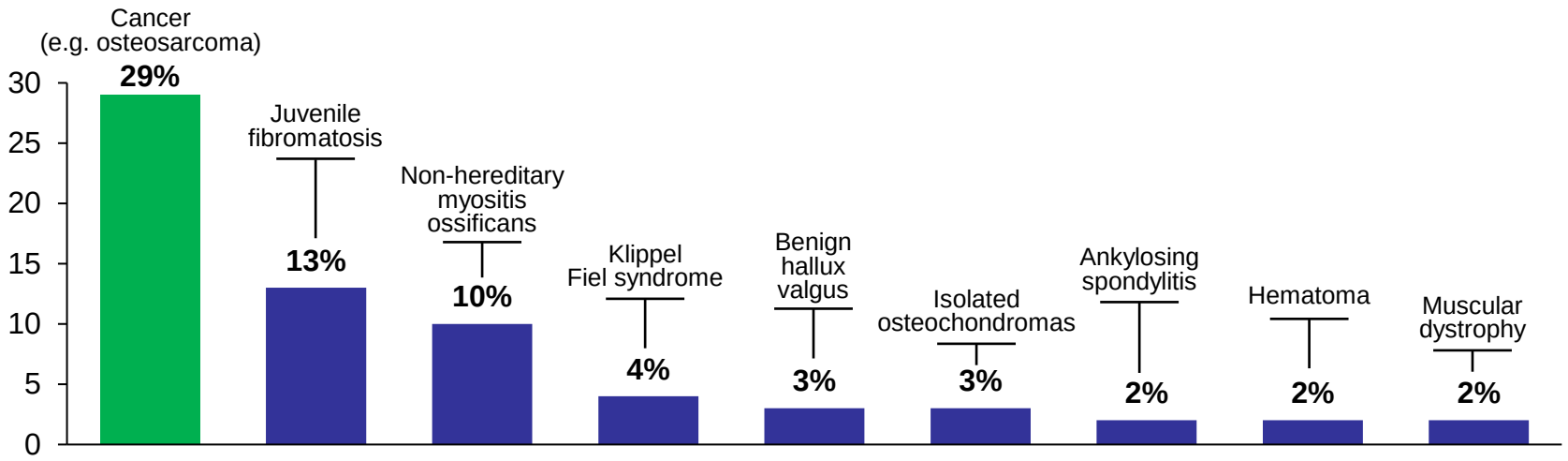


Pignolo RJ, et al. J Bone Miner Res. 2016;31:650-6

Misdiagnosis is Common in FOP

- Approximately 53% of patients are misdiagnosed worldwide which can lead to unnecessary surgical intervention and disastrous results of early disability
- Mistaken diagnoses: aggressive juvenile fibromatosis, lymphoedema, soft tissue sarcoma

Most common misdiagnoses in FOP[4]



FOP, fibrodysplasia ossificans progressiva

Sherman A, et al. JBMR 2020; 35: S1 (P-841)

2020 FOP Registry Annual Report - IFOPA - International Fibrodysplasia Ossificans Progressiva Association, Accessed 12-May-2022

Risks of Surgery and Biopsy

- 25% of those who had received an intramuscular injection reported an immediate flare-up at the injection site, 84% of whom developed HO[1]
- Orthopaedic surgeries to remove HO or to correct deformities in the extremities or trunk have been reported, but most of them led to HO and worsening of motion/deformity; there is 100% risk of recurrence of HO after jaw surgery, which should be highly discouraged[2,3]

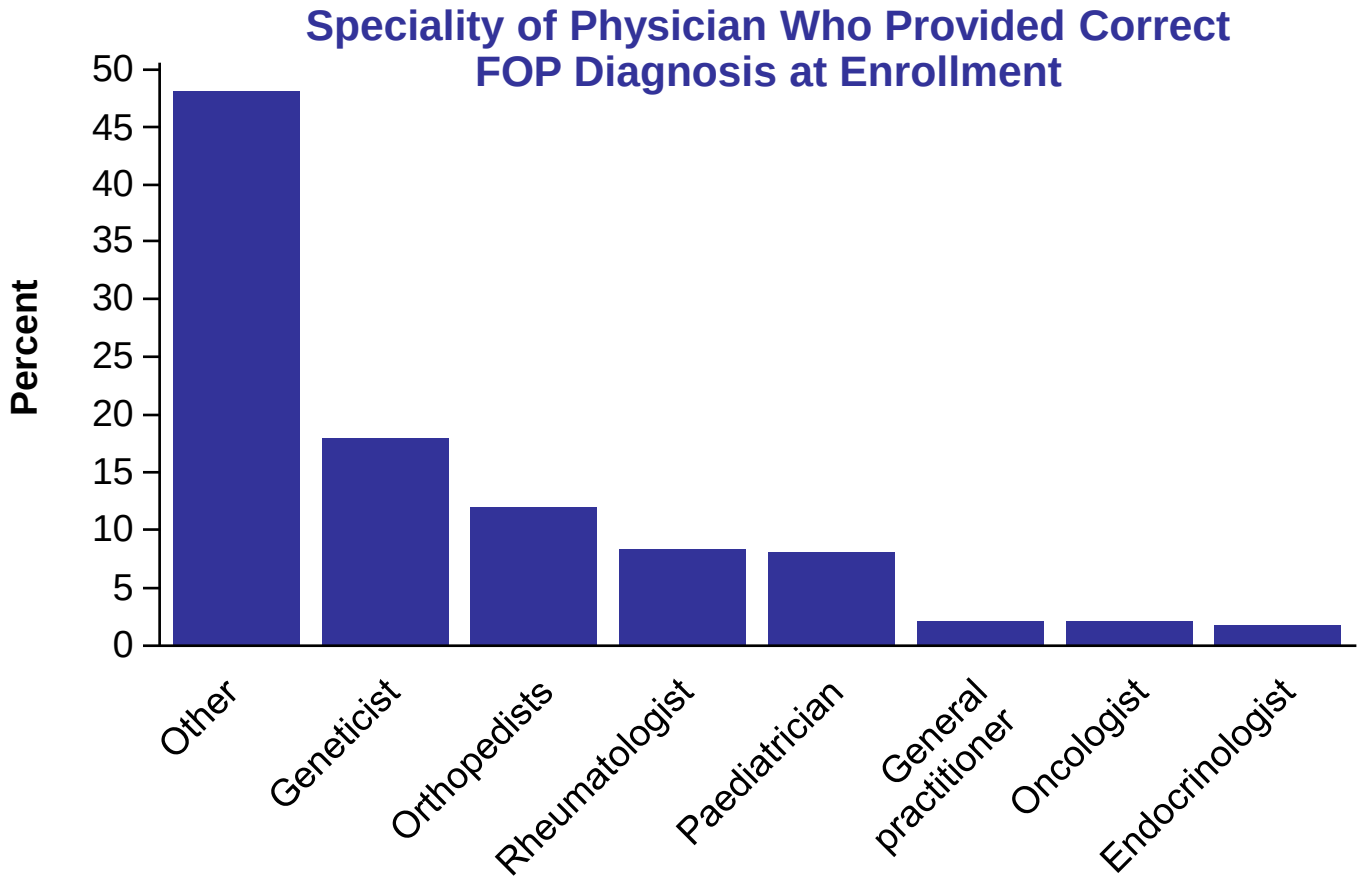
HO, heterotopic ossification

1. Pignolo RJ, et al. J Bone Miner Res. 2016;31:650-6;
2. Kaplan FS, et al. Proc Intl Clin Council FOP. 2019;1:1-111;
3. Eekhoff EMW, et al. JBMR Plus. 2017;2:55-8

Patients Come into Contact with a Number of Specialists during their Journey

Approximately one quarter of Registry participants first sought care from a paediatrician for their FOP symptoms

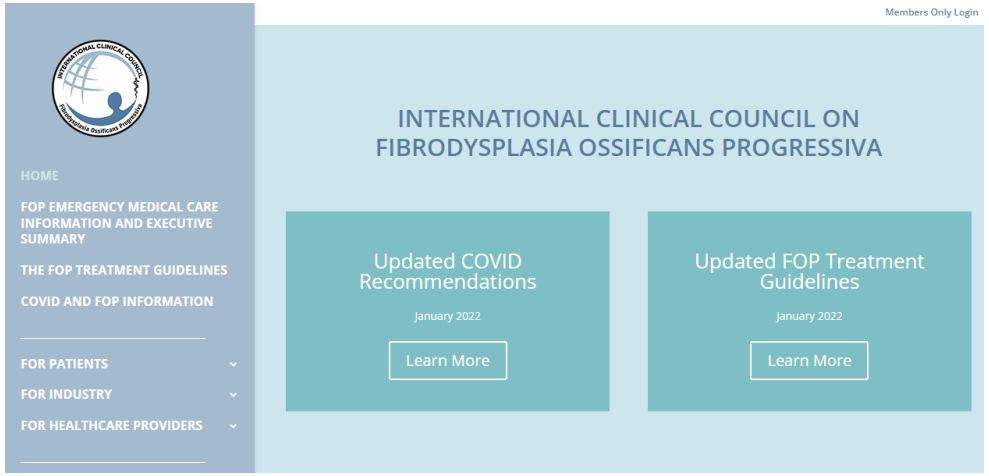
Only 8% of participants reported that a paediatrician provided their correct diagnosis.

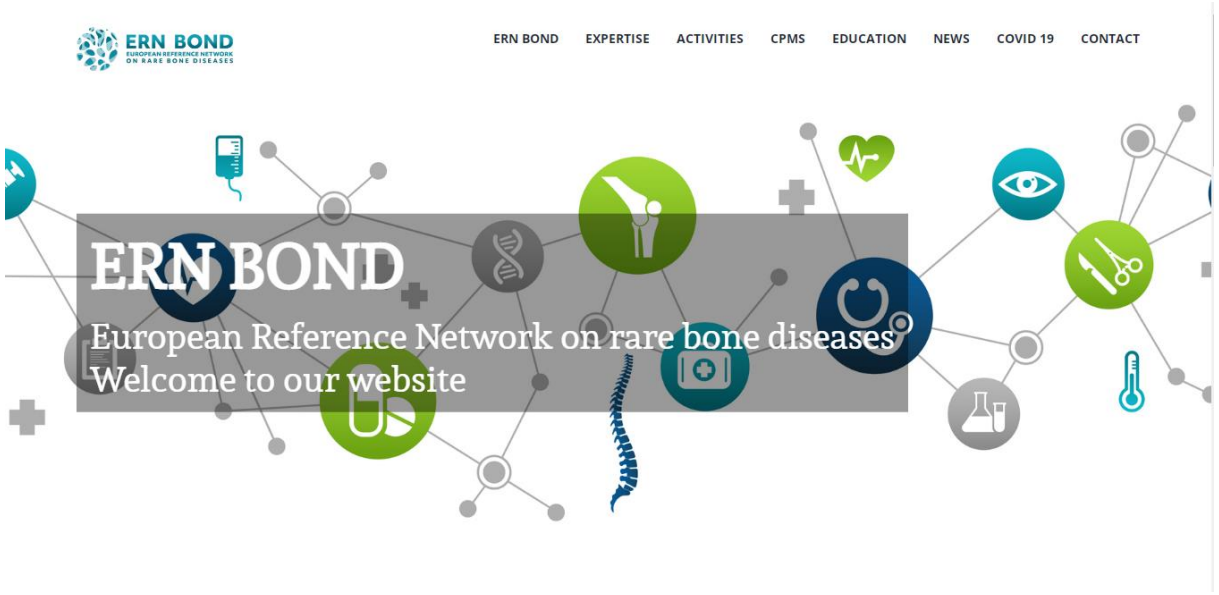


Sherman A, et al. JBMR 2020; 35: S1 (P-841)

Scientific poster example (d3n8a8pro7vhmx.cloudfront.net), Accessed 12-May-2022

Finding an Expert





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Patient Support

- Patients and their families should be informed about the International Clinical Council on FOP, the International FOP Association (IFOPA), and country-specific support groups at the time of diagnosis

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FOP, fibrodysplasia ossificans progressiva

Summary

- Recognition of greater toe abnormalities at birth should raise suspicion of FOP
- FOP can be confirmed with genetic testing of ACVR1
- Avoid biopsies, surgery to remove heterotopic ossifications and IM injections/vaccines
- Refer patient to expert clinician for further advice and management

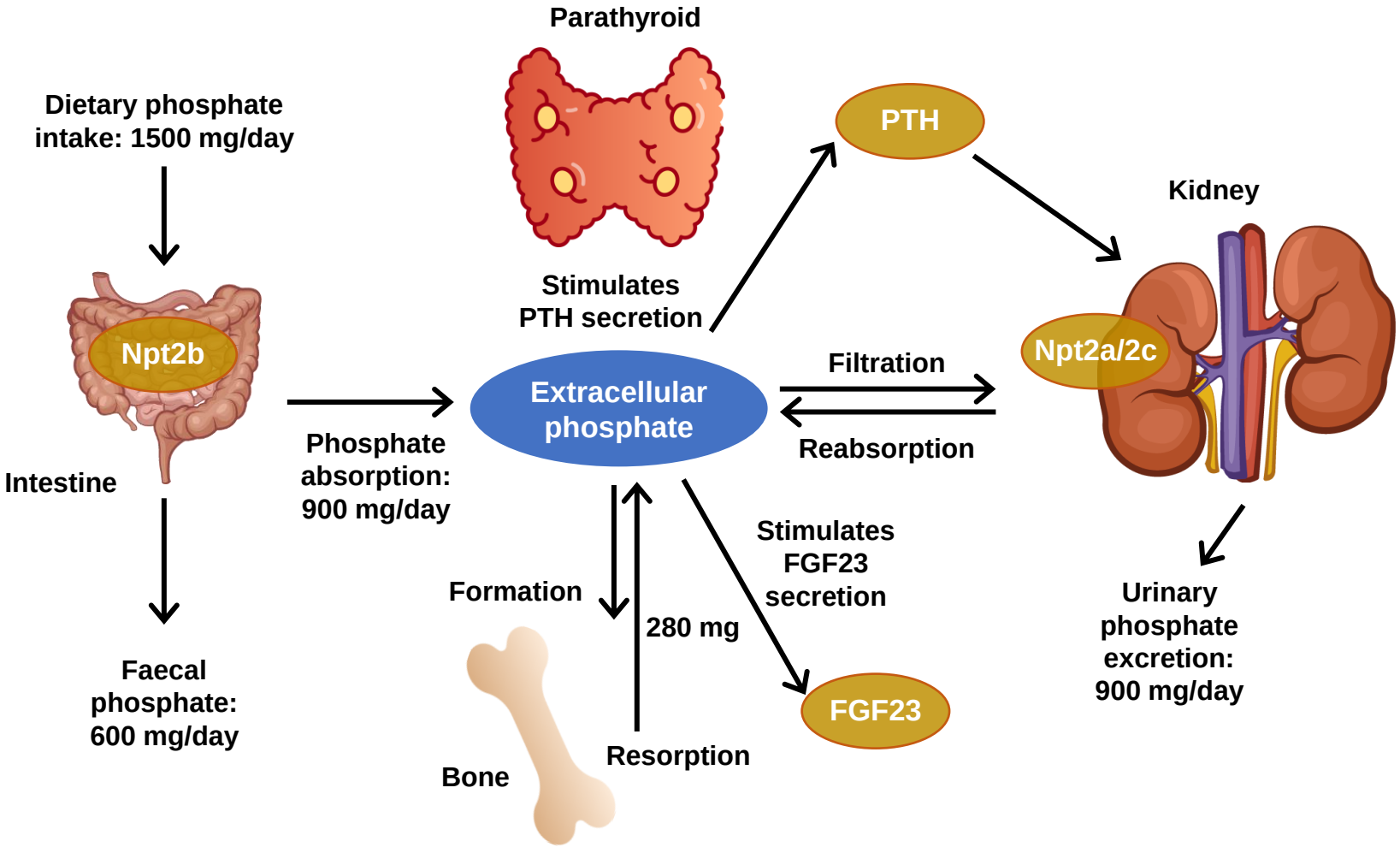
FGF23-RELATED HYPOPHOSPHATAEMIC RICKETS/OSTEOMALACIA

Maria Luisa Brandi MD, PhD
FIRMO Foundation
Florence, Italy

DISCLOSURES

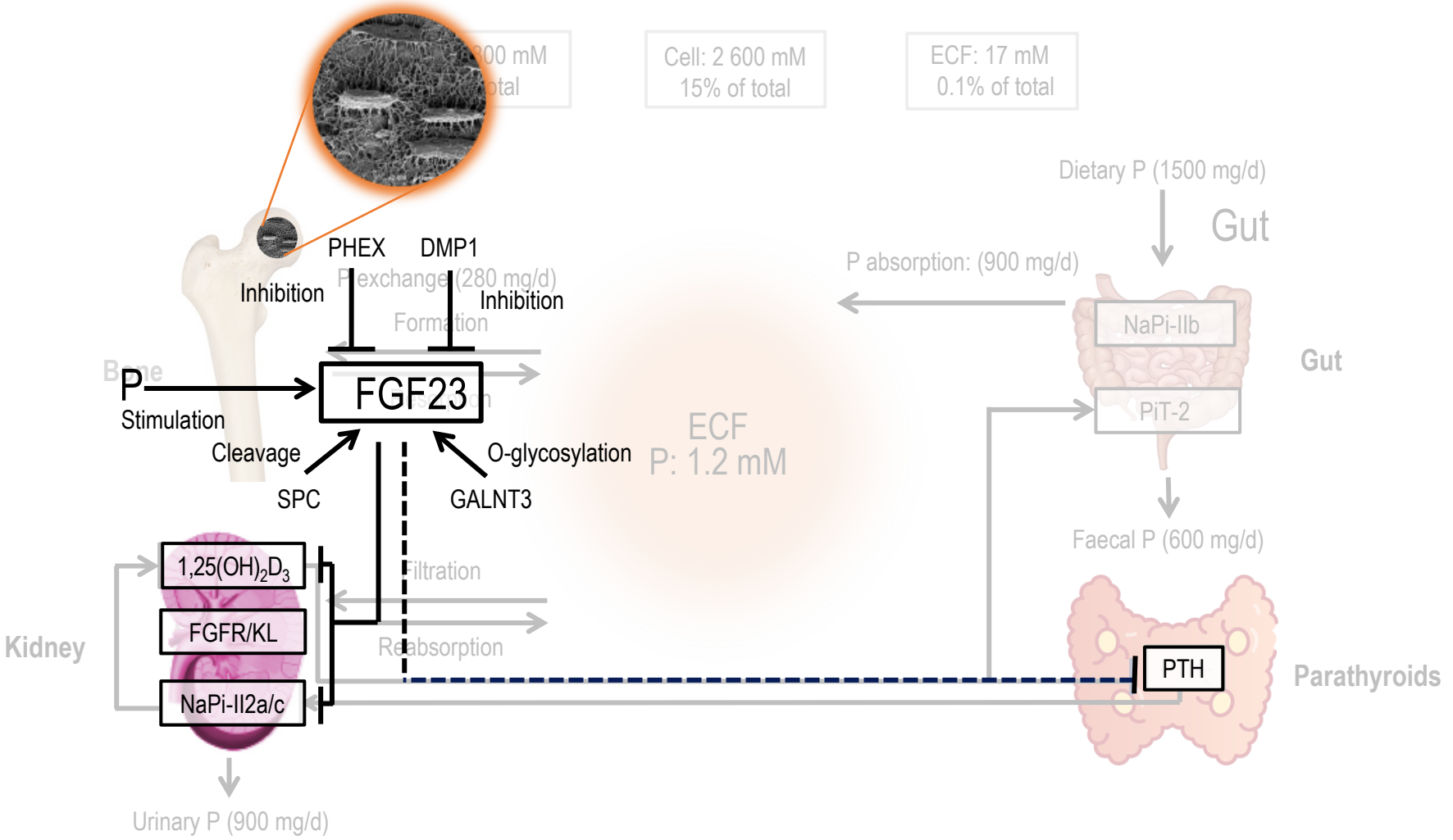
- Dr Brandi has received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB
- Grants and/or speaker: Abiogen, Alexion, Amgen, Amolyt, Amorphical, Bruno Farmaceutici, CoGeDi, Echolight, Eli Lilly, Enterabio, Gedeon Richter, Italfarmaco, Kyowa Kirin, Menarini, Monte Rosa, SPA, Takada, Theramex, UCB
- Consultant: Aboca, Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Echolight, Kyowa Kirin, Personal Genomics, UCB

PHOSPHATE HOMEOSTASIS IN NORMAL PHYSIOLOGY



FGF23, fibroblast growth factor 23; Npt2b/2c, sodium-dependent phosphate transport protein 2b/2c; PTH, parathyroid hormone
Adapted from: Komaba H, Fukagawa M. Kidney Int. 2016;90:753-63

PHOSPHATE HOMEOSTASIS IN NORMAL PHYSIOLOGY



DMP1, dentin matrix acidic phosphoprotein 1; ECF, extracellular fluid; FGF23, fibroblast growth factor 23; FGFR/KL, fibroblast growth factor receptor klotho; GALNT3, polypeptide N-acetylgalactosaminyltransferase 3; P, phosphate; PHEX, phosphate regulating endopeptidase homolog X-linked; PTH, parathyroid hormone; SPC, subtilisin-like protein convertases

NORMAL RANGES FOR TMP/GFR (ADAPTED FROM CHONG ET AL.)

Age	Female mg/dL (mmol/L)	Male mg/dL (mmol/L)
Newborn	5.7-8.1 (1.27-2.59)	
1 month-2 years	3.6-5.4 (1.15-1.73)	
2-12 years	3.8-5.0 (1.22-1.60)	
12-16 years	3.4-4.6 (1.09-1.47)	
16-25 years	3.18-6.41 (1.01-2.05)	3.33-5.9 (1.07-1.89)
25-45 years	2.97-4.45 (0.95-1.42)	3.09-4.18 (0.99-1.34)
45-65 years	2.72-4.39 (0.87-1.40)	2.78-4.18 (0.89-1.34)
65-75 years	2.47-4.18 (0.79-1.34)	2.47-4.18 (0.79-1.34)

TmP/GFR, maximum tubular phosphate reabsorption to glomerular filtration rate
Adapted from: Chong WH, et al. Endocr Relat Cancer. 2011;18:R53-77

FGF23: A NEW HORMONE

- Tissue source (bone), physiology (metabolism strictly controlled and action on kidney), biology (receptors are recognised)
- Implications for human diseases of FGF23 excess and deficiency
- Drug targets for FGF23-related disorders

FGF23, fibroblast growth factor 23

HYPOPHOSPHATAEMIA: BASIC INSTRUCTIONS FOR THE BONE DISEASE SPECIALIST

Normal circulating levels of P in the adult:

- 2.5-4.5 mg/dL

Mechanisms that result in hypophosphataemia:

- Reduction of intestinal absorption
- Increase of renal excretion
- Redistribution of P inside the cells

Main causes of hypophosphataemia:

Mostly present in intensive care department

- Malnutrition
- Parenteral nutrition
- Alterations in the acid–basic equilibrium (i.e. acute respiratory alkalosis)
- Drugs

Often seen the bone disease specialist

- Primary or secondary hyperparathyroidism
- Hungry bone syndrome
- Osteomalacia
- Rickets
- Malabsorption
- Chronic use of thiazides
- Excessive use of antacids
- Steatorrhoea and chronic diarrhoea
- Kidney tubulopathies
  - FGF23
  - Secreted frizzled protein 4
  - FGF7
  - Matrix extracellular phosphoglycoprotein

FGF, fibroblast growth factor; P, phosphate

CAUSES OF DISEASES/CONDITIONS CHARACTERISED BY HYPOPHOSPHATAEMIA

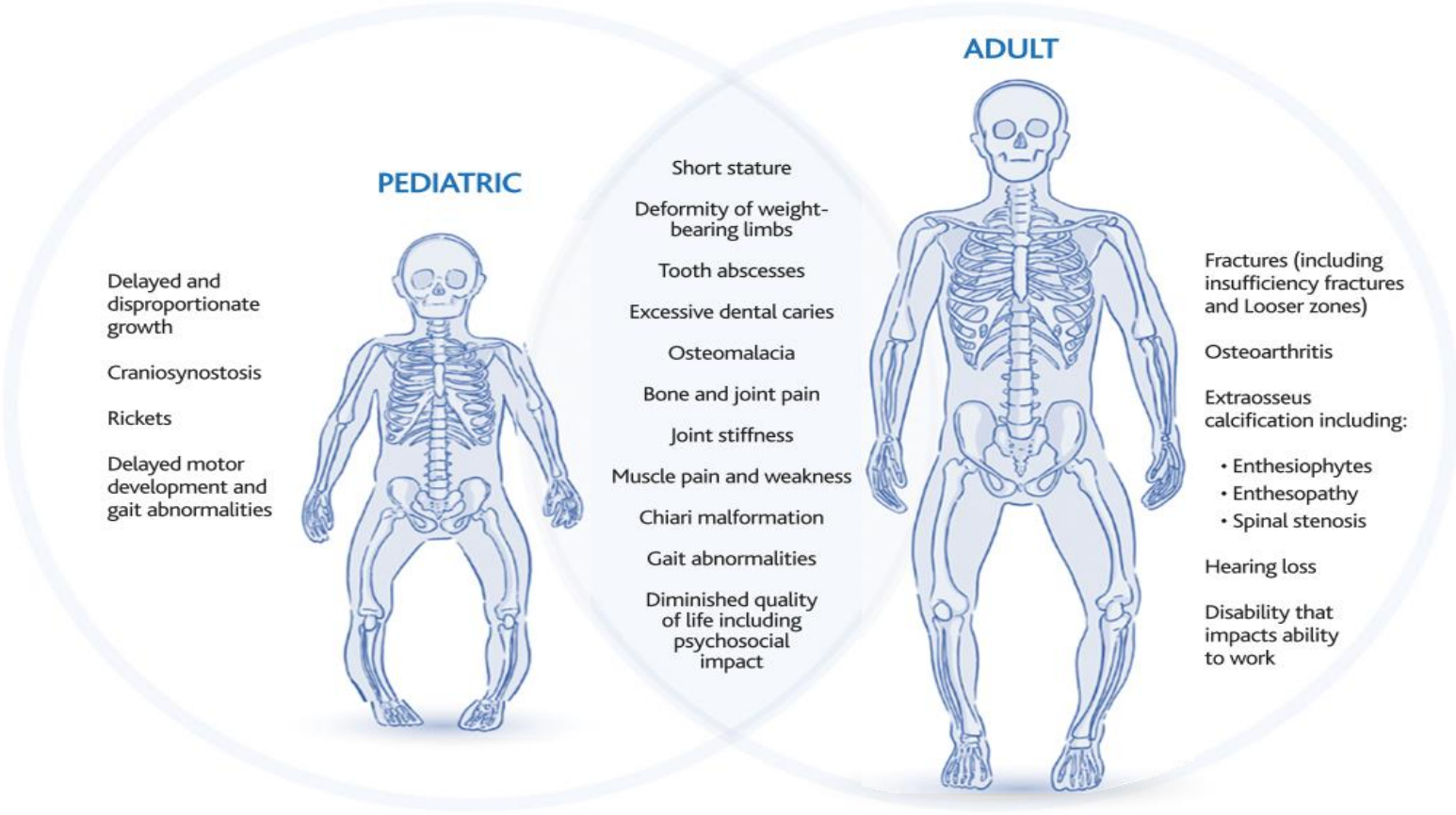
Human disease	Cause/mechanism of disease
FGF23-associated hypophosphataemic conditions/diseases (high plasma FGF23)	
Genetic (hereditary)	
X-linked hypophosphataemia	*PHEX* mutation
Autosomal dominant hypophosphataemic rickets	*FGF23* mutation
Autosomal recessive hypophosphataemic rickets 1/osteomalacia	*DMP1* mutation
Autosomal recessive hypophosphataemic rickets 2	*ENPP1* mutation
Raine syndrome-associated hypophosphataemic rickets	*FAM20C* mutation
Osteoglophonic dysplasia	*FGFR1* mutation
Genetic (mosaicism)	
Fibrous dysplasia/McCune-Albright syndrome	*GNAS1* gain of function
Epidermal nevus syndrome	*FGFR3* mutation
Sporadic/acquired	
Tumour-induced osteomalacia	*FGF23*-producing tumour
Drug-induced	
Chronic intravenous iron supplementation therapy-induced hypophosphataemia	Intravenous iron-induced increase in FGF23 levels (dependent on the type of intravenous iron, detailed mechanism not fully elucidated)
Non-FGF23-associated hypophosphatemic conditions/diseases (low-to-normal plasma FGF23)	
Genetic (hereditary)	
Hypophosphataemic rickets with hypercalciuria	*SLC34A3* (encoding the proximal tubule phosphate NaPi-IIc) loss of function
Infantile idiopathic hypercalcemia	*SLC34A1* (encoding the proximal tubule phosphate NaPi-IIc) mutation
Genetic Fanconi syndrome (including Wilson's disease, Lowe syndrome, Dent's disease)	
Inherited Vitamin D-dependent rickets	*CYP2R1*, *CYP27B1*, or *VDR* mutation
Sporadic/acquired	
Primary hyperparathyroidism	PTH effect on sodium-phosphate cotransporters
Secondary hyperparathyroidism due to nutritional phosphate, calcium, and/or vitamin D deficiencies	Lack of adequate sun exposure, dietary insufficiency, or malabsorptive disorders
Intracellular phosphate shift	Insulin administration or refeeding after starvation, respiratory or metabolic alkalosis, drug-induced redistribution of phosphate, alcohol intake and withdrawal
Acquired Fanconi syndrome	Direct renal tubular damage by a drug or toxin, which results in a generalized proximal tubulopathy

FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

Adapted from: Aljuraibah F, et al. J Bone Miner Res. 2022;37:12-20

XLH RICKETS/OSTEOMALACIA

- The condition is congenital
- As the defect of mineralisation starts in the growing skeleton the resulting disease is usually rickets, but if bone abnormalities are not recognised in childhood the bone doctor will be the first to make the diagnosis

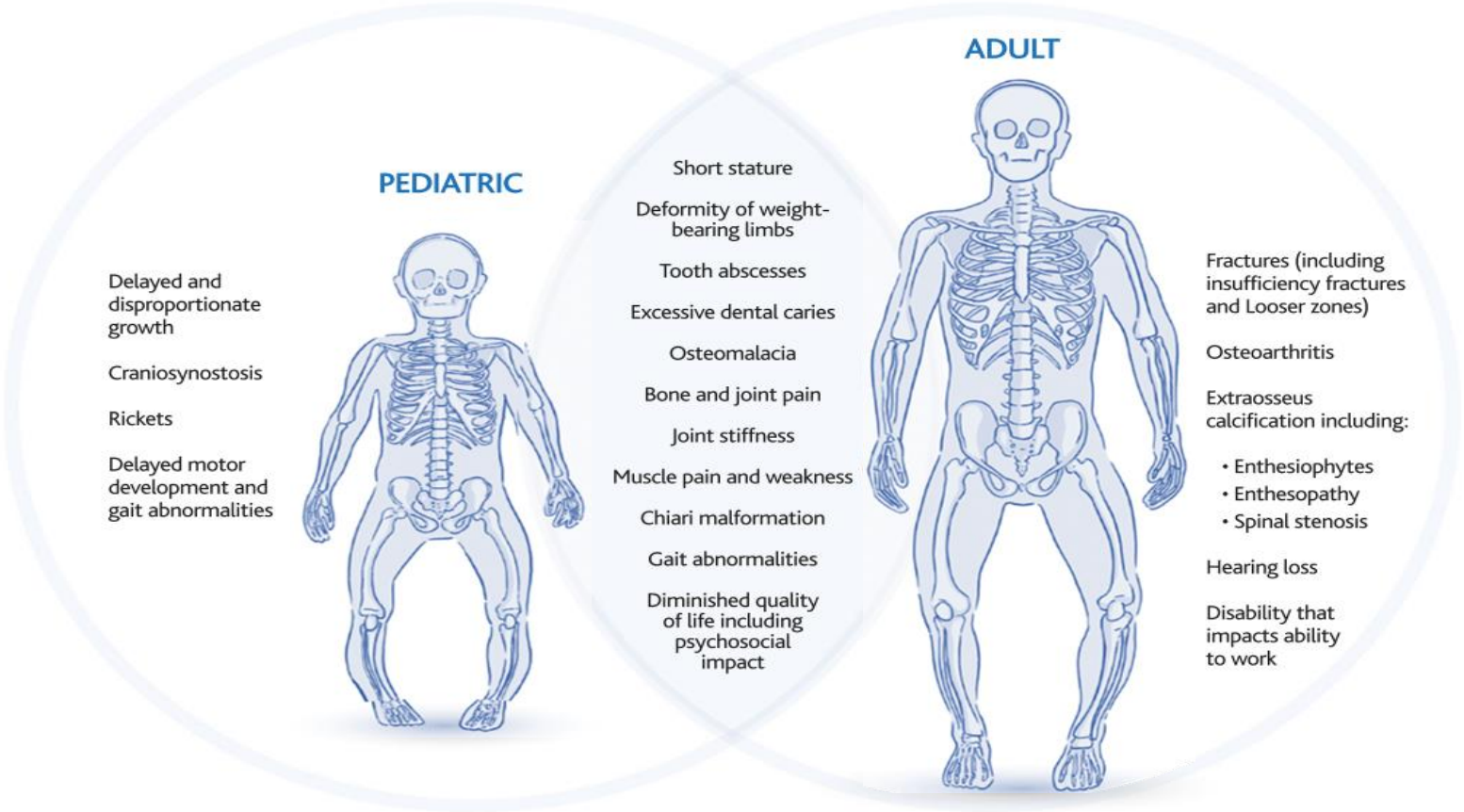


XLH, X-linked hypophosphataemia

Adapted from: Beck-Nielsen S, et al. Orphanet J Rare Dis. 2019;14:58

DIFFERENTLY TO XLH, TUMOUR-INDUCED OSTEOMALACIA (TIO) IS USUALLY DIAGNOSED IN THE ADULT

XLH



TIO

XLH, X-linked hypophosphataemia

Adapted from: Beck-Nielsen S, et al. Orphanet J Rare Dis. 2019;14:58; Florenzano P, et al. Bone Rep. 2017;7:90-7; Haffner D, et al. Nat Rev Nephrol. 2019;15:435-55; Minisola S, et al. Nat Rev Dis Primers. 2017;3:17044

CHARACTERISTICS OF INHERITED OR ACQUIRED CAUSES OF PHOSPHOPENIC RICKETS IN COMPARISON TO CALCIPENIC RICKETS

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25(OH)D[a]	1,25$(OH)_2$D	Pathogenesis
Rickets and/or osteomalacia with high PTH levels (calcipenic rickets)												
Nutritional rickets (vitamin D and/or calcium deficiency)	*NA*	N, ↓	N, ↓	↑↑↑	↓	Varies	↓	N	↑↑↑	↓↓, N	Varies	Vitamin D deficiency
Vitamin-D-dependent rickets type 1A; (VDDR1A; OMIM#264700)	*CYP27B1* (12q14.1)	↓	N, ↓	↑↑↑	↓	Varies	↓	N, ↓	↑↑↑	N	↓	Impaired synthesis of 1,25$(OH)_2$D
Vitamin-D-dependent rickets type 1B; (VDDR1B; OMIM#600081)	*CYP2R1* (11q15.2)	↓	N, ↓	↑↑↑	↓	Varies	↓	N	↑↑↑	↓↓	Varies	Impaired synthesis of 25(OH)D
Vitamin-D-dependent rickets type 2A; (VDDR2A; OMIM#277440)	*VDR* (12q13.11)	↓	N, ↓	↑↑↑	↓	Varies	↓	N, ↓	↑↑↑	N	↑↑	Impaired signalling of the VDR
Vitamin-D-dependent rickets type 2B; (VDDR2B; OMIM#164020)	*HNRNPC* (14q11.2)	↓	N, ↓	↑↑↑	↓	Varies	↓	N	↑↑↑	N	↑↑	Impaired signalling of the VDR
Vitamin-D-dependent rickets type 3; (VDDR3; OMIM# pending)	*CYP3A4* (7q21.1)	↓	↓	↑↑↑	↓	Varies	↓	?	↑↑↑	↓	↓	↑ Inactivation of 1,25$(OH)_2$D
Phosphopenic rickets and/or osteomalacia due to dietary phosphate deficiency or impaired bioavailability												
▪ Breastfed very-low-birthweight infants ▪ Use of elemental or hypoallergenic formula diet or parental nutrition ▪ Excessive use of phosphate binders ▪ Gastrointestinal surgery or disorders	*NA*	N, ↑	↓	↑,↑↑	?	↓	N[b]	N, ↓	N	N	N, ↑	Phosphate deficiency

[a] Cave: prevalence of vitamin D deficiency was reported to be up to 50% in healthy children. [b] Normal after restoration of P, but falsely reduced before restoration.

↑, elevated; ↑↑ or ↑↑↑, very elevated; ↑(↑↑), might range widely; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase;

Ca, serum levels of calcium; FGF23, fibroblast growth factor 23; N, normal; NA, not applicable; P, serum levels of phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate; U_{Ca}, urinary calcium excretion; U_P, urinary phosphate excretion; VDR, vitamin D receptor

Adapted from: Haffner D, et al. Nat Rev Nephrol. 2019;15:435-55

CHARACTERISTICS OF INHERITED OR ACQUIRED CAUSES OF PHOSPHOPENIC RICKETS IN COMPARISON TO CALCIPENIC RICKETS

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	P	ALP	U_{Ca}	U_P	TmP/ GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	Pathogenesis
Phosphopenic rickets and/or osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels and/or signalling												
XLH (OMIM#307800)	*PHEX* (Xp22.1)	N	↓	↑,↑↑	↓	↑	↓	↑, N	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone and impaired FGF23 cleavage
Autosomal dominant hypophosphataemic rickets (ADHR; OMIM#193100)	*FGF23* (12p13.3)	N	↓	↑,↑↑	↓	↑	↓	↑, N	N, ↑[b]	N	N[c]	FGF23 protein resistant to degradation
Autosomal recessive hypophosphataemic rickets 1 (ARHR1; OMIM#241520)	*DMP1* (4q22.1)	N	↓	↑,↑↑	↓	↑	↓	↑, N	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone
Autosomal recessive hypophosphataemic rickets 2 (ARHR2; OMIM#613312)	*ENPP1* (6q23.2)	N	↓	↑,↑↑	↓	↑	↓	↑, N	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone
Raine syndrome-associated (ARHR3; OMIM#259775)	*FAM20C* (7q22.3)	N	↓	↑,↑↑	?	↑	↓	↑, N	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone
Fibrous dysplasia (FD; OMIM#174800)	*GNAS* (20q13.3)	N, ↑	↓	↑,↑↑	↓	↑	↓	N, ↑	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone
TIO	NA	N, ↓	↓	↑,↑↑	↓	↑	↓	N, ↑	N, ↑[b]	N	N[c]	↑ FGF23 expression in tumoral cells
Cutaneous skeletal hypophosphataemia syndrome (SFM; OMIM#163200)	*RAS* (1p13.2)	N, ↓	↓	↑,↑↑	↓	↑	↓	N, ↑	N, ↑[b]	N	N[c]	Unknown
Osteoglophonic dysplasia (OGD; OMIM#166250)	*FGFR1* (8p11.23)	N	↓	↑, N	N	↑	↓	N	N, ↑[b]	N	N[c]	↑ FGF23 expression in bone
Hypophosphataemic rickets and hyperparathyroidism (OMIM#612089)	*KLOTHO (13q13.1)*	N	↓	↑,↑↑	↓	↑	↓	↑	↑↑	N	N[c]	Unknown; translocation of the KLOTHO promoter

[a] Cave: prevalence of vitamin D deficiency was reported to be up to 50% in healthy children. [b] PTH might be moderately elevated. [c] Decreased relative to the serum phosphate concentration

↑, elevated; ↑↑ or ↑↑↑, very elevated; ↑(↑↑), might range widely; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase;

Ca, serum levels of calcium; FGF23, fibroblast growth factor 23; N, normal; NA, not applicable; P, serum levels of phosphate; PTH, parathyroid hormone; TIO, Tumour-induced osteomalacia; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate; U_{Ca}, urinary calcium excretion; U_P, urinary phosphate excretion; VDR, vitamin D receptor; XLH, X-linked hypophosphataemia

Adapted from: Haffner D, et al. Nat Rev Nephrol. 2019;15:435-55

CHARACTERISTICS OF INHERITED OR ACQUIRED CAUSES OF PHOSPHOPENIC RICKETS IN COMPARISON TO CALCIPENIC RICKETS

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	P	ALP	U_{Ca}	U_P	TmP/ GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	Pathogenesis
Phosphopenic rickets and/or osteomalacia due to primary renal tubular phosphate wasting												
Hereditary hypophosphataemic rickets with hypercalciuria (HHRH; OMIM#241530)	*SLC34A3* (9q34.3)	N	↓	↑(↑↑)	N, ↑	↑	↓	↓	Low N, ↓	N	↑↑	Loss of function of NaPi2c in the proximal tubule
X-linked recessive hypophosphataemic rickets (OMIM#300554)	*CLCN5* (Xp11.23)	N	↓	↑(↑↑)	N, ↑	↑	↓	Varies	Varies	N	↑	Loss of function of CLCN5 in the proximal tubule
Hypophosphataemia and nephrocalcinosis (NPHLOP1; OMIM#612286) and Fanconi reno-tubular syndrome 2 (FRTS2; OMIM#613388)	*SLC34A1* (5q35.3)	N	↓	↑(↑↑)	↑	↑	↓	↓	Varies	N	↑	Loss of function of NaPi2a in the proximal tubule
Cystinosis (OMIM#219800) and other hereditary forms of Fanconi syndrome	*CTNS* (17p13.2)	N, ↓	↓	↑(↑↑)	N, ↑	↑	N, ↓	N, ↑[b]	N, ↑[b]	N	N[c]	Cysteine accumulation in the proximal tubule
Iatrongenic proximal tubulopathy	NA	N	↓	↑(↑↑)	Varies	↑	↓	↓	Varies	N	↑	Drug toxicity

[a] Cave: prevalence of vitamin D deficiency was reported to be up to 50% in healthy children. [b] Depending on the stage of chronic kidney disease. [c] Decreased relative to the serum phosphate concentration.

↑, elevated; ↑↑ or ↑↑↑, very elevated; ↑(↑↑), might range widely; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase;

Ca, serum levels of calcium; FGF23, fibroblast growth factor 23; N, normal; NA, not applicable; P, serum levels of phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate per glomerular filtration rate; U_{Ca}, urinary calcium excretion; U_P, urinary phosphate excretion; VDR, vitamin D receptor

Adapted from: Haffner D, et al. Nat Rev Nephrol. 2019;15:435-55

A MISSING LINK: UNDERSTANDING X-LINKED HYPOPHOSPHATAEMIA AND FGF23-MEDIATED OSTEOMALACIA

- Skeletal deformities in childhood and repeated unexplained fractures in later life are clues to rare bone disorders
- It is important to be aware of the clues to find the ‘missing link’ and refer the patient as early as possible for specialist investigation

FGF23, fibroblast growth factor 23

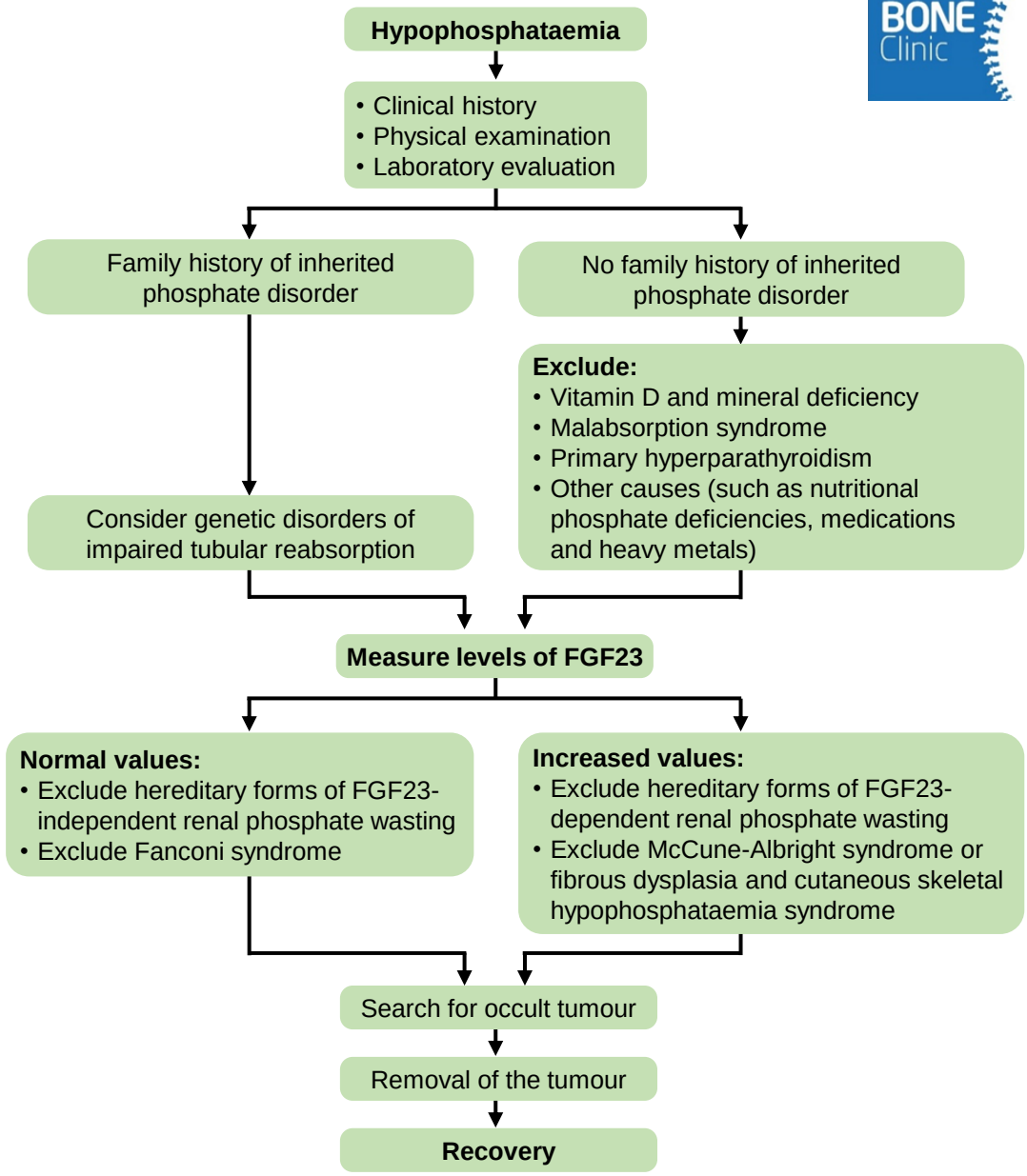
HYPOPHOSPHATAEMIC CONDITIONS WITH RENAL TUBULAR PHOSPHATE WASTING DUE TO ELEVATED FGF23 LEVELS/SIGNALING

Disorder (abbreviation; OMIM#)	Gene/location	Pathogenesis
Congenital		
XLH (OMIM#307800)	*PHEX/Xp22.1*	↑ FGF23 expression in bone and impaired FGF23 cleavage
Autosomal dominant hypophosphataemic rickets (ADHR; OMIM#193100)	*FGF23/12p13.3*	FGF23 protein resistant to degradation
Autosomal recessive hypophosphataemic rickets 1 (ARHR1; OMIM#241520)	*DMP1/4q22.1*	↑ FGF23 expression in bone
Autosomal recessive hypophosphataemic rickets 2 (ARHR2; OMIM#613312)	*ENPP1/6q23.2*	↑ FGF23 expression in bone
Raine syndrome associated (ARHR3; OMIM#259775)	*FAM20C/7q22.3*	↑ FGF23 expression in bone
Fibrous dysplasia (FD; OMIM#174800)	*GNAS/20q13.3*	↑ FGF23 expression in bone
Cutaneous skeletal hypophosphataemia syndrome (SFM; OMIM#163200)	*RAS/1p13.2*	?
Osteoglophonic dysplasia (OGD; OMIM#166250)	*FGFR1/8p11.23*	↑ FGF23 expression in bone
Hypophosphataemic rickets and hyperparathyroidism (OMIM#612089)	*KLOTHO/13q13.1*	Unknown; translocation of the KLOTHO promoter
Acquired		
TIO	*NA*	↑ FGF23 and other phosphatonins expression in the tumour

FGF23, fibroblast growth factor 23; TIO, tumour induced osteomalacia; XLH, X-linked hypophosphataemia
Adapted from: Haffner D, et al. Nat Rev Nephrol. 2019;15:435-55

TUMOUR-INDUCED OSTEOMALACIA (TIO)

- Rare paraneoplastic syndrome with overproduction of phosphaturic hormones, as FGF23, by tumours (the majority are mesenchymal in nature)
- The disorder is usually described in adults, and an algorithm for its management has been published

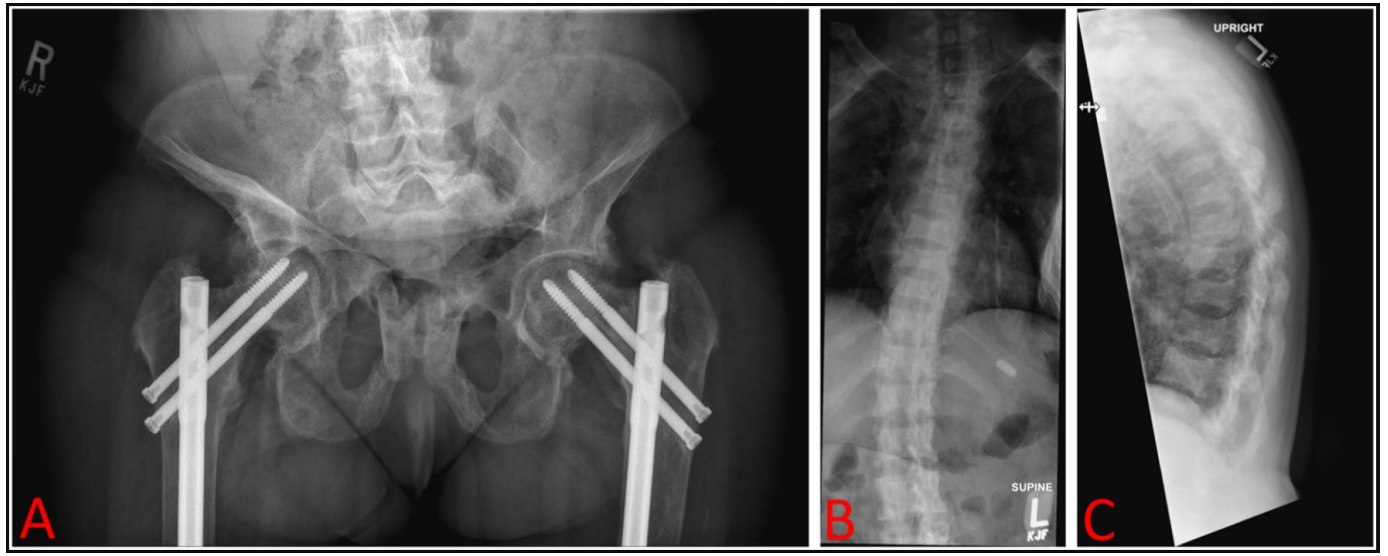


FGF23, fibroblast growth factor 23

Adapted from: Minisola S, et al. Nat Rev Disease Primers. 2017;3:17044

MISDIAGNOSIS: TIO MASQUERADING AS XLH

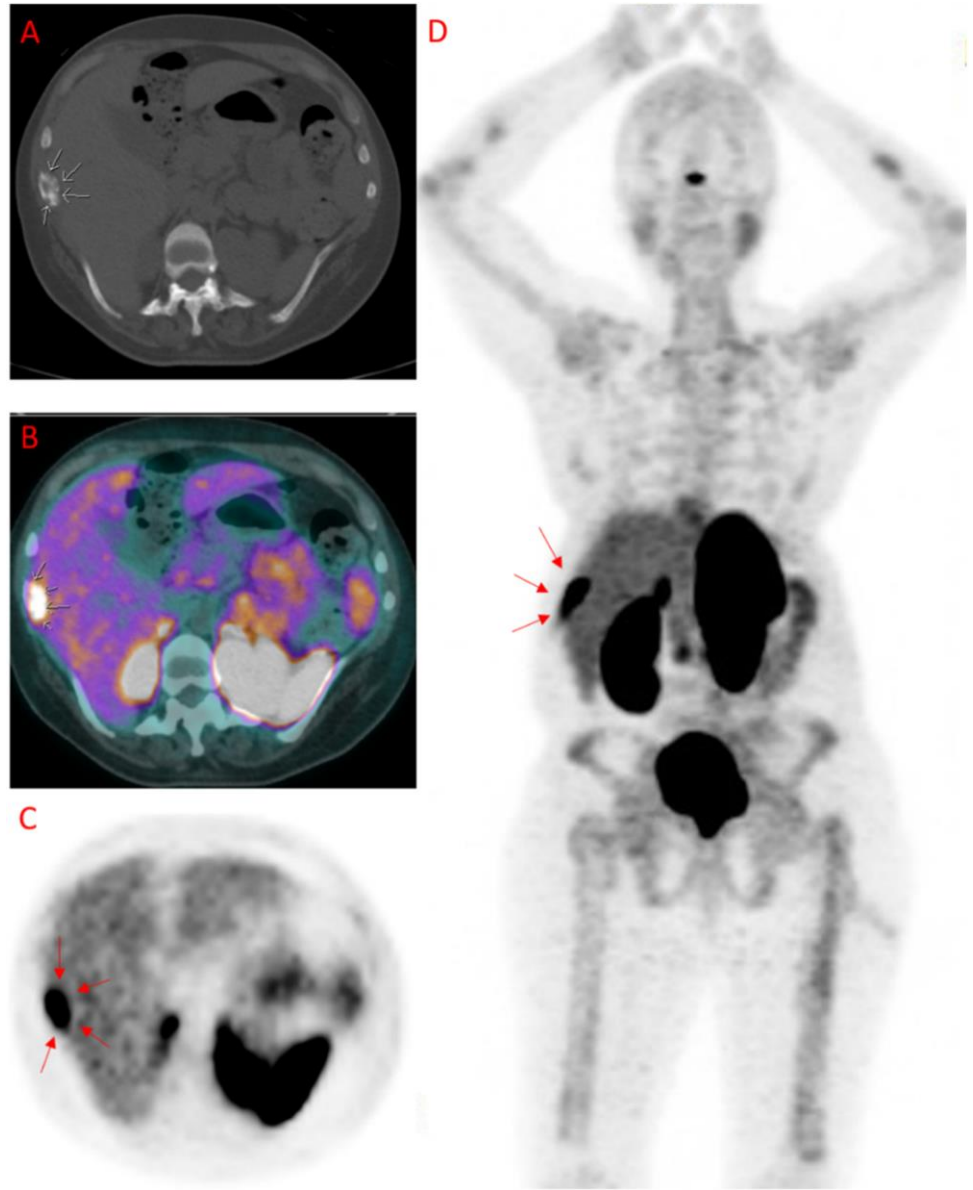
- 41-year-old female. Prior diagnosis of hypophoshataemic rickets
  - 26-year history of low phosphorus, bone pain, proximal muscle weakness, gait abnormalities, multiple traumatic and insufficiency fractures
  - Lost all secondary teeth. No family history of low phosphorus
  - Maximum height 5’2’’ but presented at 4’8’’ due to progressive spine deformities
  - Developed progressive gait abnormalities and decreased hip strength
  - Sustained bilateral hip fractures and small fractures throughout her spine despite intermittent treatment with conventional therapy with phosphorus supplements and calcitriol during her teens and 20’s



Colazo J, et al. Bone Reports 2021; 14:100744

MISDIAGNOSIS– TIO MASQUERADING AS XLH

- Patient deteriorated further over 10 years requiring stability rods and screws in her femurs and hips and surgery following a traumatic left humerus fracture.
- Patient was eventually confined to a wheelchair
- Reevaluation of her history resulted in a diagnosis of XLH
- DXA revealed normal bone density in spine and significantly lower than expected density in the forearm
- Renal ultrasound showed a 4-mm non-obstructing calculus in the lower pole of the right kidney, indicating nephrolithiasis, a well-documented complication of long-term phosphorus and calcitriol therapy
- A 13-gene Invitae hypophosphatemia panel was performed to adjudicate her clinical diagnosis of XLH. No pathogenic variants were detected. Medical team suspected TIO not XLH
- Suspected TIO was further confirmed with a combined 68Ga-DOTATATE PET/CT scan



CT, computed tomography; DXA, Dual-energy X-ray absorptiometry; PET, positron emission tomograph; TIO, tumour induced osteomalacia; XLH, X-linked hypophosphataemia

Colazo J, et al. Bone Reports 2021; 14:100744

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- Patient was eventually confined to a wheelchair
- Reevaluation of her history resulted in a diagnosis of XLH
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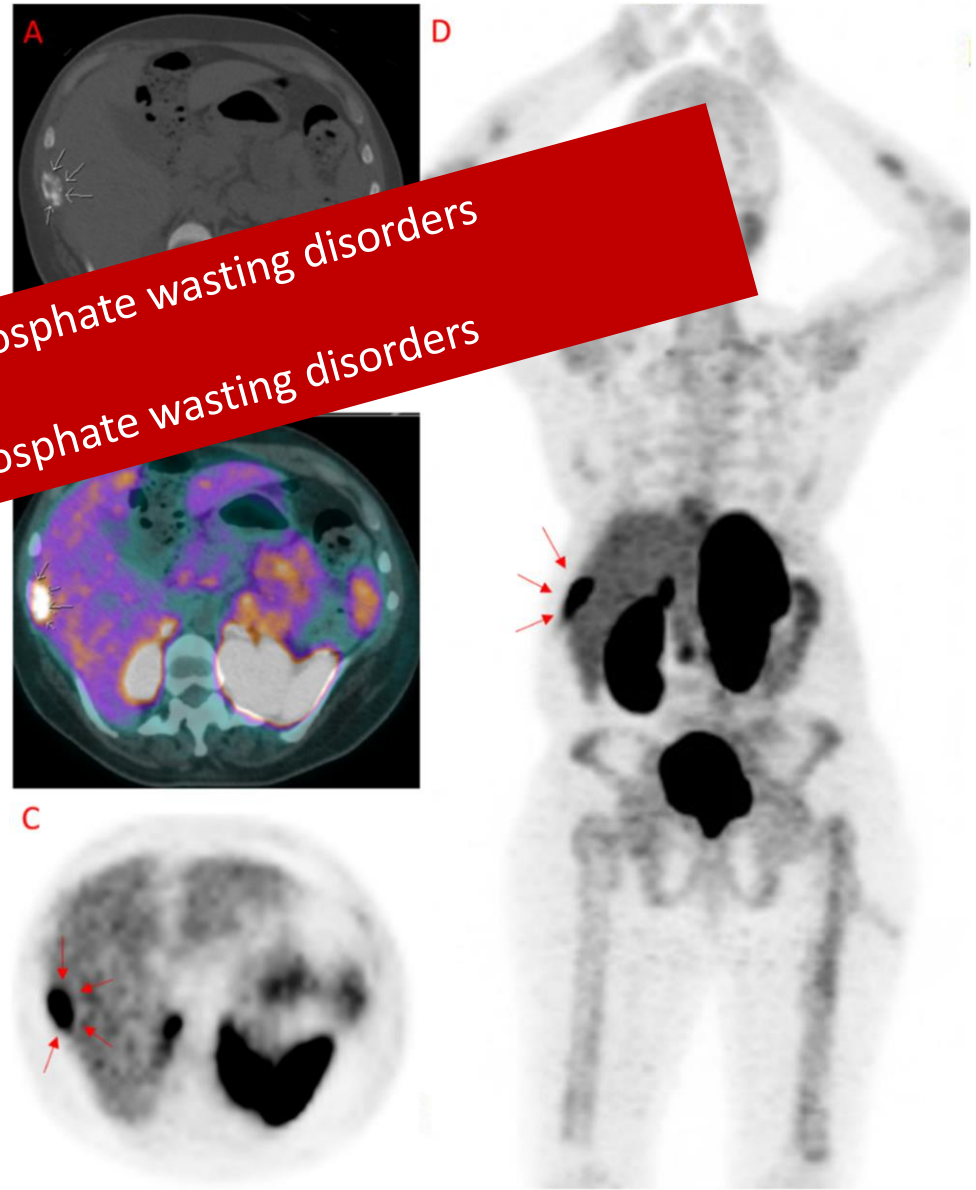
- Renal ultrasound sho… in the lower p… neph… …lication of long-…erapy
- …hypophosphatemia panel was performed …icate her clinical diagnosis of XLH. No pathogenic variants were detected. Medical team suspected TIO not XLH
- Suspected TIO was further confirmed with a combined 68Ga-DOTATATE PET/CT scan

- Demonstrates the utility of genetic testing in the diagnosis of phosphate wasting disorders
- Importance of personal and family histories
- The pitfalls of using exclusively clinical criteria in diagnosing phosphate wasting disorders



CT, computed tomography; DXA, Dual-energy X-ray absorptiometry; PET, positron emission tomograph; TIO, tumour induced osteomalacia; XLH, X-linked hypophosphataemia
Colazo J, et al. Bone Reports 2021; 14:100744

LIMITS IN THE MEASUREMENT OF FGF23

- Intact and C-terminal FGF23 concentrations are important in the diagnosis of hypo- and hyperphosphataemic diseases
- FGF23 is stable when stored at 4°C and 22°C for 48 hours
- FGF23 is stable under five freeze–thaw cycles
- Long-term storage at −80°C induces some variability
- Available assays do not give superimposable data

Sample type, handling, and choice of assay are factors that affect FGF23 levels

FGF23, fibroblast growth factor 23

El-Maouche D, et al. Osteoporos Int. 2016;27:2345-53

KEY SUMMARY POINTS

- FGF23 plays a central role in the mechanisms involved in disorders linked to phosphate wasting
- Differential diagnosis of FGF23-related rickets/osteomalacia should be incorporated in the educational background of the endocrinologist
- The bone doctor is a central figure in the management of these patients

FGF23, fibroblast growth factor 23

HYPOPHOSPHATASIA

Lothar Seefried

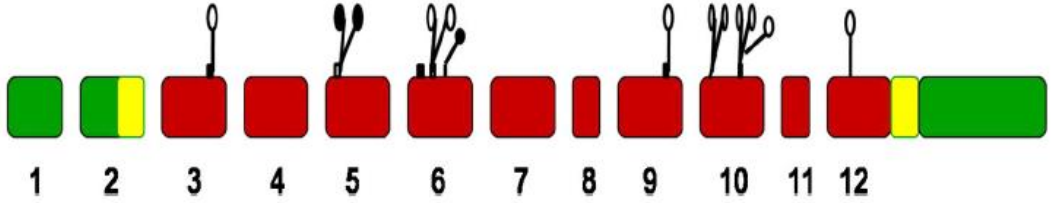
Disclosures:

Honoraria for lectures and advice: AstraZeneca/Alexion, Amgen, Chiesi, GlaxoSmithKline, Ipsen, Kyowa Kirin, medi, STADA, Theramx and UCB.
Support for scientific projects: AstraZeneca/Alexion, Kyowa Kirin and Novartis.

Genetic and Biochemical Background of HPP

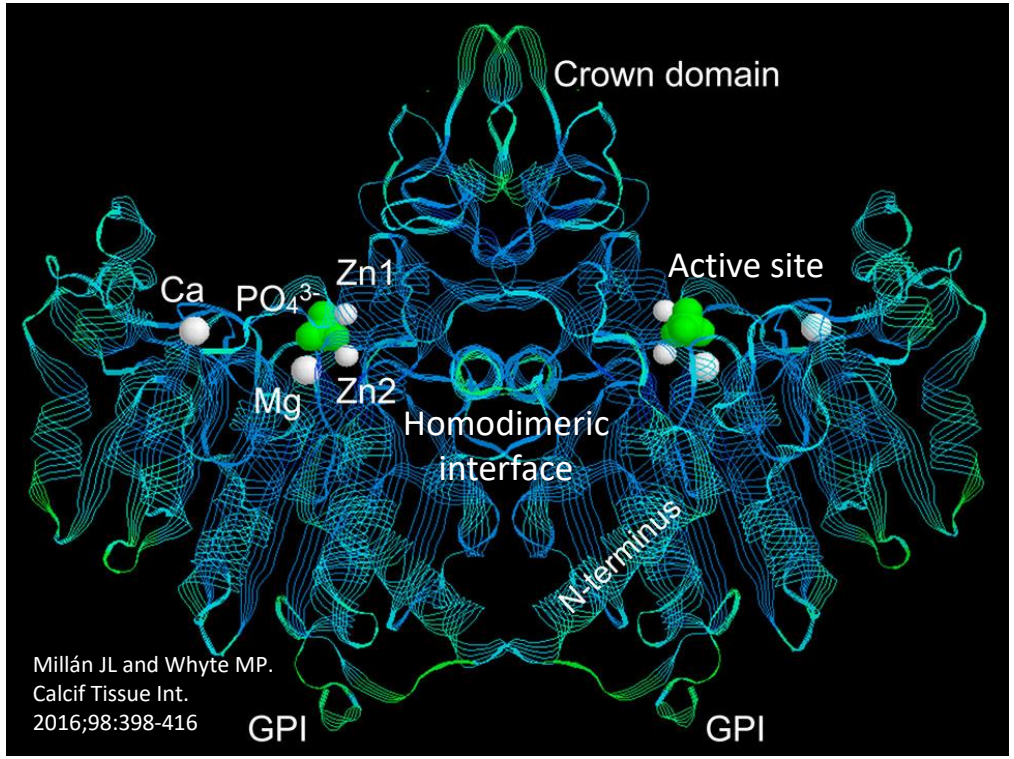
ALPL-Gene, Chromosome 1p36.12 (OMIM 171760)

Length 50kb, 12 Exons Reference cDNA: NM_000478.4



Untranslated regions indicated by green colour. Signal peptide at amino terminus and hydrophobic stretch at the carboxyl terminus in exons 2 and 12, respectively, shown in yellow.

Post-translational modifications incl. five putative *N*-glycosylation sites (Asn140, Asn230, Asn271, Asn303, Asn430) and an undetermined *O*-glycosylation site.

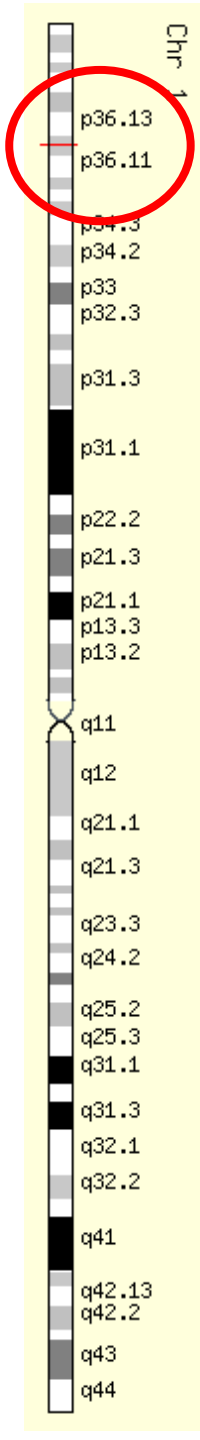


Currently (2022):

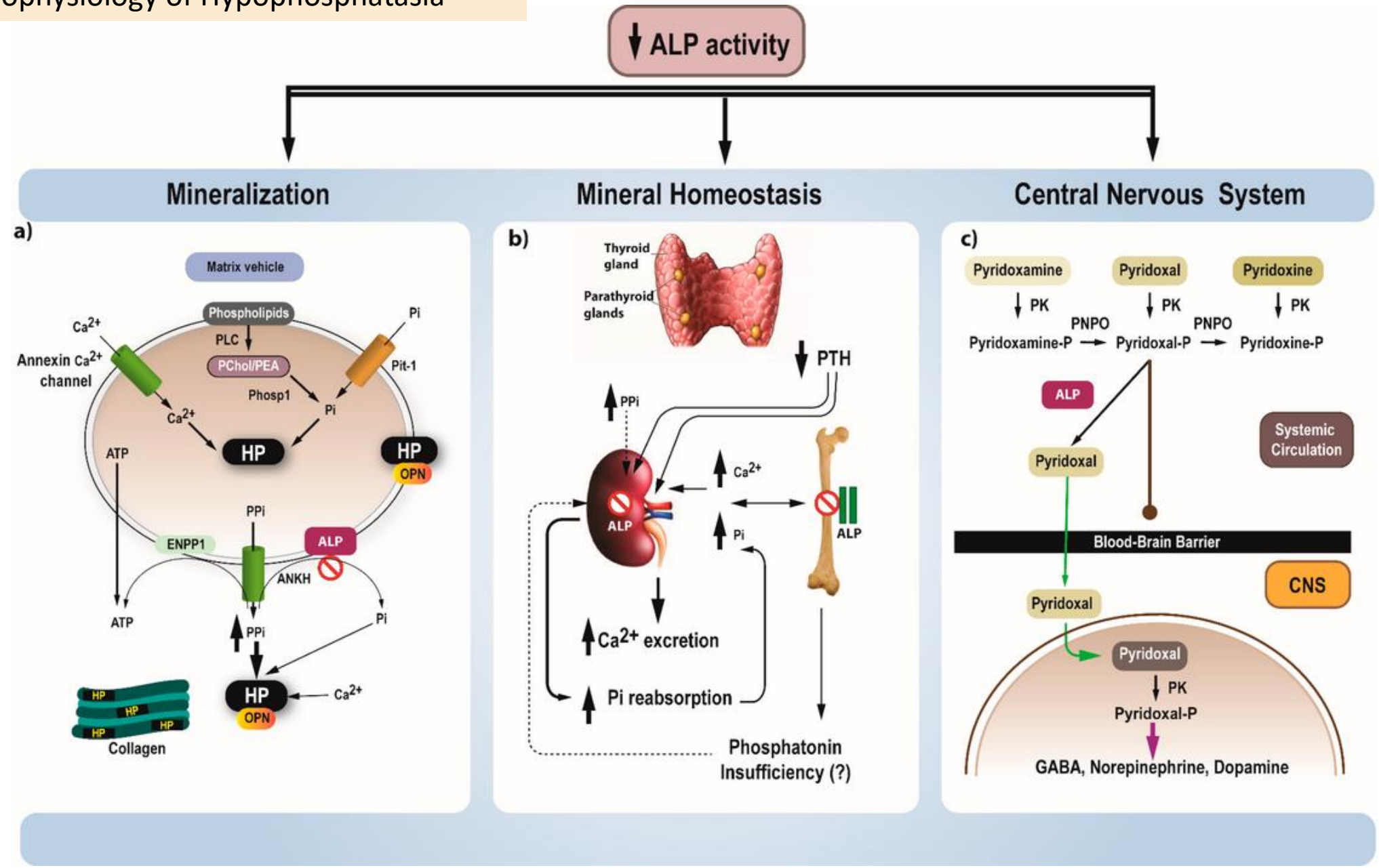
- > 400 known genetic variants
- Pathogenicity TBD

HPP subtype	Severe	Moderate	Mild	Wild-type
Inheritance	AR	AR or AD_{DNE}	$AD_{haploinsuff}$	-
Prevalence	1/300,000	1/2430	1/508	-
Actual classification	Perinatal, infantile	Infantile, childhood, odonto, adult (typical)	Adult (unspecific signs)	-
Genotypes	s/s, Sd/S, Sd/Sd, m/m_{homoz}	Sd/m, s/m, Sd/N	s/N, m/N	N/N

Mornet E, et al. Eur J Hum Genet. 202;29:289-99.

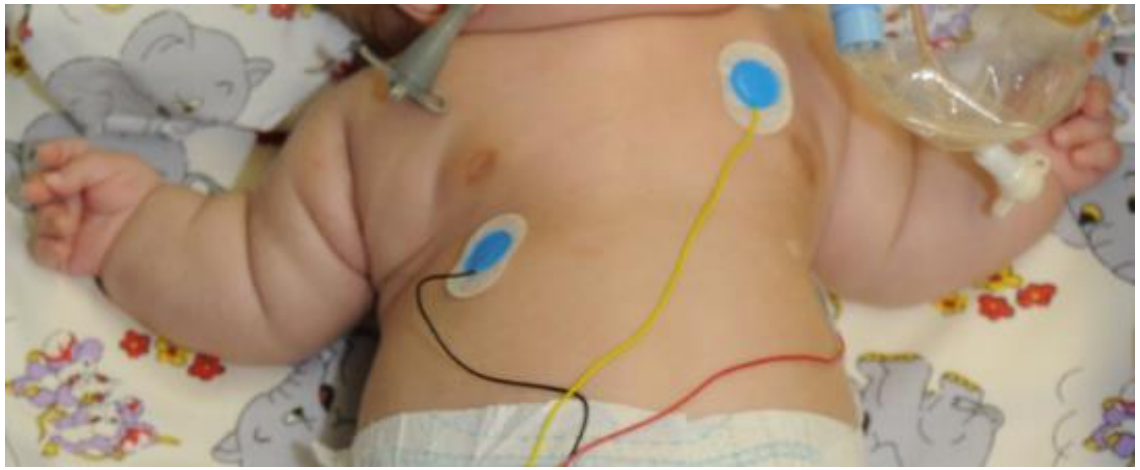


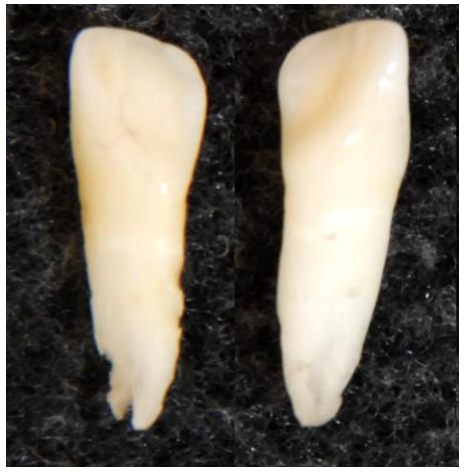
Pathophysiology of Hypophosphatasia

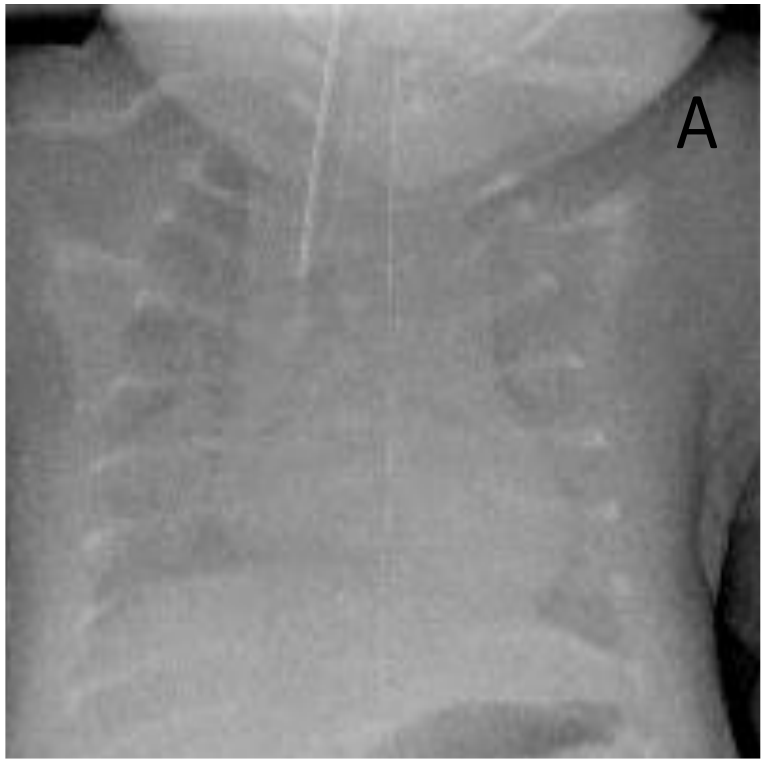


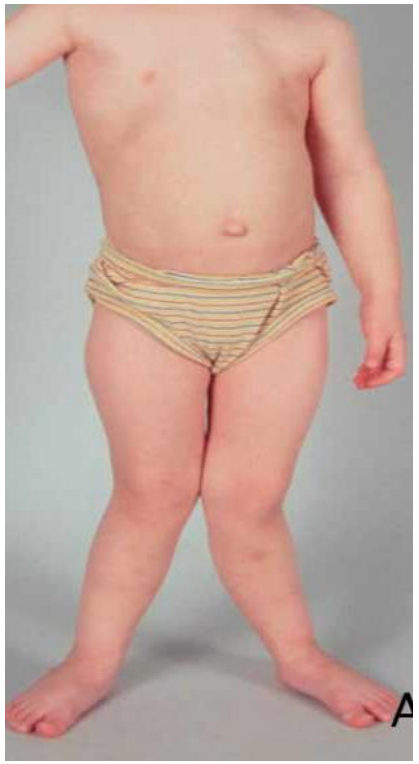
Tournis S, et al. J Clin Med. 2021;10:5676

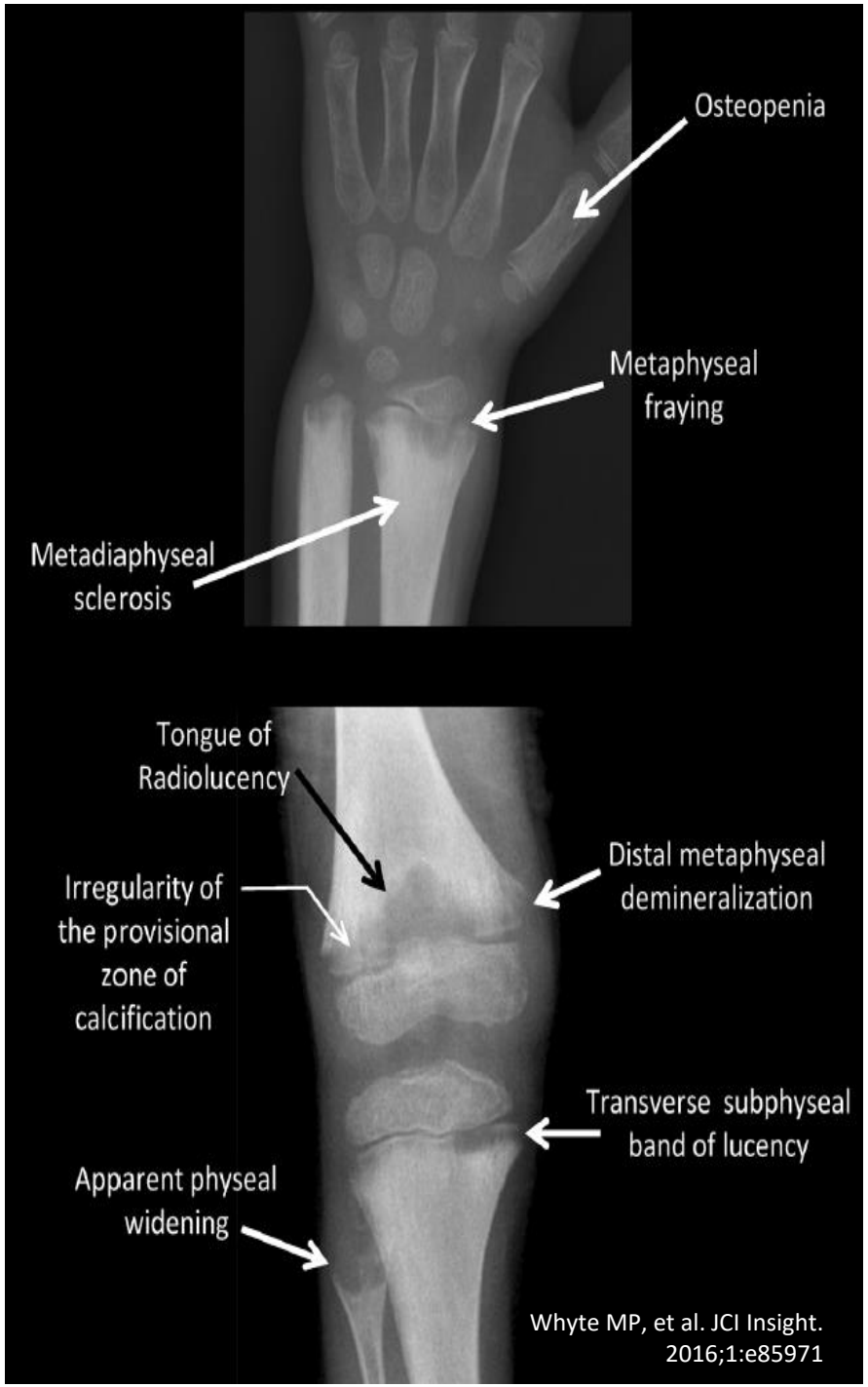
Pediatric HPP











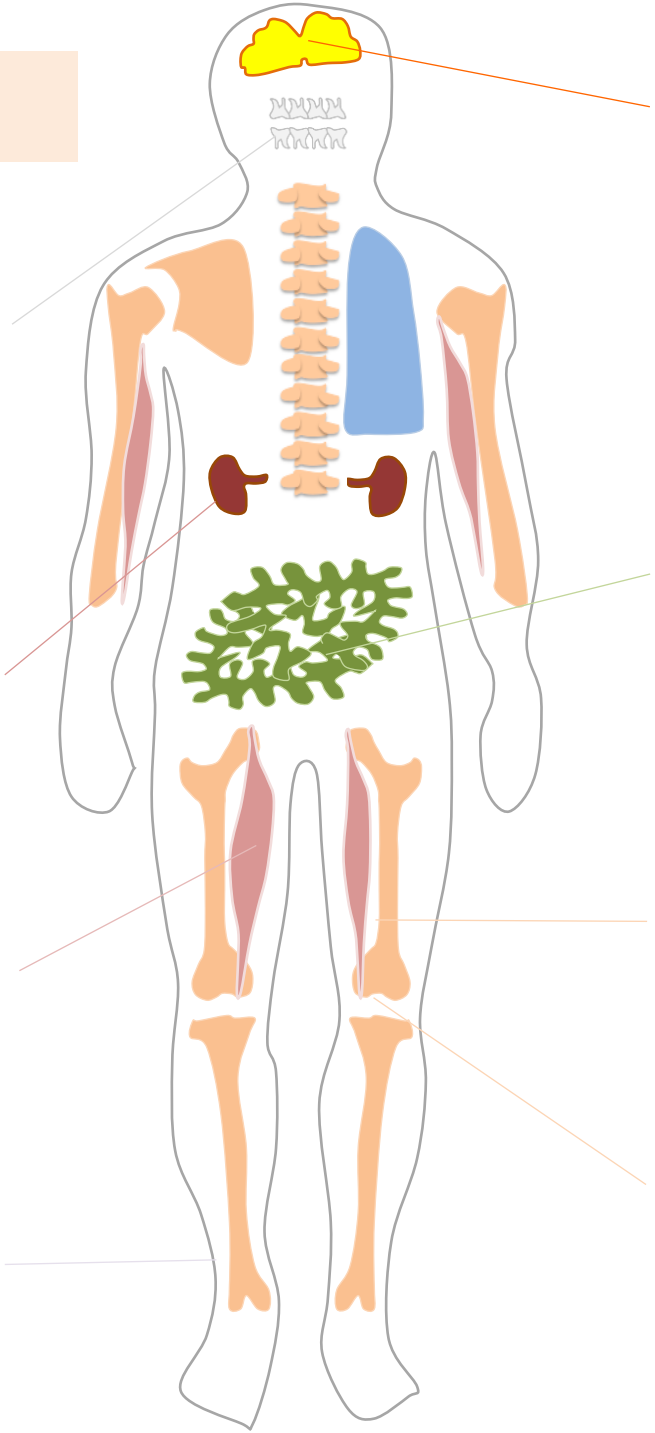
Clinical Picture in Adult HPP

Teeth:
Tooth loss
Periodontal disease

Kidney:
Nephrocalcinosis
Renal insufficiency
Kidney stones

Muscle:
Weakness
Fatigue/induration

Tendons:
Tendinosis calcarea
Enthesiopathy
Tendinitis/Enthesitis



CNS/sensory organs:
Cephalgia/Migraine
Depression/Anxiety
Visual/auditory compromise

GI issues:
Diarrhea/constipation
Meteorism
Intolerances

Bone:
Pseudofractures
Insufficiency fractures
Bone marrow edema
Osteomalacia

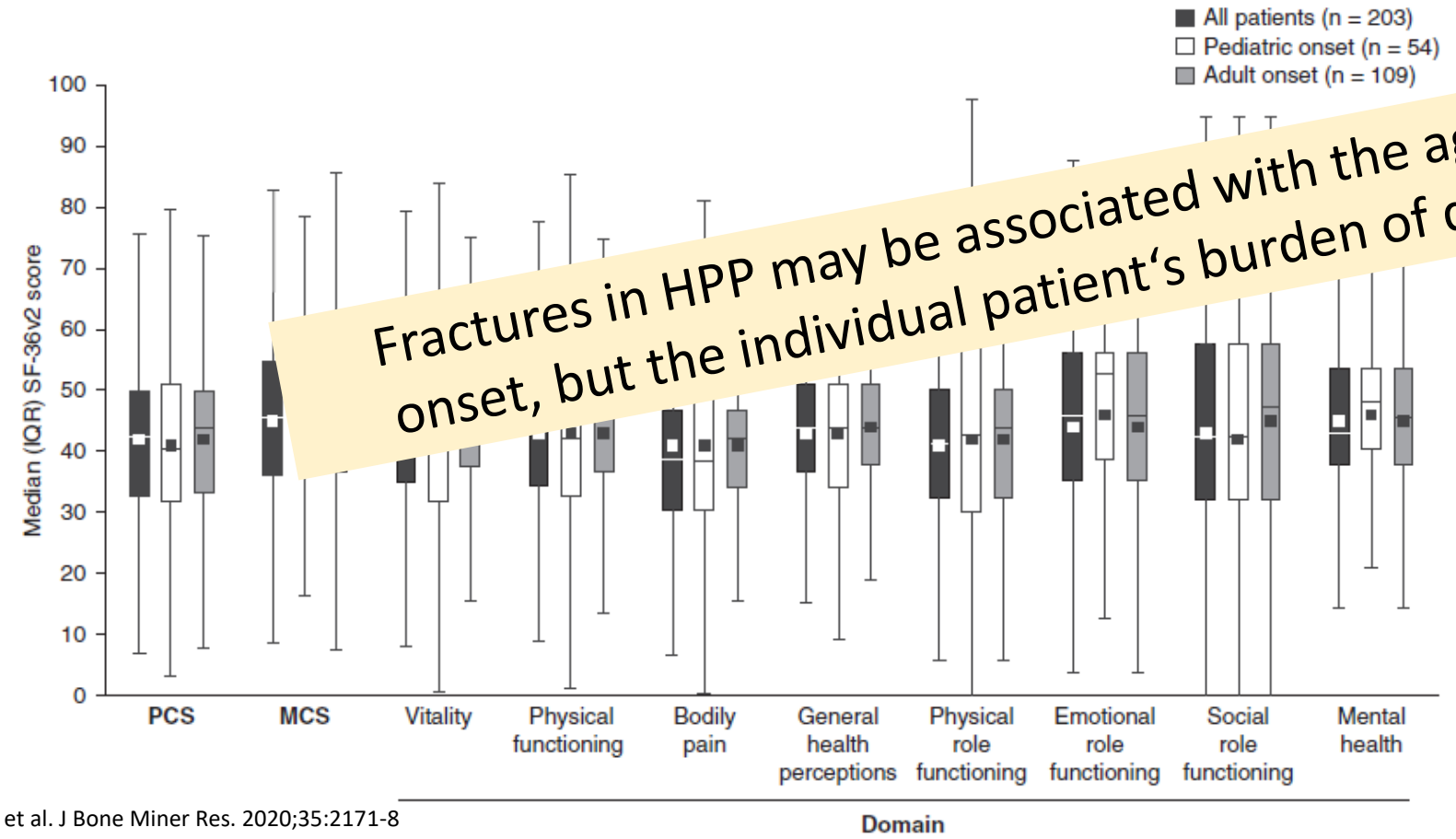
Joint:
Osteoarthritis
Chondrocalcinosis
Pseudogout

Modified according to:
Seefried L, et al. Symptoms and Diagnosis in Adults. In: Hofmann, Girschick, Seefried eds, Diagnosis and Management of Hypophosphatasia, 2nd Edition, Uni-Med, 2022

Burden of Illness in Adults With Hypophosphatasia: Data From the Global Hypophosphatasia Patient Registry

Lothar Seefried,[1] Kathryn Dahir,[2] Anna Petryk,[3] Wolfgang Högler,[4] Agnès Linglart,[5] Gabriel Ángel Martos-Moreno,[6,7,8] Keiichi Ozono,[9] Shona Fang,[3] Cheryl Rockman-Greenberg,[10] and Priya S Kishnani[11]

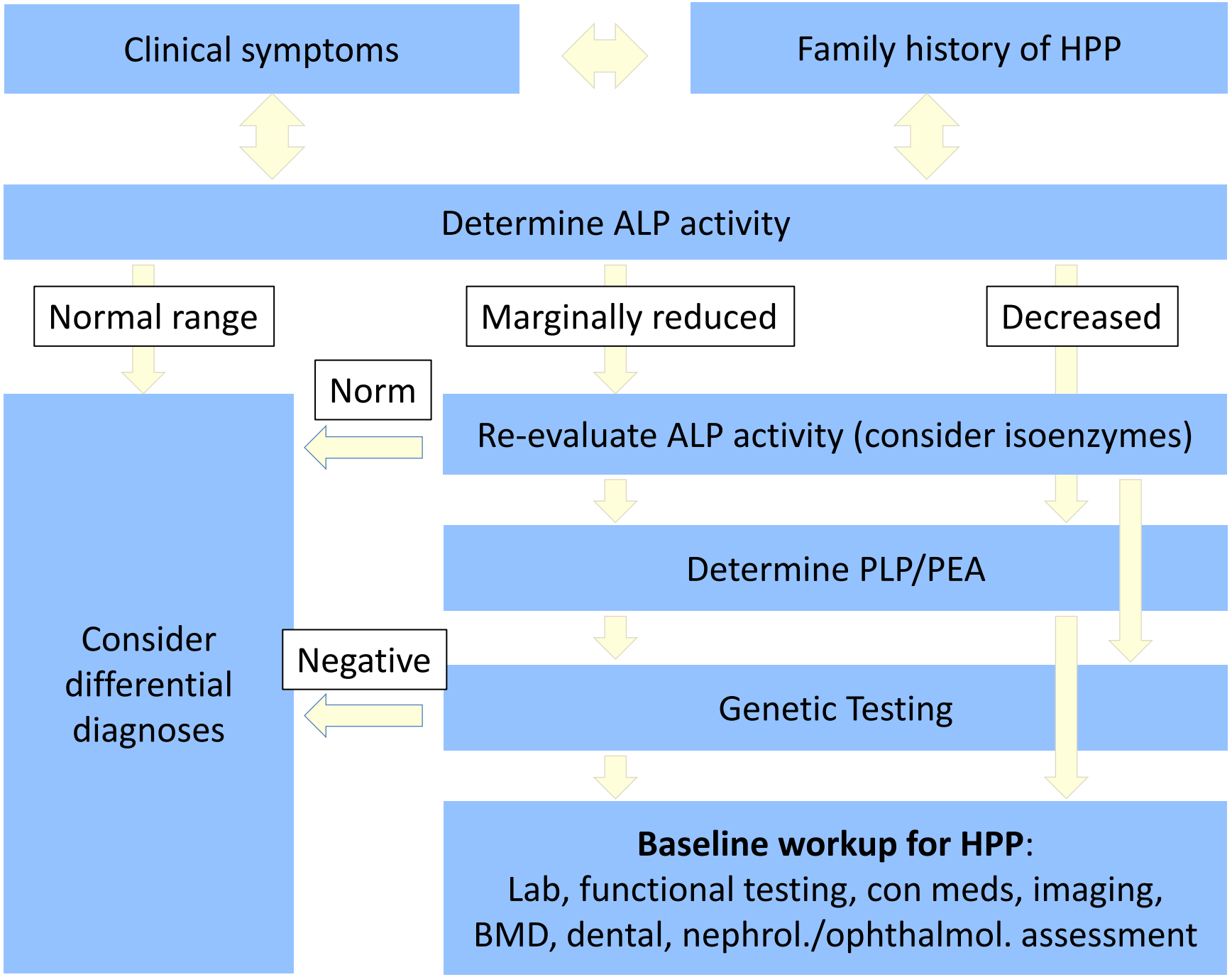
Fracture/pseudofracture	All patients $n = 240$	Pediatric onset $n = 67$	Adult onset $n = 123$	p value
Patients with any fracture/pseudofracture, *n* (%)	149 (62.1)	48 (71.6)	70 (56.9)	**0.046**
Patients with ≥3 fractures/pseudofractures, *n* (%)	52 (21.7)	21 (31.3)	22 (17.9)	**0.034**
No. of fracture(s)/pseudofracture(s) per patient, median (min, max)	2 (1, 21)	2 (1, 12)	2 (1, 21)	0.421



Fractures in HPP may be associated with the age of disease onset, but the individual patient's burden of disease is not

Characteristic	Participants ($N = 304$)
Sex, *n* (%)	
Male	78 (25.7)
Female	226 (74.3)
Age (years) at study enrollment	
Mean (SD)	47.6 (14.7)
Median (min, max)	48.6 (18.8, 79.8)
Age (years) at occurrence of first HPP sign/symptom ($n = 205$)	
Mean (SD)	26.0 (21.1)
Median (min, max)	20.4 (0.0, 75.3)
Age of HPP onset category, *n* (%) ($n = 296$)	
Perinatal/infantile	9 (3.0)
Childhood	87 (29.4)
Pediatric-onset, spec… nknown	2 (0.7)
Adult	132 (44.6)
	66 (22.3)
	40.9 (18.9)
	42.8 (0.0, 77.0)
…ears) to diagnosis,[a] ($n = 194$)	
Mean (SD)	14.2 (17.3)
Median (min, max)	5.7 (−1.1,[b] 62.2)
ALP level at enrollment or at last assessment before treatment with asfotase alfa (if treated), U/L[c] ($n = 270$)	
Mean (SD)	26.5 (12.8)
Median (min, max)	24.0 (2.0, 98.0)
History of HPP-related clinical manifestations, *n* (%)	
Pain ($n = 300$)	202 (67.3)
Dental ($n = 300$)	163 (54.3)
Skeletal ($n = 298$)	129 (43.3)
Constitutional/metabolic ($n = 298$)	99 (33.2)
Muscular ($n = 300$)	86 (28.7)
Renal ($n = 300$)	45 (15.0)
Rheumatic ($n = 300$)	40 (13.3)
Neurologic ($n = 298$)	34 (11.4)
Respiratory ($n = 300$)	12 (4.0)

Seefried L, et al. J Bone Miner Res. 2020;35:2171-8



Seefried L, Genest F.
Osteologie/Osteology. 2017;26:36-41

Multidisciplinary Management of HPP

Imaging:
- X-ray: osteomalacia, fractures, pseudofractures
- Ultrasound: calcifications (e.g. nephrocalcinosis)
- MRI: bone marrow lesions

Consultations
- Dentist
- Nephrologist
- Neurologist
- Ophthalmologist
- Physiotherapist…

Bone biopsy: conceivable/not diagnostic

Bone Mineral Density (DXA, qCT): helpful information, not diagnostic

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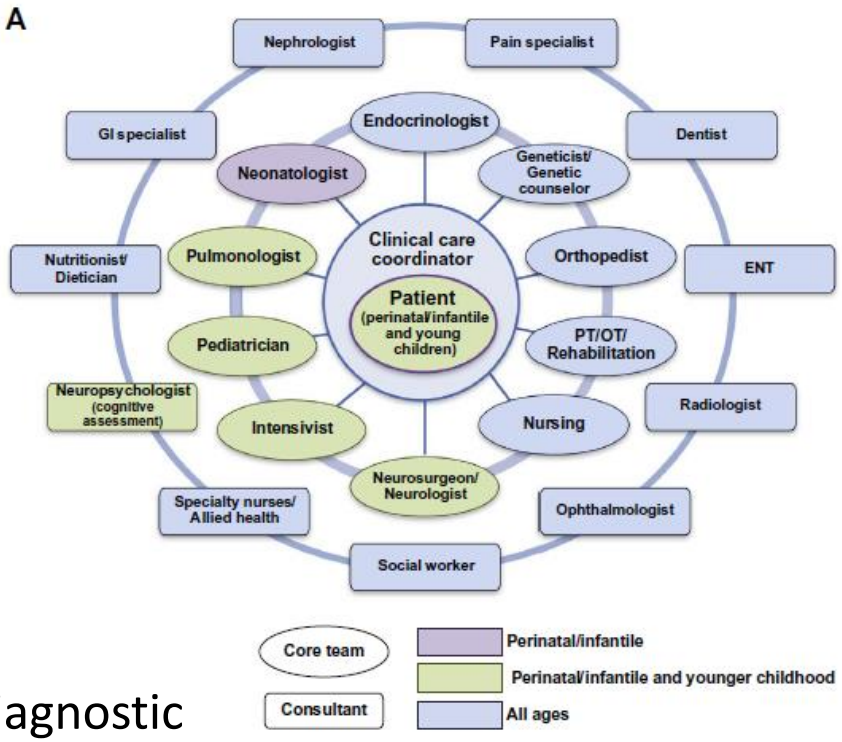
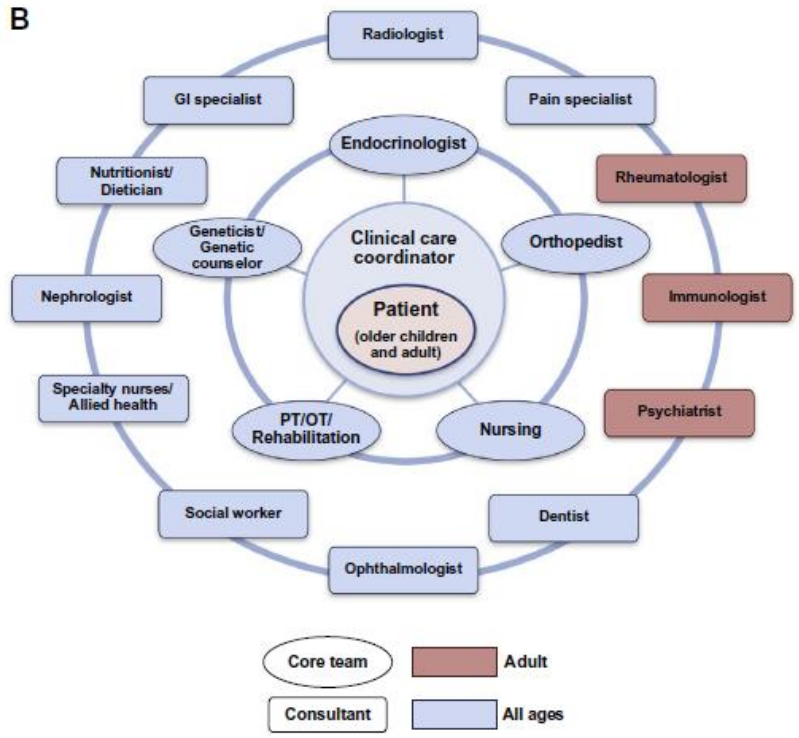
Review article

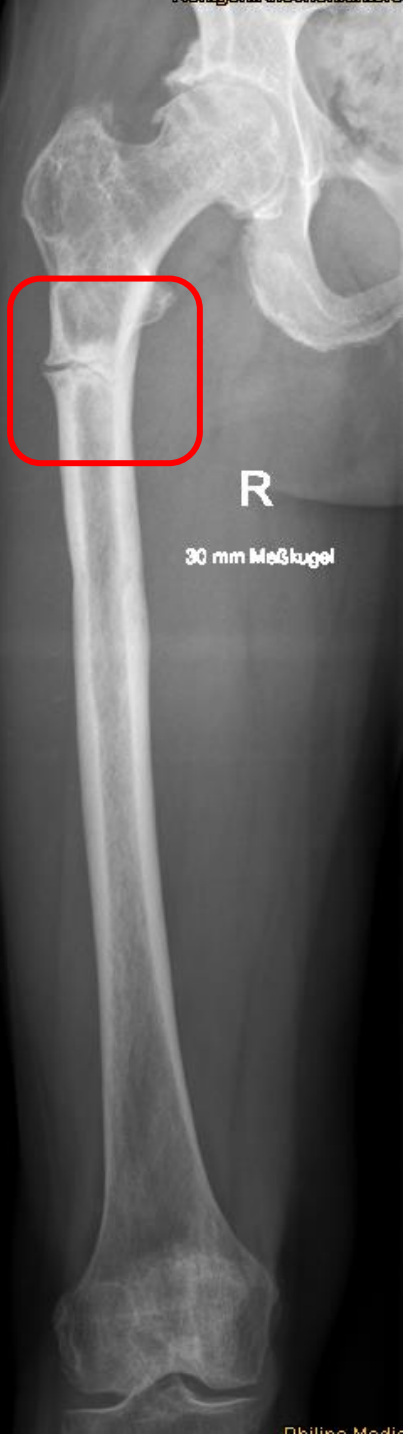
Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa

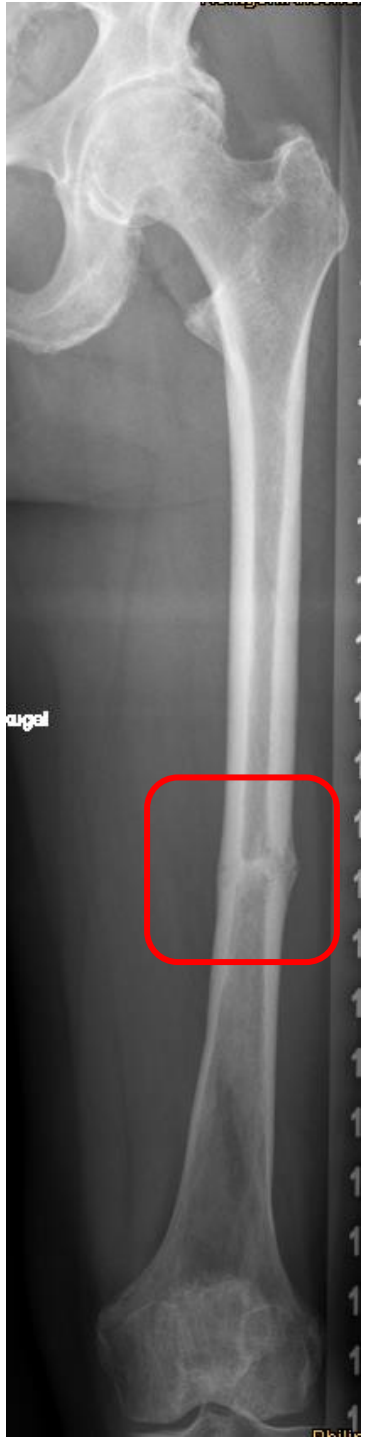
Priya S. Kishnani[a,*,1], Eric T. Rush[b,1], Paul Arundel[c], Nick Bishop[d], Kathryn Dahir[e], William Fraser[f], Paul Harmatz[g], Agnès Linglart[h], Craig F. Munns[i,j], Mark E. Nunes[k], Howard M. Saal[l], Lothar Seefried[m], Keiichi Ozono[n,1]

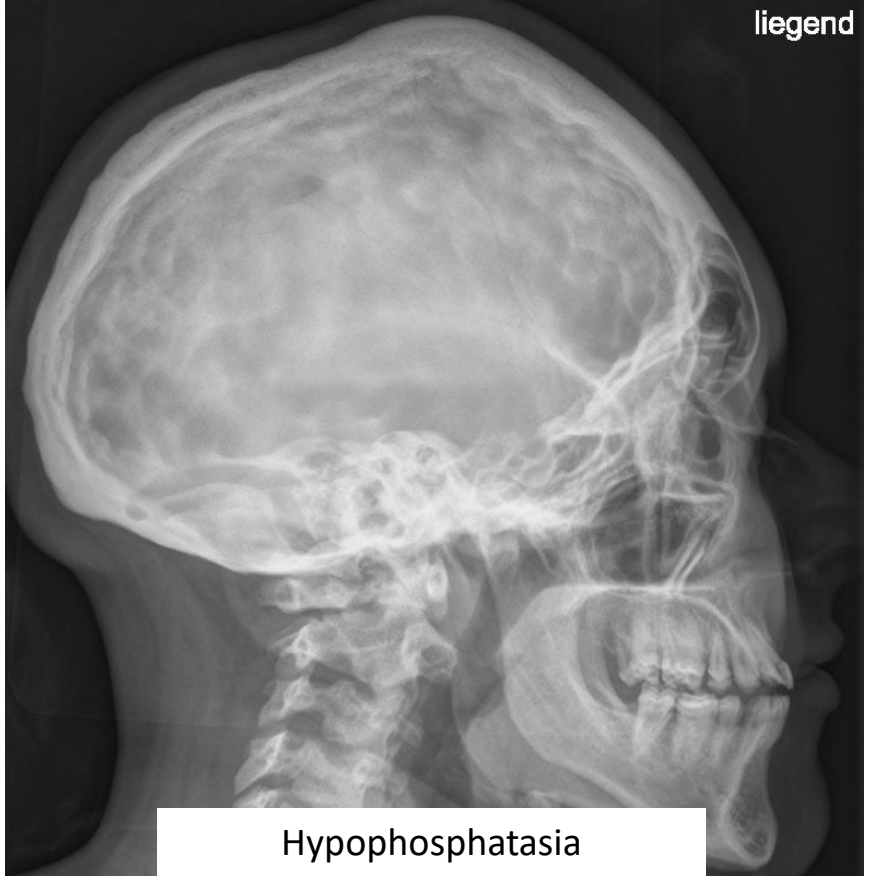




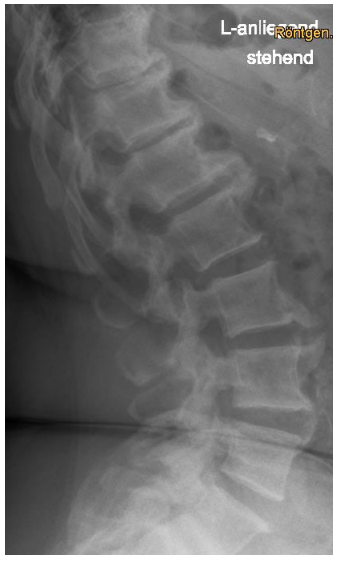
Kishnani PS, et al. Mol Genet Metab. 2017;122:4-17

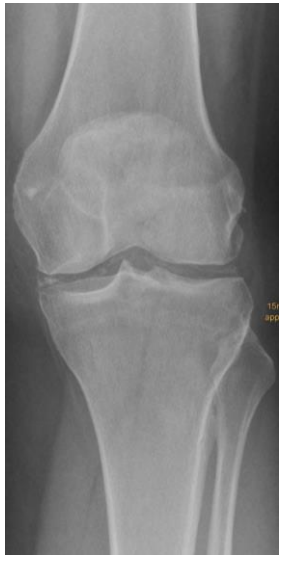


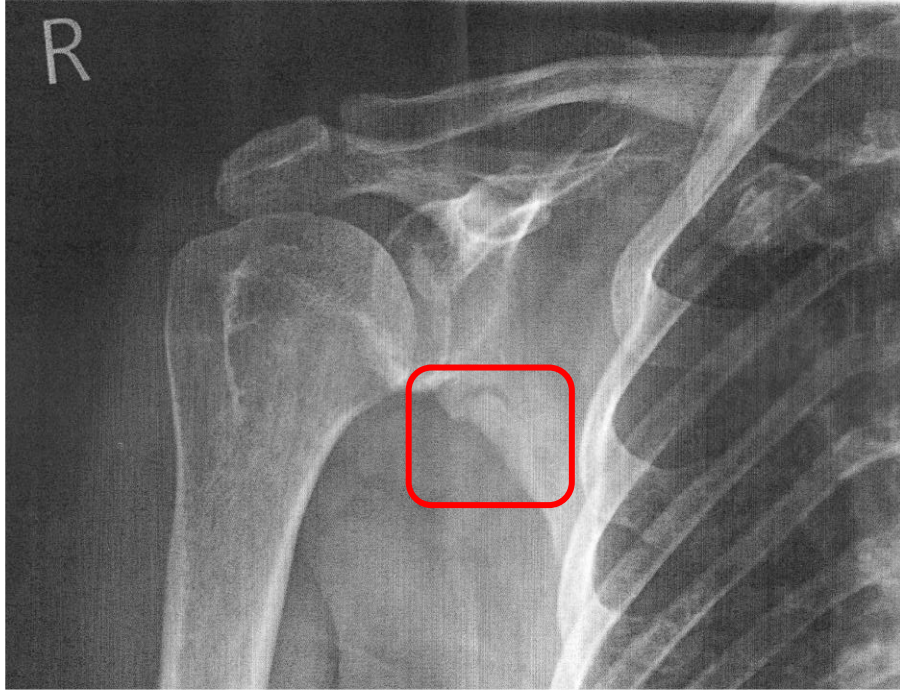


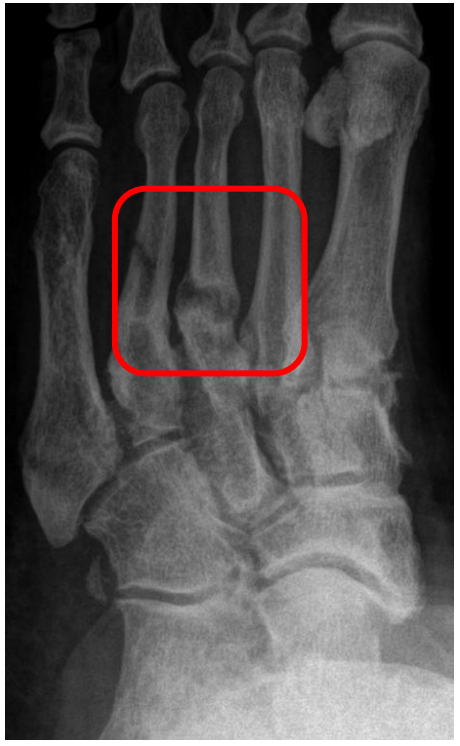


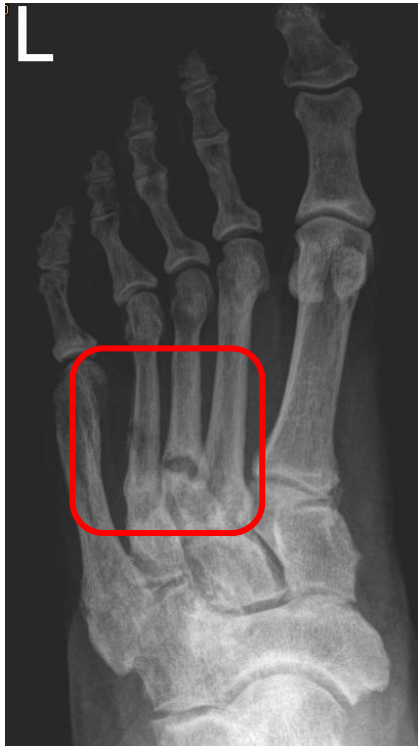
Hypophosphatasia











Osteoporosis International
https://doi.org/10.1007/s00198-018-4552-3

ORIGINAL ARTICLE

Subtrochanteric and diaphyseal femoral fractures in hypophosphatasia—not atypical at all

Bisphosphonates: 7/15
Hypovitaminosis D: 10/15

F. Genest[1] · L. Seefried[1]

Table 1 Individual patient characteristics including BMD, fracture types, and mutational analysis. *D* diaphyseal, *S* subtrochanteric, *n.a.* not available

ID no.	Age (year)	Gender	Weight (kg)	Height (cm)	BMI (kg/m^2)	LS T-score	LS Z-score	Fracture side		Exon	cDNA	Protein	Exon	cDNA	Protein
								Right	Left						
01	44	Female	57	160	22.3	+ 3.3	+ 3.7	D	D	6	c.530C > T	p.Ala177Val	6	c.530C > T	p.Ala177Val
02	54	Female	85	154	35.8	+ 0.2	+ 1.2	D	D	6	c.526G > A	p.Ala176Thr	7	c.661G > T	p.Gly221Cys
03	55	Female	82	166	29.8	+ 0.9	+ 2.0	S	D	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
04	71	Female	69	158	27.6	n.a.	n.a.	S	S	6	c.526G > A	p.Ala176Thr	6	c.535G > A	p.Ala179Thr
05	62	Female	68	160	26.6	− 0.2	+ 1.4	S	S	6	c.571G > A	p.Glu191Lys	12	c.1354G > A	p.Glu452Lys
06	39	Male	64	160	25.0	− 0.6	− 0.5	S	–	4	c.211C > A	p.Arg71Ser	6	c.571G > A	p.Glu191Lys
07	46	Female	115	157	46.7	+ 7.0	+ 7.5	S	D	5	c.379A > G	p.Thr127Ala	6	c.526G > A	p.Ala176Thr
08	51	Female	48	134	26.7	+ 3.8	+ 4.7	D	D	5	c.382G > A	p.Val128Met	11	c.1276G > A	p.Gly426Ser
09	45	Female	51	155	21.2	+ 1.0	+ 1.5	S	–	10	c.1009G > A	p.Asp337Asn	12	c.1363G > A	p.Gly455Ser
10	76	Female	53	152	22.9	+ 3.5	+ 5.9	S	D	6	c.500C > T	p.Thr167Met	6	c.571G > A	p.Glu191Lys
11	55	Male	78	175	25.5	− 0.8	− 0.3	–	D	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
12	73	Female	63	146	29.6	+ 3.1	+ 5.4	–	S	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
13	56	Male	83	168	29.4	+ 0.5	+ 1.1	D	–	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
14	43	Female	65	160	25.4	+ 1.3	+ 1.6	S	S	3	c.119C > T	p.Ala40Val	7	c.746G > T	p.Gly249Val
15	50	Female	80	160	29.7	− 0.6	0.0	D	D	6	c.571G > A	p.Glu191Lys	12	c.1354G > A	p.Glu452Lys
Mean	54.7		70.7	157.9	28.3	+ 1.6	+ 2.5								

Adapted from: Genest F, Seefried L. Osteoporos Int. 2018;29:1815-25

ORIGINAL ARTICLE

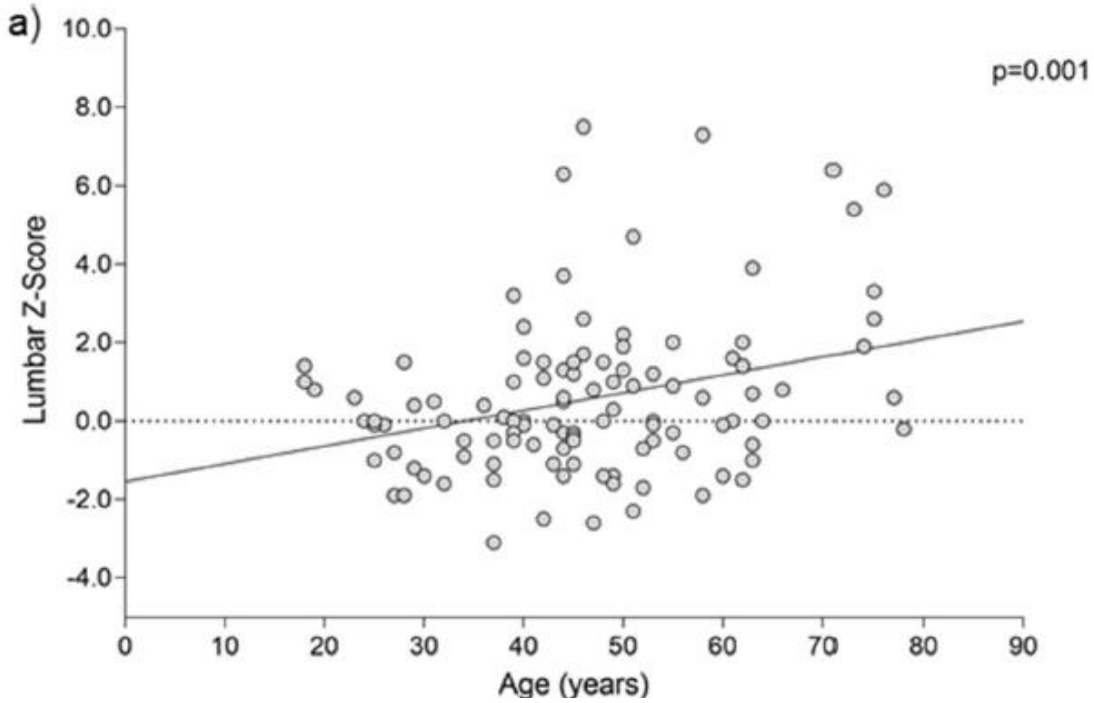
Bone mineral density and fracture risk in adult patients with hypophosphatasia

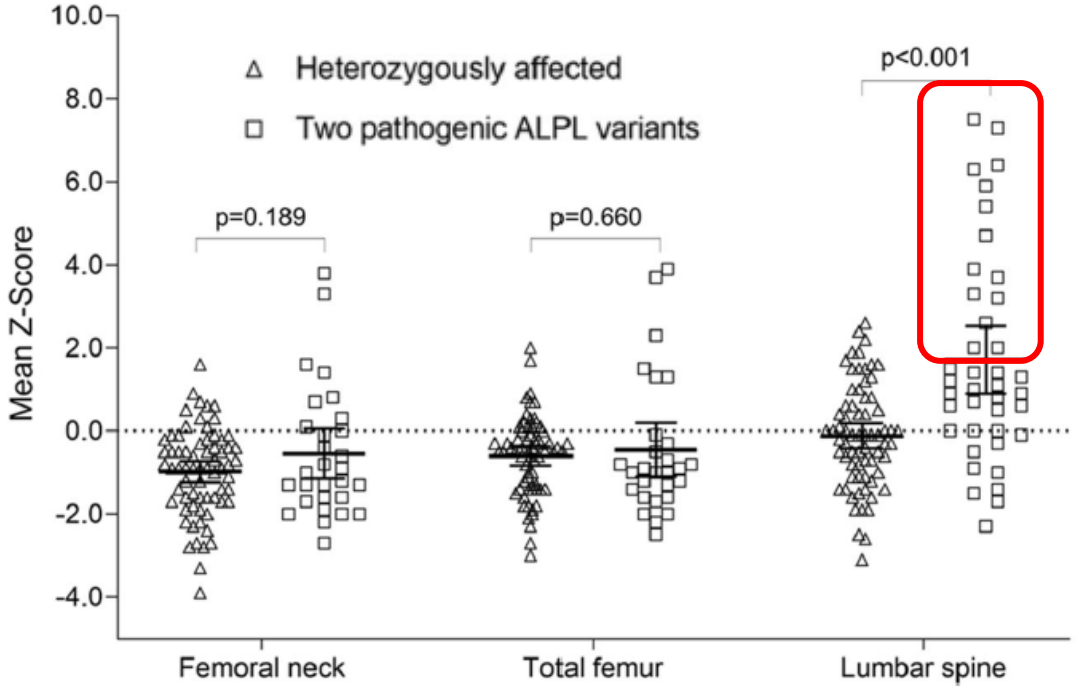
F. Genest[1] · L. Claußen[1] · D. Rak[1] · L. Seefried[1]

Mean (SD)	HPP-related fractures (n = 22/20%)	Other patients (n = 88/80%)	p value*
Anthropometrics			
Age (year)	52.73 (14.0)	44.57 (13.4)	0.013*
Height (cm)	167.18 (10.6)	167.36 (9.7)	0.939
Weight (kg)	77.05 (16.2)	71.93 (17.0)	0.205
BMI (kg/m^2)	27.37 (4.0)	25.63 (5.6)	0.177
Lab values (normal range)			
ALP (f:42-98/m: 53-128 U/l)	16.68 (11.1)	26.32 (11.0)	< 0.001*
Phosphate (0.6-1.8 mmol/l)	1.58 (0.1)	1.30 (0.2)	< 0.001*
PLP (5-30 ng/ml)	462.78 (483.2)	75.33 (104.4)	0.001*
uPEA (2.3-11.3 mmol/mol Krea)	59.36 (51.9)	16.10 (17.3)	0.001*
NTX (12.9-22.7 nM BCE/l)	15.55 (13.4)	12.96 (4.9)	0.040*
Vitamin D (20-40 ng/ml)	28.27 (11.6)	24.82 (13.8)	0.301
BMD			
Lumbar spine T-Score	+ 1.33 (2.1)	− 0.44 (1.7)	< 0.001*
Lumbar spine Z-Score	+ 2.32 (2.4)	+ 0.11 (1.7)	< 0.001*
Total femur T-Score	− 1.36 (1.1)	− 1.03 (1.2)	0.368
Total femur Z-Score	− 0.77 (1.4)	− 0.53 (1.2)	0.527
Femoral neck T-Score	− 1.71 (1.0)	− 1.74 (1.3)	0.943
Femoral neck Z-Score	− 0.72 (1.2)	− 0.87 (1.3)	0.698

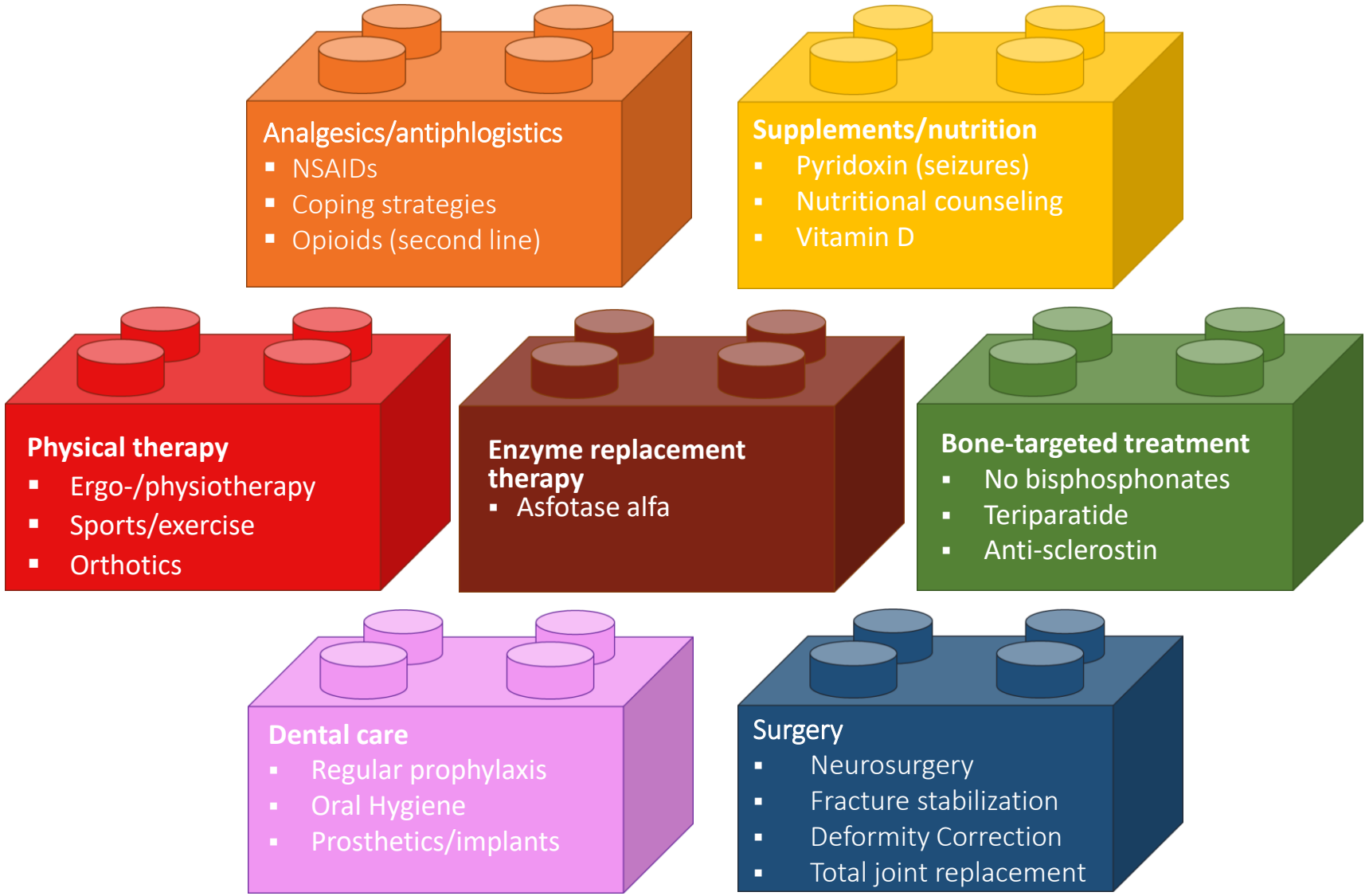
*Significant differences between patients with and without HPP-related fractures

Adapted from: Genest F, et al. Osteoporos Int. 2021;32:377-385





Modules of HPP Treatment



Seefried F, Jakob F. Internist (Berl). 2021;62:486-95

Hypophosphatasia

- ✓ Multisystemic disorder due to deficient ALP activity:
  - Rickets/pseudofractures (severe forms)
  - Extraskeletal manifestations: generalized pain, muscle weakness, periodontal disease, neuropsychiatric issues, GI symptoms

- ✓ Diagnostic approach:
  - Low serum-ALP activity
  - Elevated substrates: PLP/Vit B6, (urinary) PEA, PPi
  - Genetic confirmation recommended

- ✓ Multidisciplinary treatment:
  - Enzyme replacement therapy
  - Analgesics (NSAIDs)
  - Physical therapy
  - Surgery
  - Dental care

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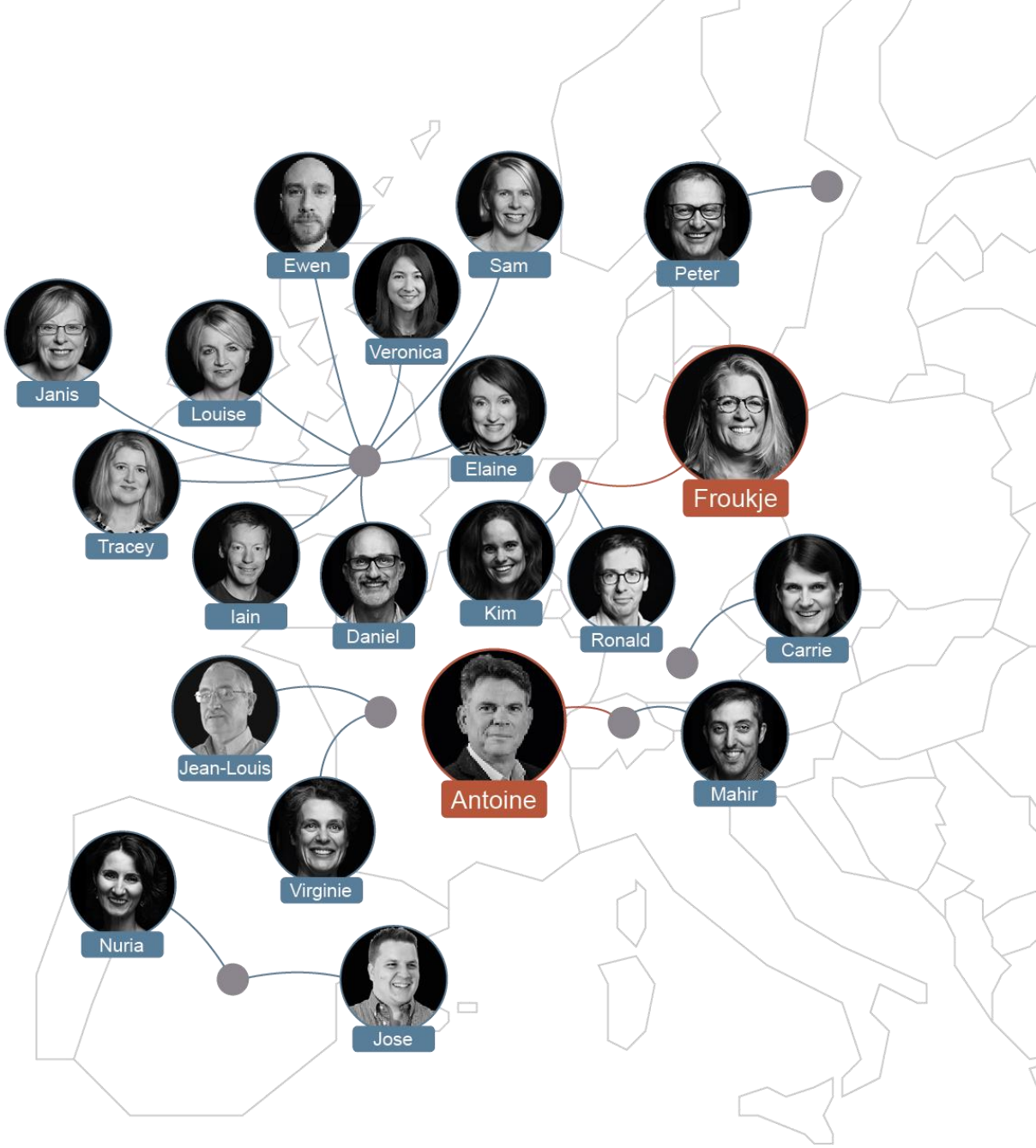

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