Fibroblast growth factor 23 (FGF23)

DIAGNOSTIC APPROACH TO RESISTANT RICKETS

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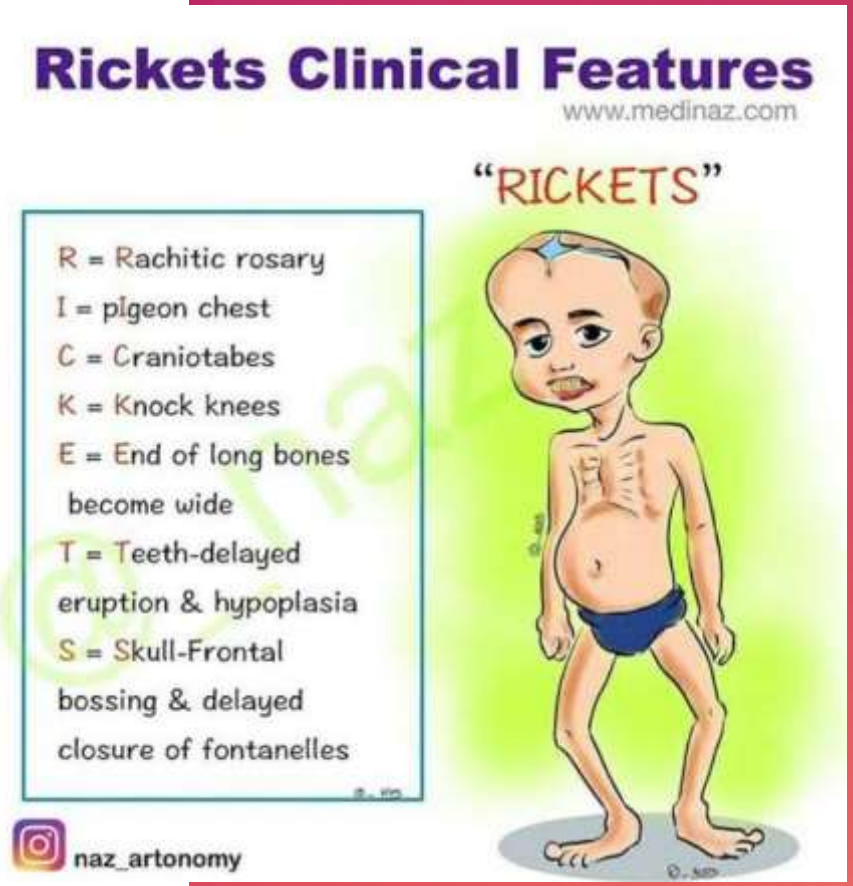
OUTLINE

- Pathophysiology of rickets
- Calcium Phosphate Metabolism
- Role of Regulators- FGF23
- Genetics in Rickets - Vit D Dependent R
  -Hypophosphatemic R
  - RTA
- Evaluation
- Approach to rickets
- Evolving therapy : Burosumab - XLHPR



INTRODUCTION

- Rickets is a disease of growing children arising from alterations in Ca and PO4 metabolism
- It results in impaired apoptosis of hypertrophic chondrocytes and thus widening of the growth plate
- Symptoms depend on the patients age, duration of disease and underlying disorder- however, clinical features alone cannot differentiate
- Nutritional rickets are due to vit D deficiency, and/or dietary deficiency of Ca- and is the most common form
- However, currently more than 20 acquired or hereditary causes of rickets are known

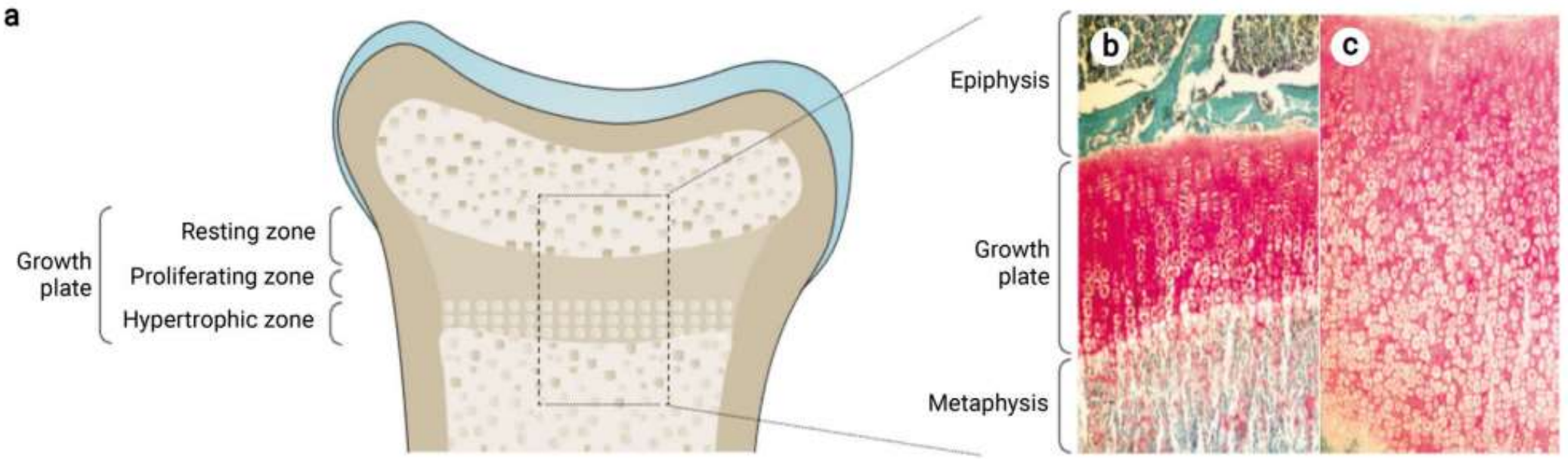
RECOGNITION OF RICKETS

- Impaired mineralization of the growth plate can be radiologically demonstrated in Xrays of Wrist or knee- showing metaphyseal fraying and widening of growth plates

- In conjunction is the elevation of the Osteoblast marker- alkaline Phosphatase

- Rickets may be classified as Calcipenic rickets and Phosphopenic Rickets

MORPHOLOGY OF GROWTH PLATE- ROLE OF PHOSPHORUS



There is growing evidence that the ultimate cause of rickets is the insufficient availability of Phosphate required for terminal differentiation and mineralization of the growth plate chondrocytes

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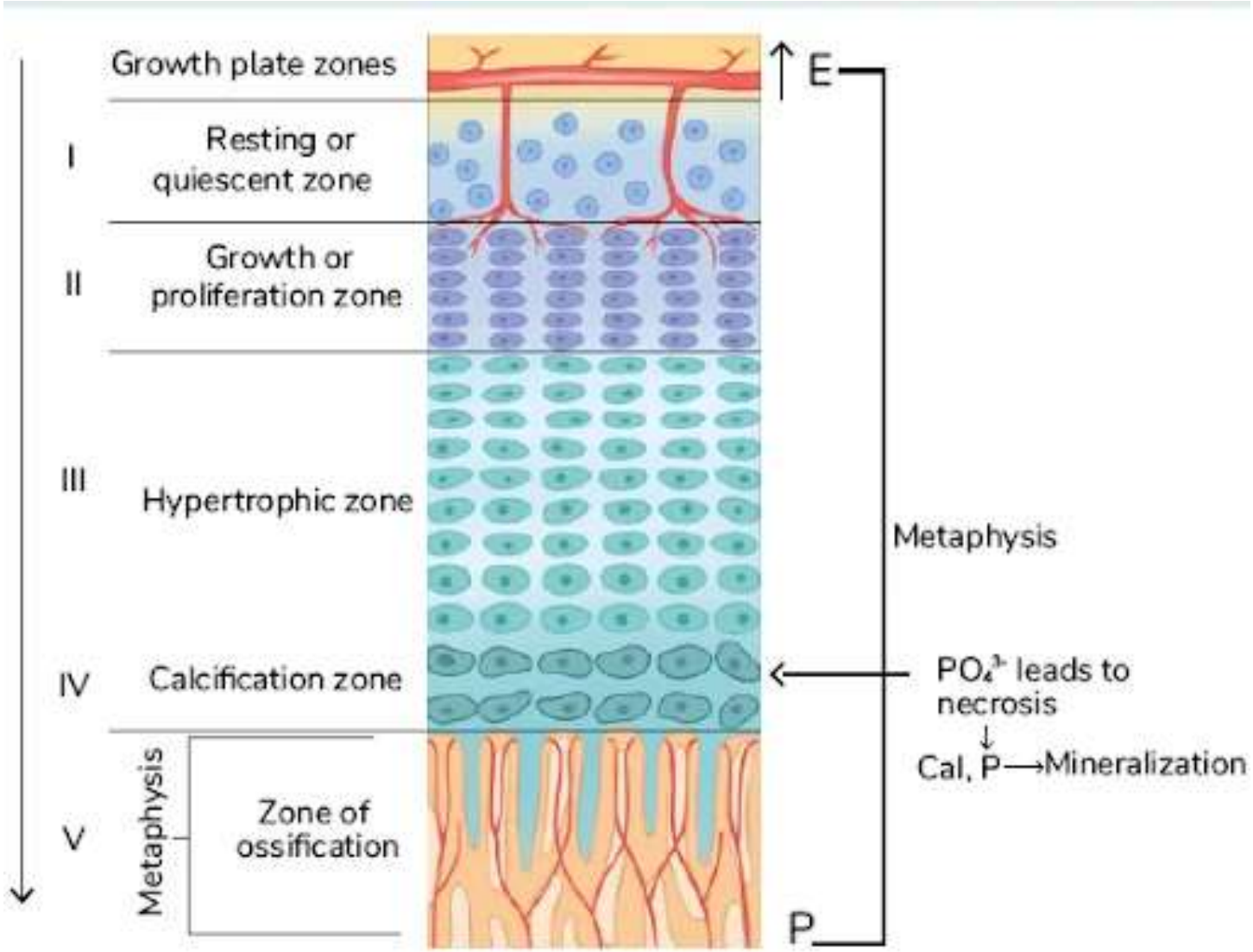


ROLE OF PO4

- Low calcium stores results in increase in PTH
- Stimulates Vit D production
- Increase Ca absorption from gut
- Mobilizes calcium from bone
- Increases PO4 excretion
- Low extracellular PO4
- Decreased apoptosis of hypertrophic chondrocytes

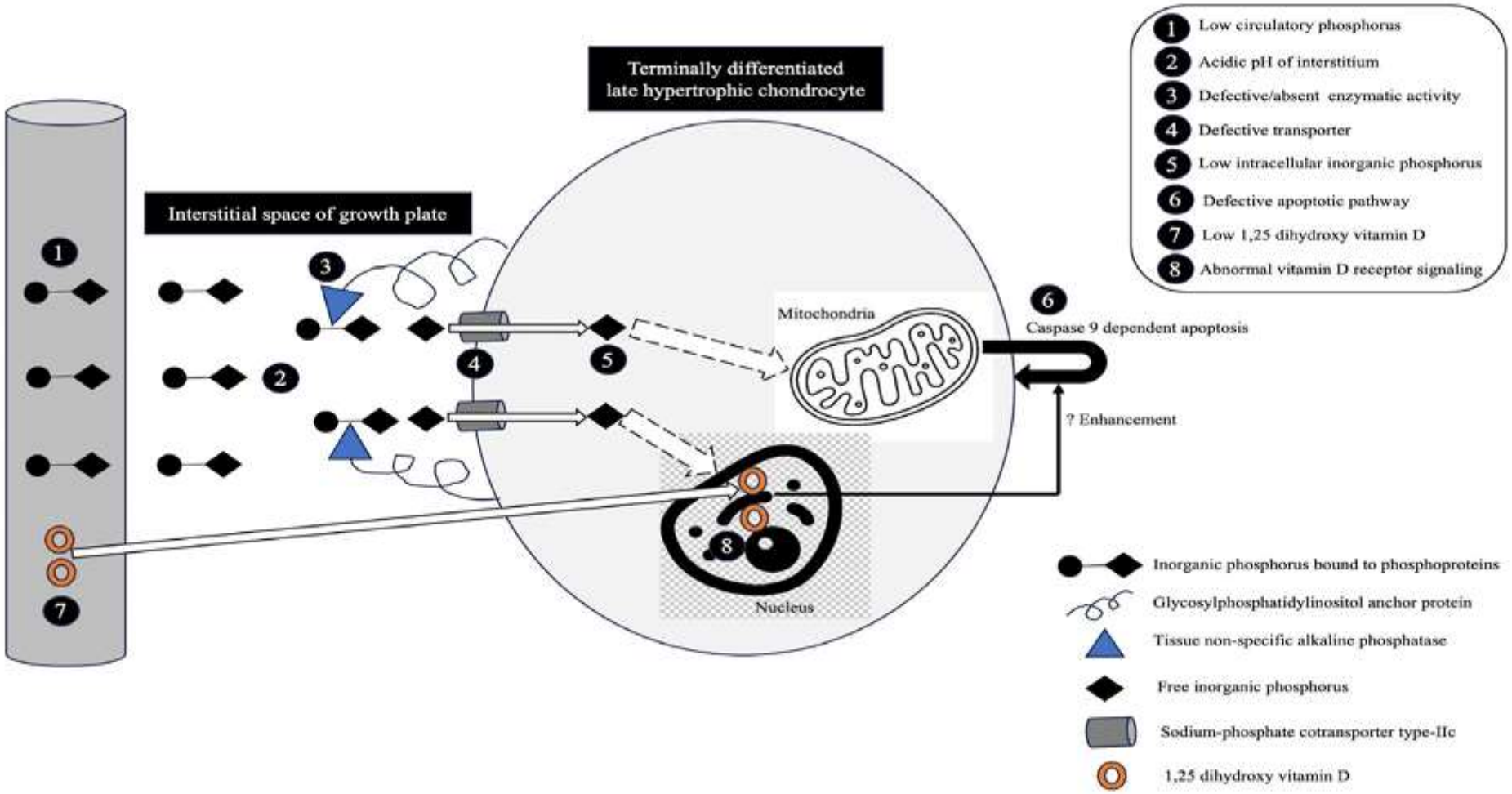
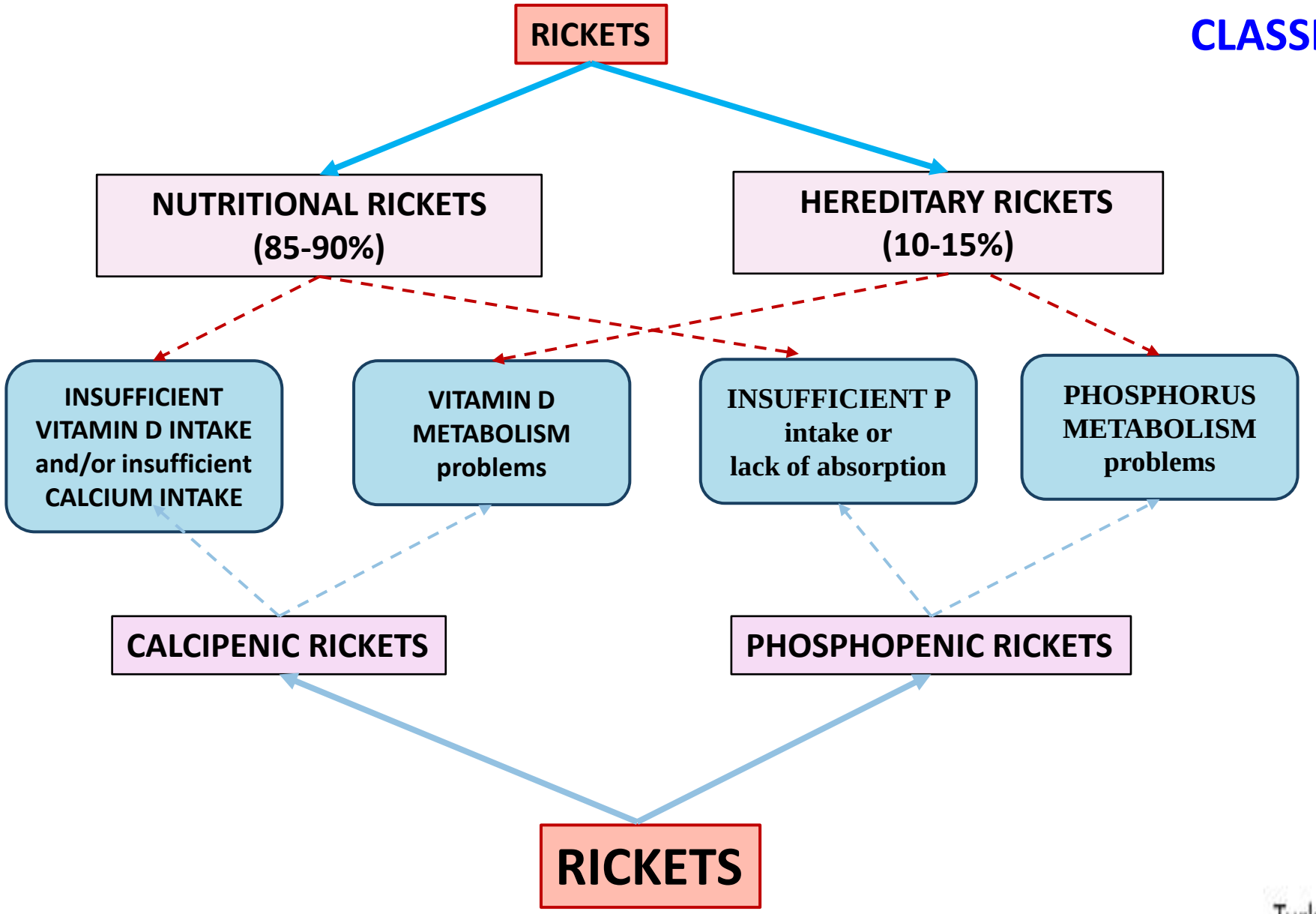


Fig. 2. Mechanism of apoptosis of late hypertrophic chondrocytes. The numbers within the black solid circles denote factors contributing to enlarged growth plates in rickets.

IMPROVED UNDERSTANDING OF PATHOPHYSIOLOGY

- Discovery of new Ca and PO4 metabolism regulator- Phosphaturic hormone- **Fibroblast Growth factor 23 (FGF23)**
- Easy availability of **genetic testing** has revolutionized the diagnosis and management of many forms of rickets
- Helped in understanding the pathophysiology in many hereditary disorders
- **Targeted therapy** has now become available for some hereditary forms like XLHR (X-linked hypophosphatemic rickets) which requires correct diagnosis before treatment

CLASSIFICATION OF RICKETS



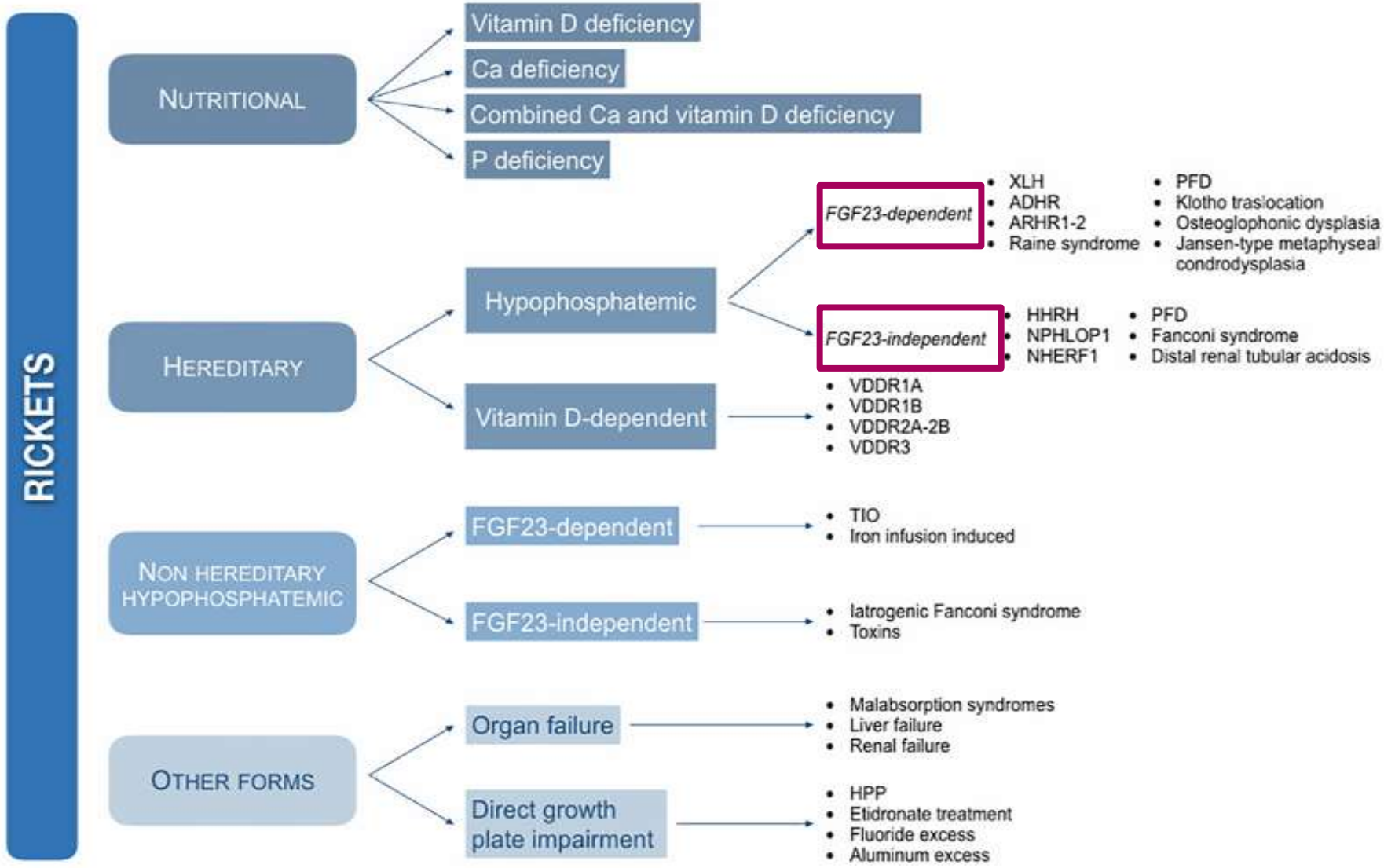
Prevalence of Vit D Deficiency:

1-4 years: 14%

School-going children (5-9 years): 18%

Adolescents (10-19 years): 24%

Turk Arch Pediatr 2023; 58(5): 458-466



Baroncelli GI,, Group of the Italian Society of Pediatric Endocrinology and Diabetology. Front. Endocrinol. 15:1383681. doi: 10.3389/fendo.2024.1383681

Types of rickets

Calcipenic rickets

- **Vitamin D deficiency or resistance**
  - Dietary deficiency
  - Malabsorption
  - Lack of sunlight exposure
  - Defect in 25 hydroxylation of vitamin D (e.g., liver disease, medications such as phenytoin)
  - Failure of 1 hydroxylation of vitamin D due to inherent deficiency of 1 alpha hydroxylase secondary to defects in the 1 alpha hydroxylase gene (VDDR I)
  - End-organ resistance to vitamin D (VDDR II)
- **Calcium deficiency**
- **Renal rickets secondary to CKD**

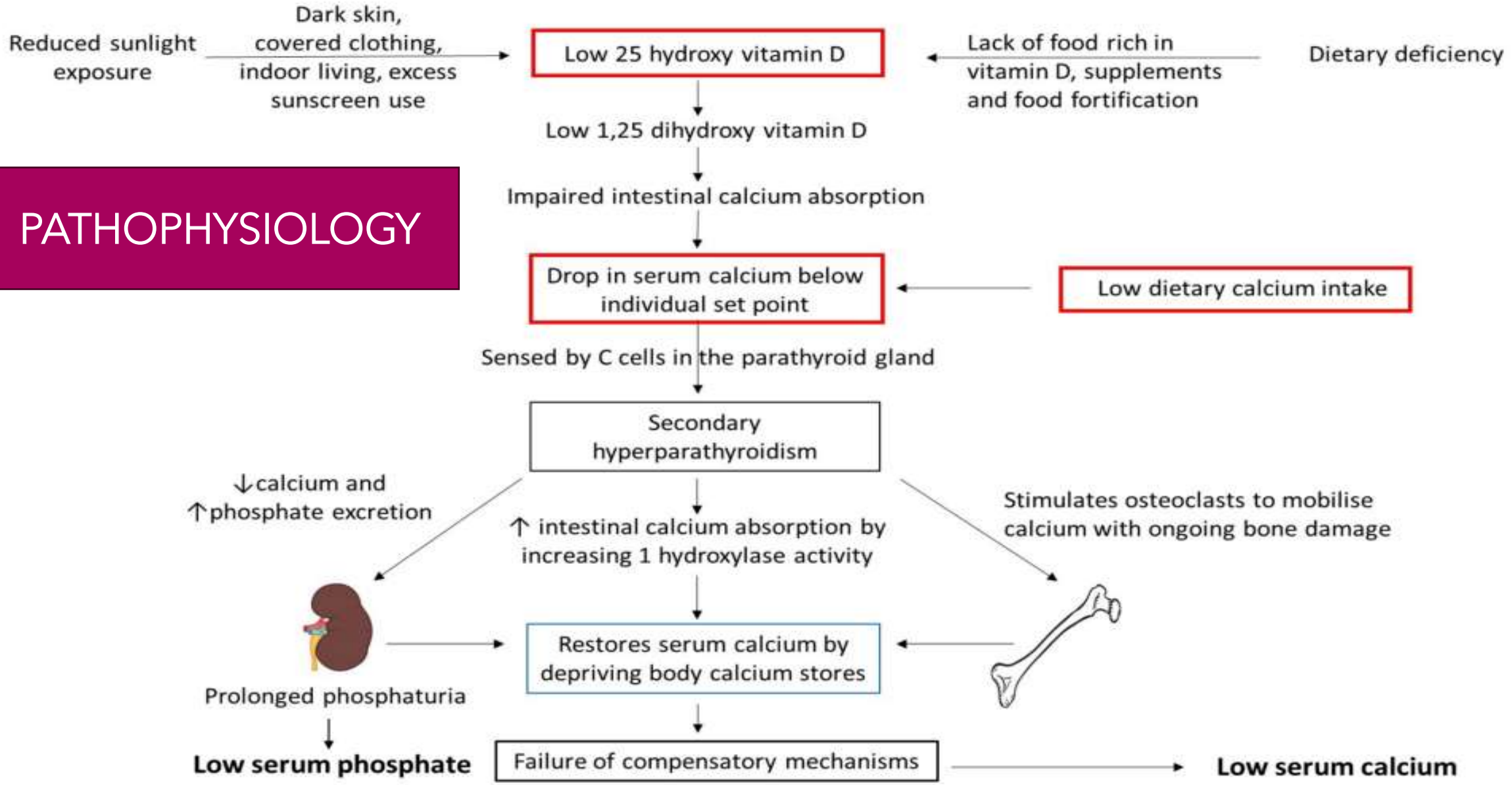
Phosphopenic rickets

Renal tubular phosphate loss

- Isolated phosphate loss secondary to genetic mutations:
  - XLHR
  - ARHR
  - ADHR
  - Hypophosphatemic rickets with hypercalciuria
- Renal Fanconi syndrome
- Dietary phosphate deficiency
- Phosphate malabsorption

An Overview of Rickets in Children REVIEW Rahul Chanchlani KI Reports Kidney Int Rep (2020) 5, 980–990; .

PATHOPHYSIOLOGY

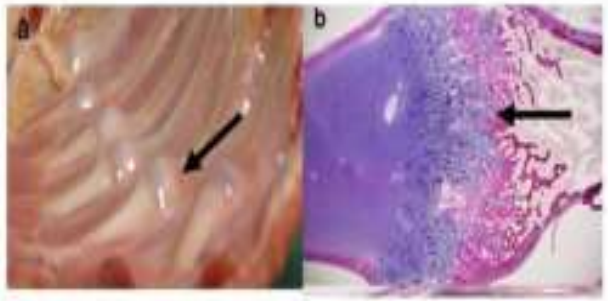


Low serum phosphate

Failure of compensatory mechanisms → Low serum calcium

Hypophosphataemic complications

Rickets

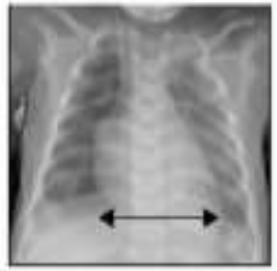


a. Rachitic rosary
b. Growth plate widening

Osteomalacia
(pink areas of un/undermineralised osteoid)

Hypocalcaemic complications

Neuromuscular irritability and Seizures



Dilated cardiomyopathy

Tetany

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https://doi.org/10.1007/s00467-021-05328-w

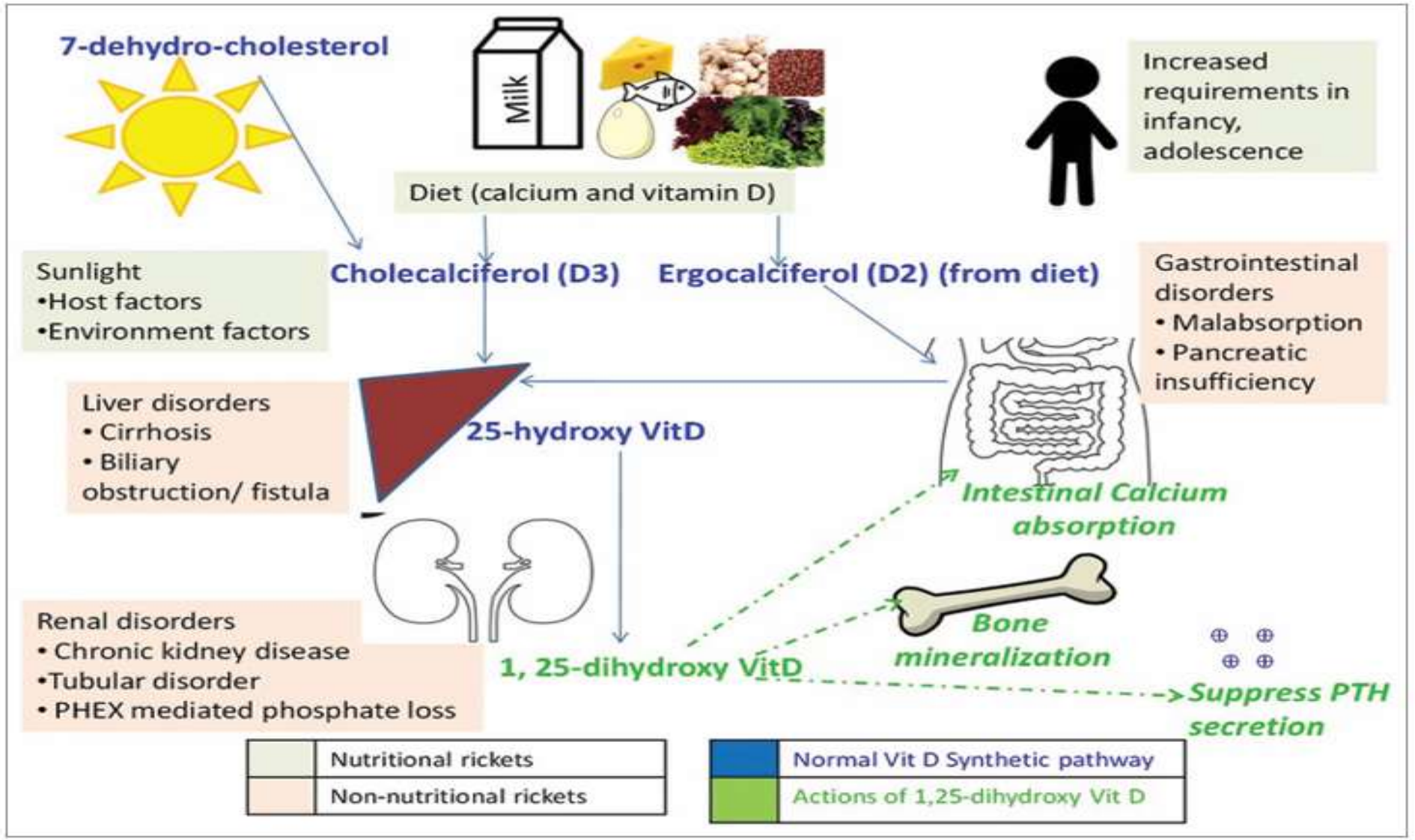

Figure 1: Normal Vitamin D metabolism and etiology of rickets. The normal biosynthetic pathway of Vitamin D is shown in Blue font with actions of active Vitamin D-1,25-dihydroxy Vitamin D in green; etiology of nutritional rickets (grey box) and non-nutritional rickets (pink box) can be deciphered. PTH: Parathyroid hormone, PHEX: Phosphate regulating endopeptidase X - linked.

Table 1. Biochemical Stages of Nutritional Rickets

	Ca	P	ALP	PTH	25(OH)D	1,25(OHD)
Stage 1	N/↓	N	N/↑	N/↑	↓	N
Stage 2	N	↓	↑	↑/↑↑	↓↓	N/↓
Stage 3	↓/↓↓	↓↓	↑↑	↑↑↑	↓↓↓	↓

ALP, alkaline phosphatase; Ca, calcium; P, phosphorus.

Turk Arch Pediatr 2023; 58(5): 458-466

Table 3. Normal age-based serum calcium and phosphorus levels in children[25]

Age	Age-based serum calcium (mg/dl)	Age-based serum phosphorus (mg/dl)
0–3 mo	8.8–11.3	4.8–7.4
1–5 yr	9.4–10.8	4.5–6.5
6–12 yr	9.4–10.3	3.6–5.8
13–20 yr	8.8–10.2	2.3–4.5

To convert units: calcium 1 mg/dl = 0.25 mmol/l; phosphorus 1 mg/dl = 0.32 mmol/l.

An Overview of Rickets in Children REVIEW Rahul Chanchlani KI Reports Kidney Int Rep (2020) 5, 980–990; .

RADIOLOGICAL SIGNS OF RICKETS

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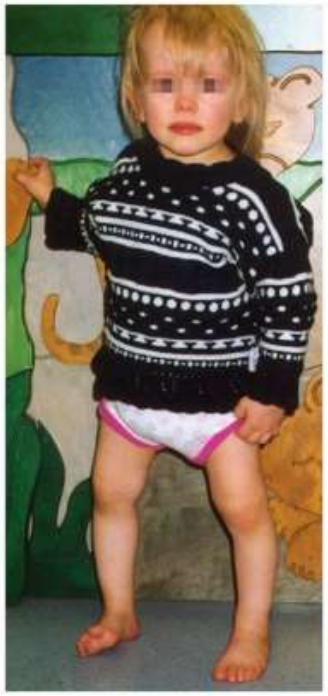

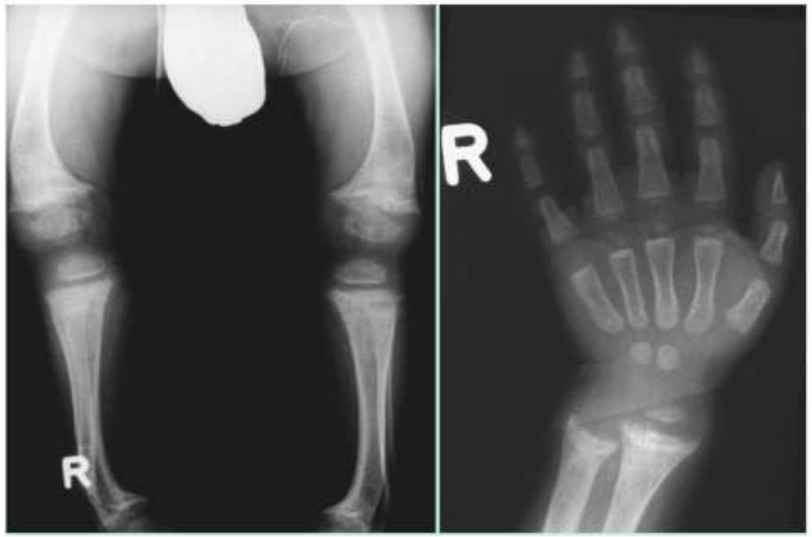

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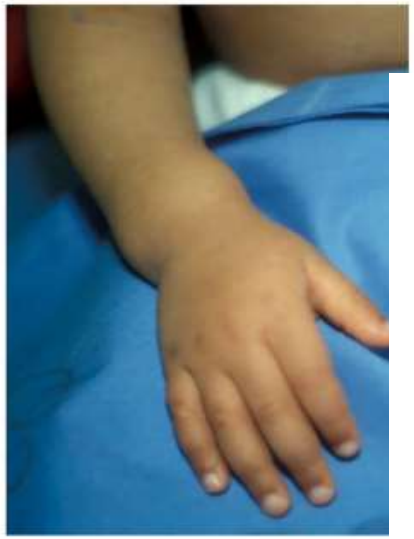

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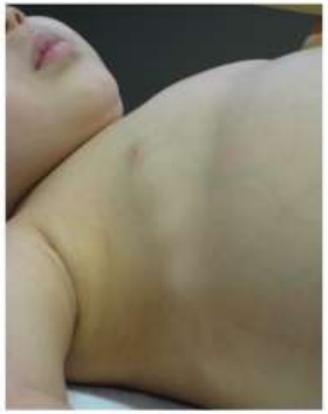

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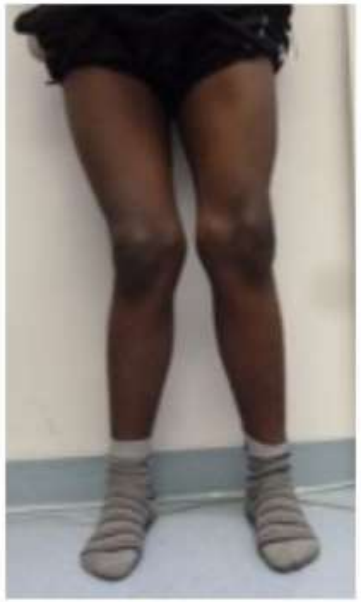

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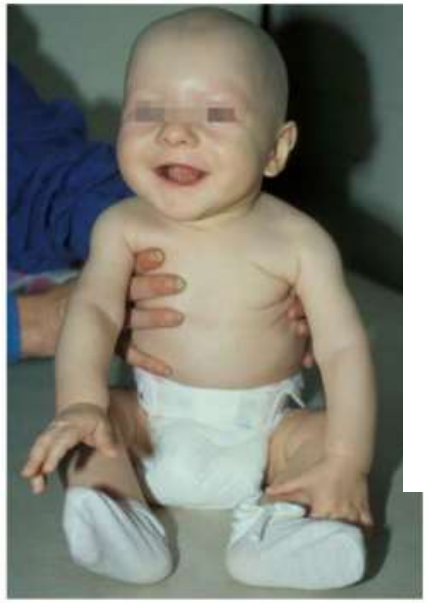

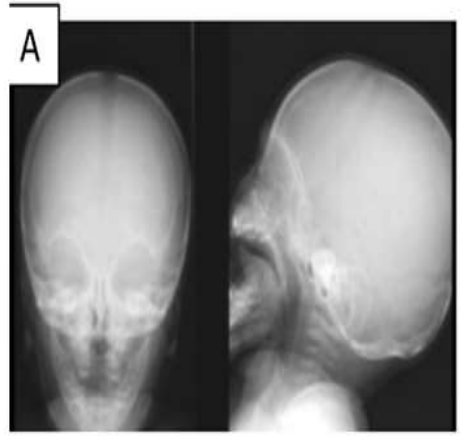

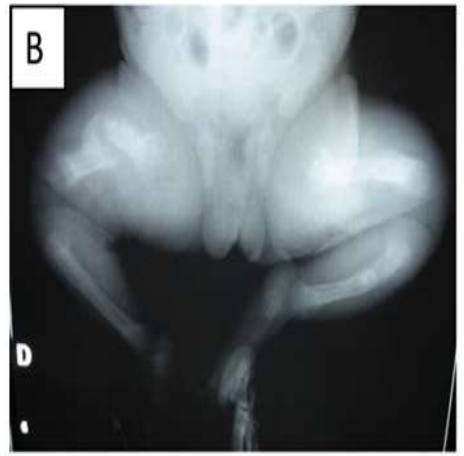

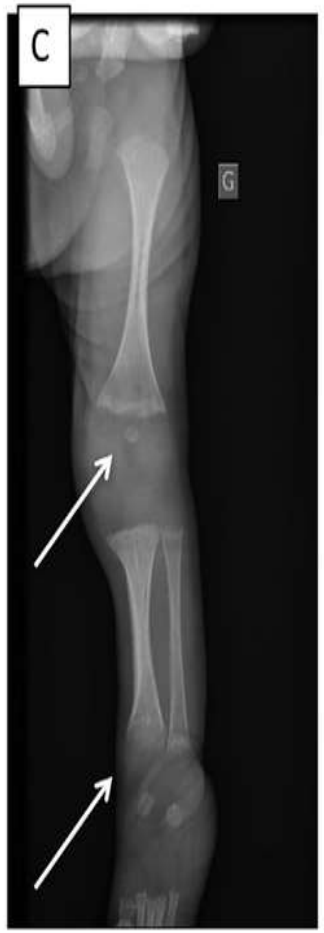

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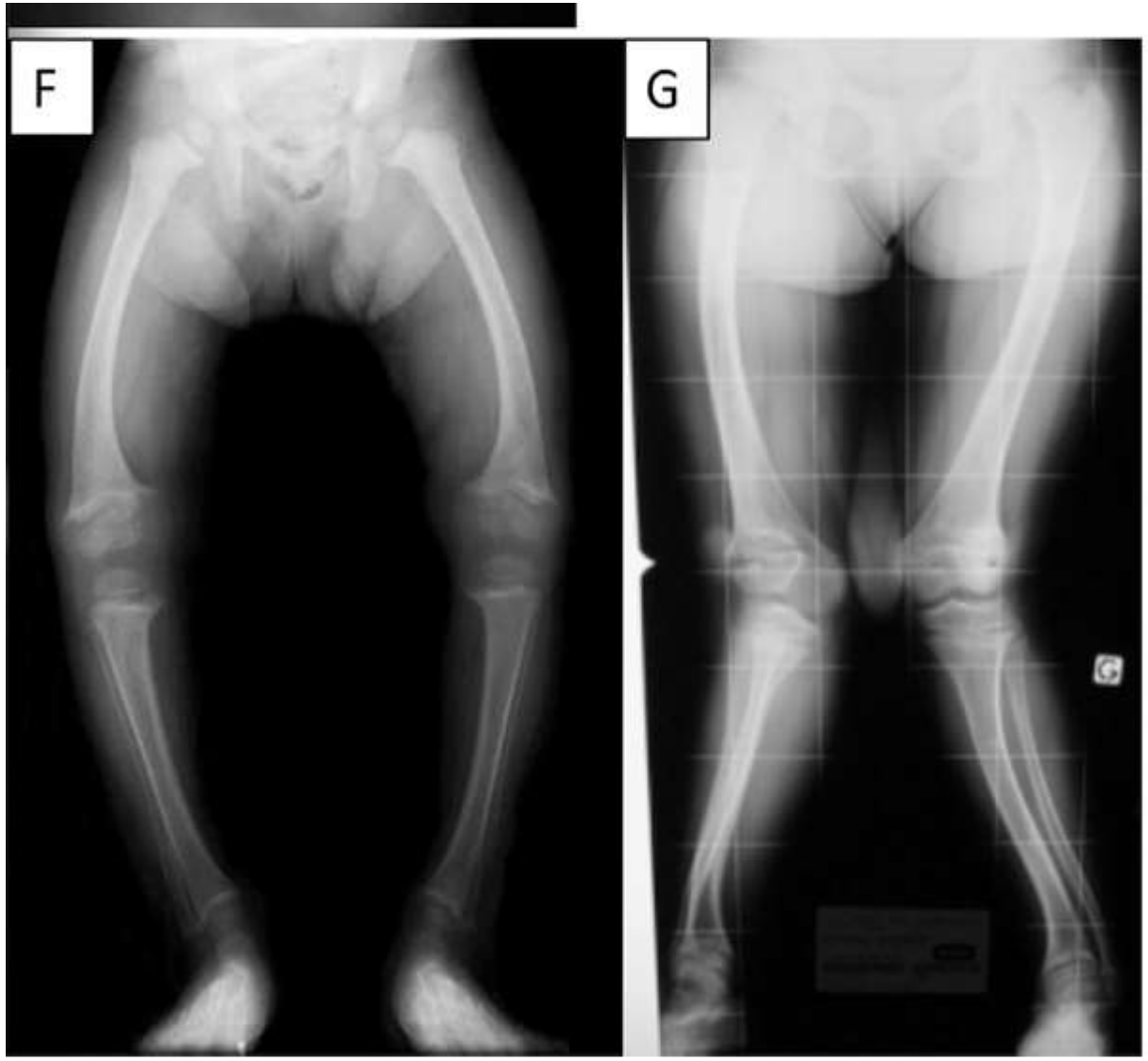
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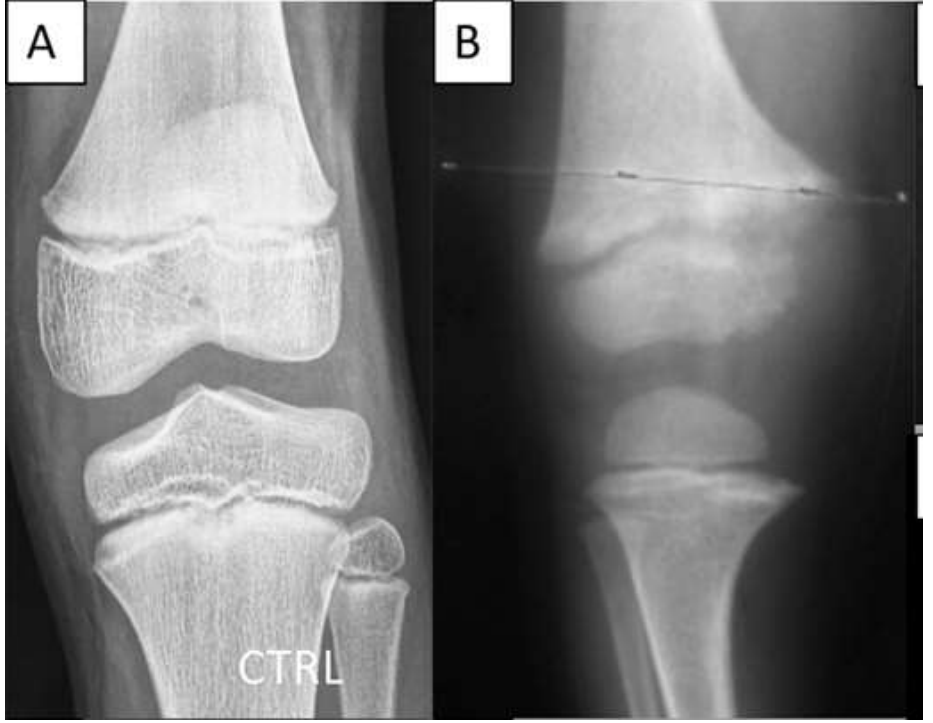
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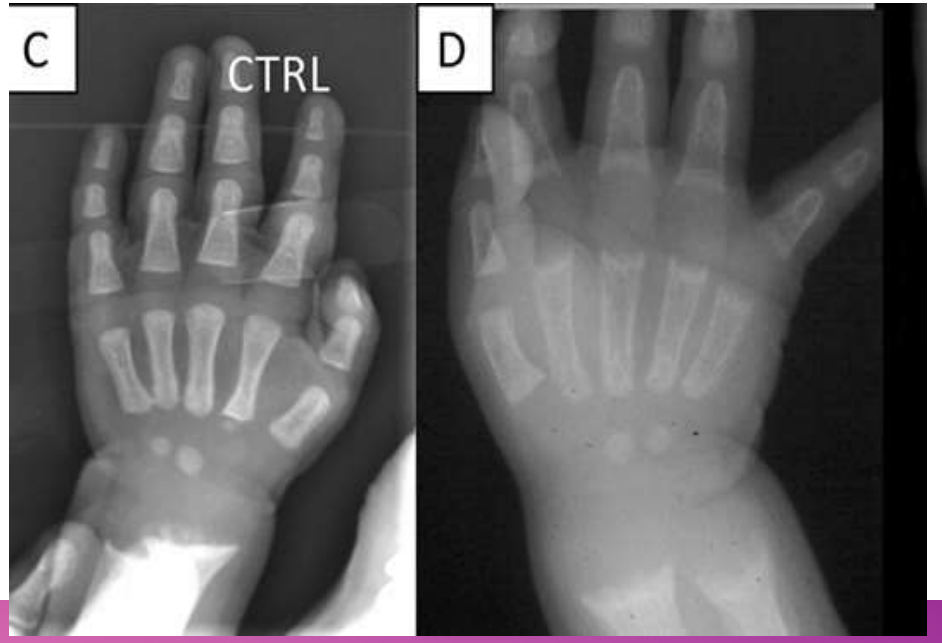
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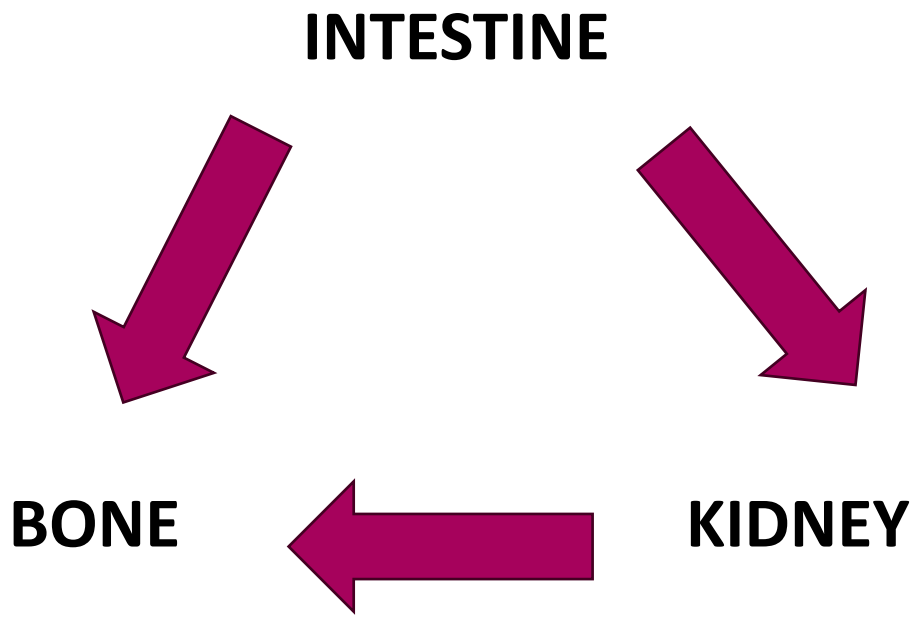
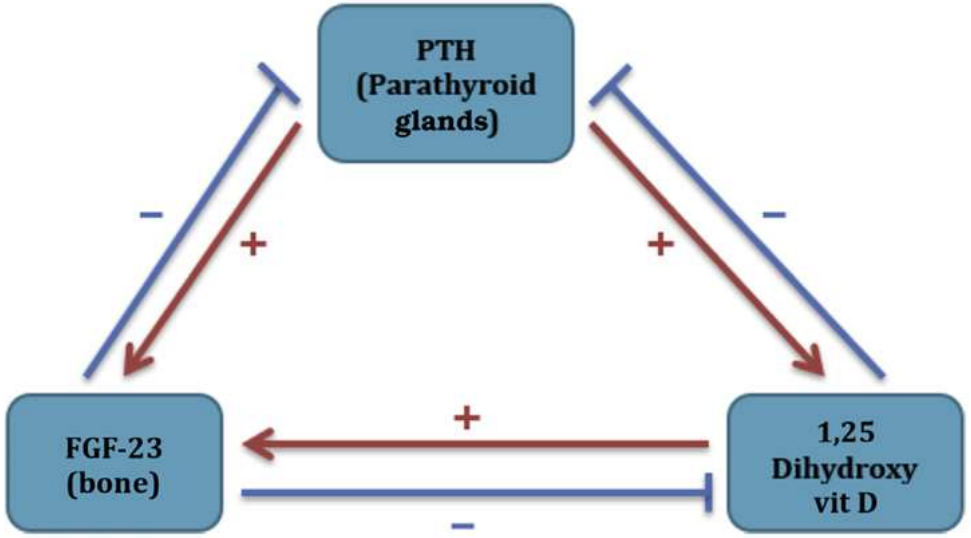
MINERAL HOMEOSTASIS

Maintained by Complex interaction between 3 systems:

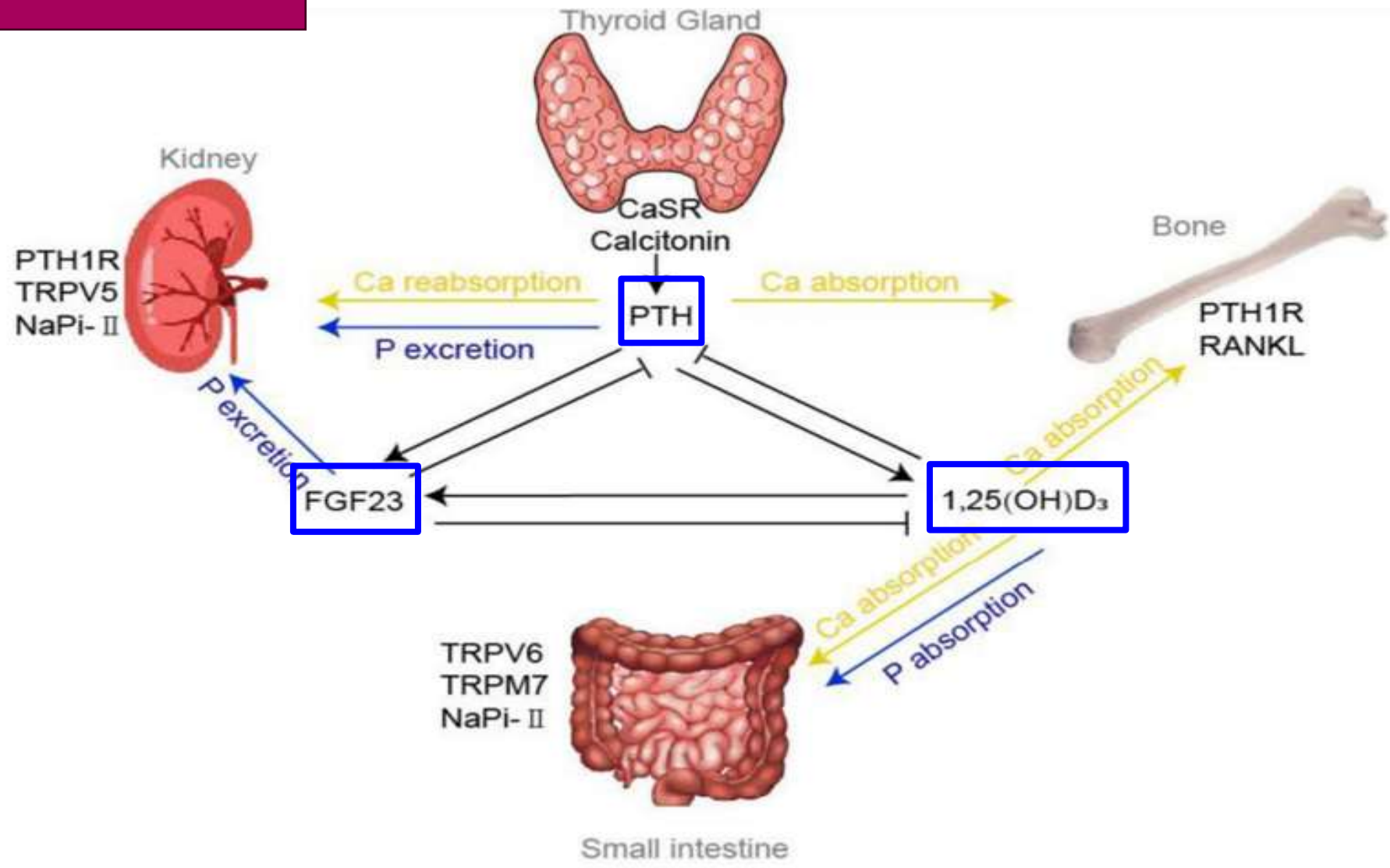
Calciotropic and Phosphate regulating hormones



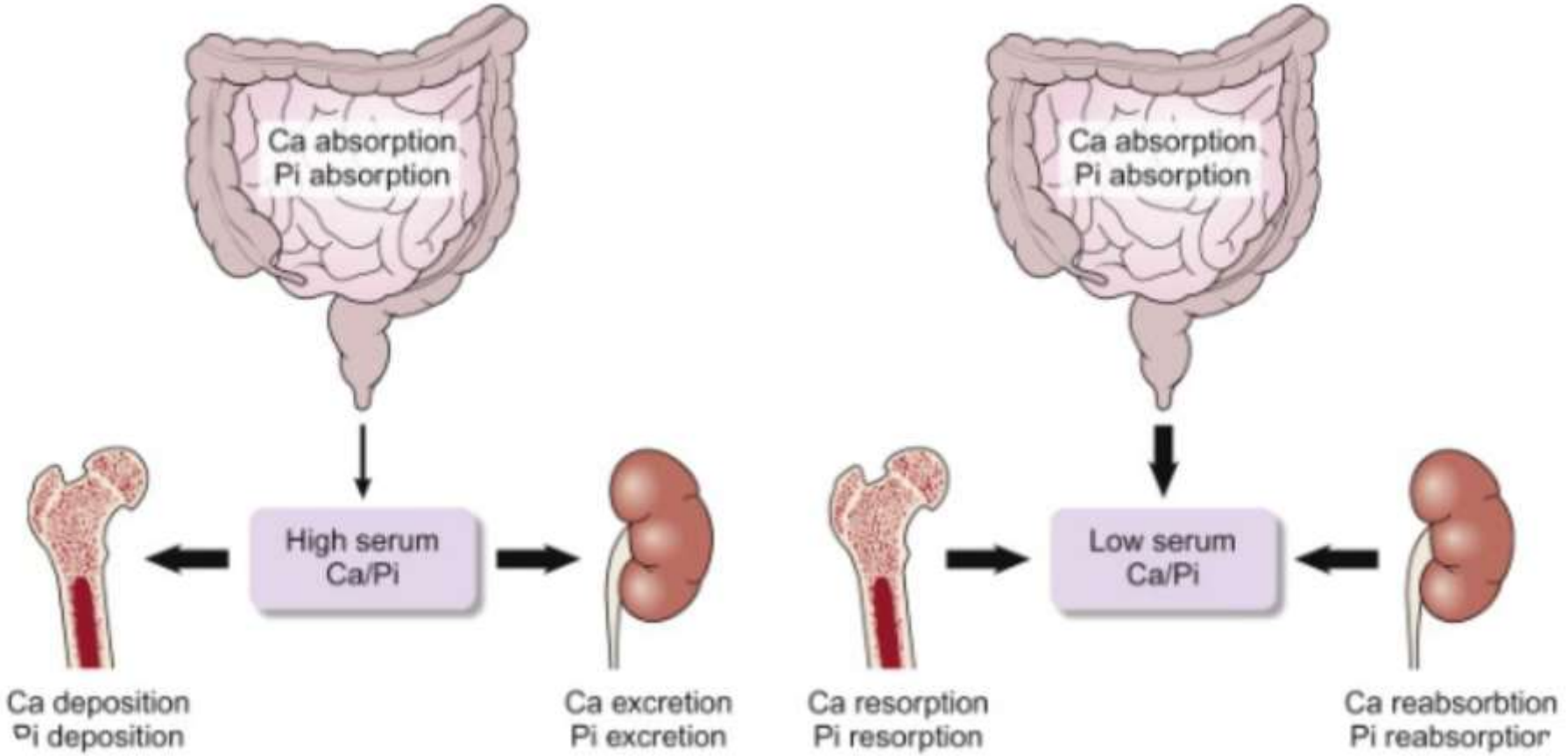


R. Chanchalani et al. Kidney International Reports (2020) 5, 980–990

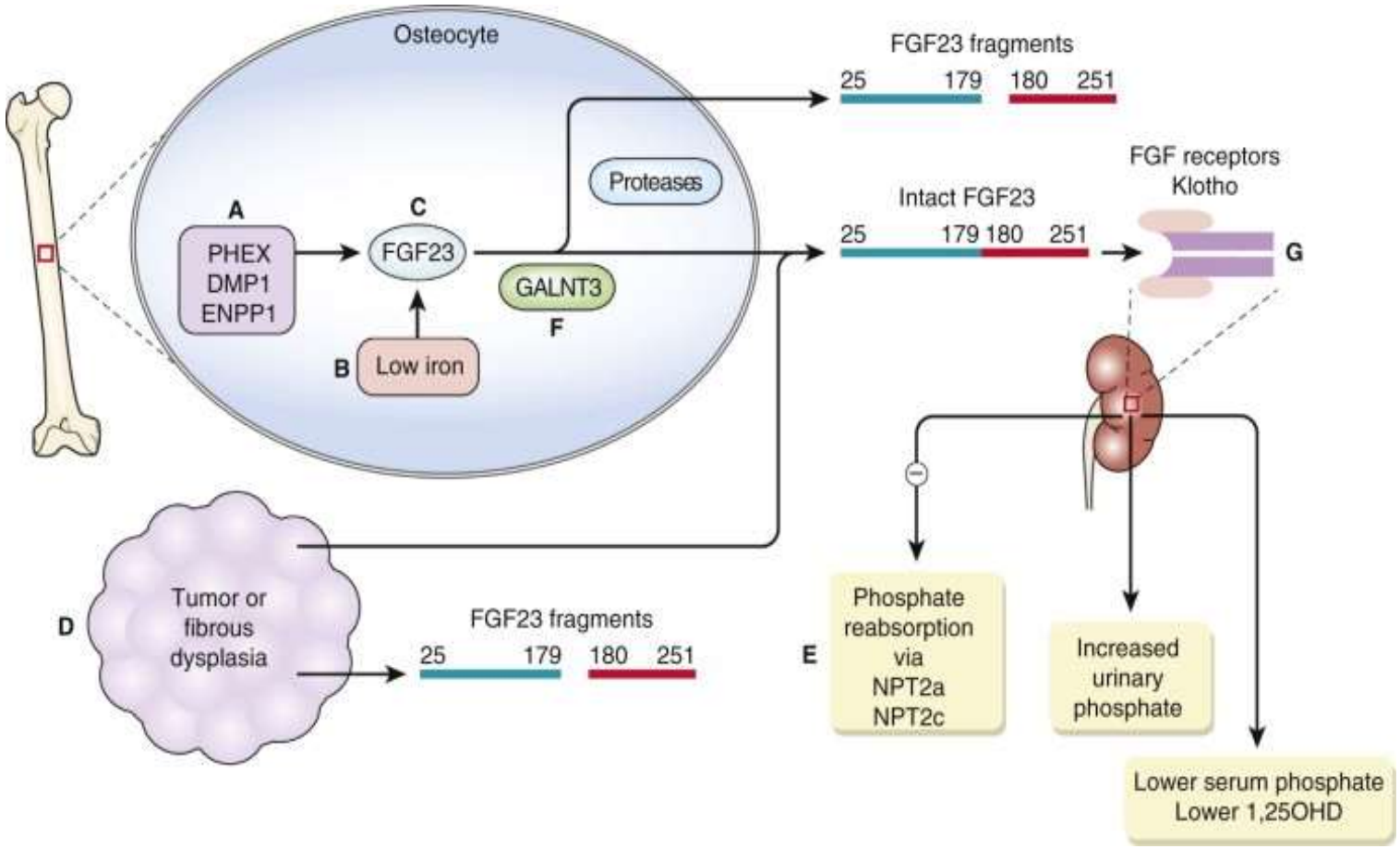
HOMEOSTASIS

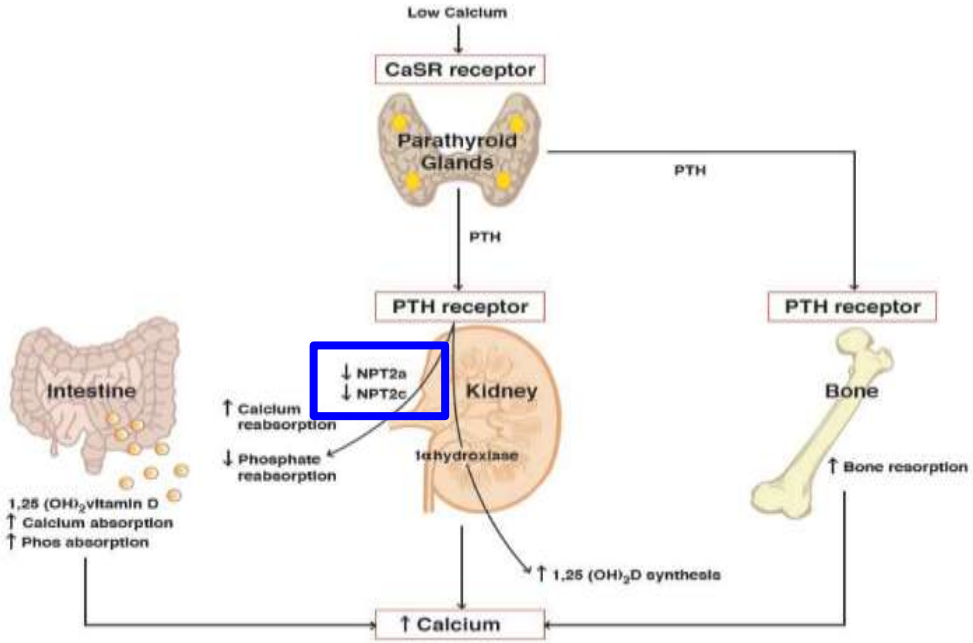


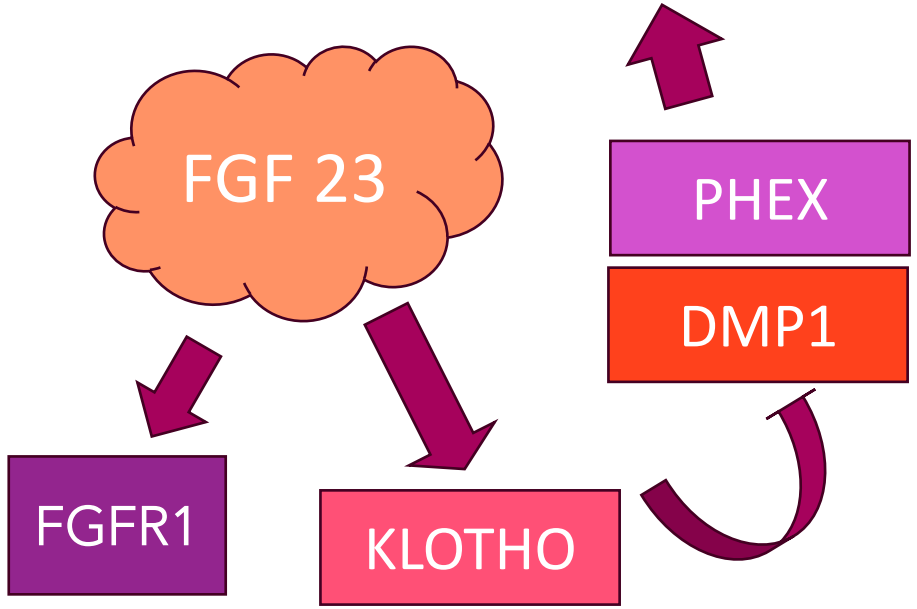
CALCIUM PHOSPHATE REGULATION



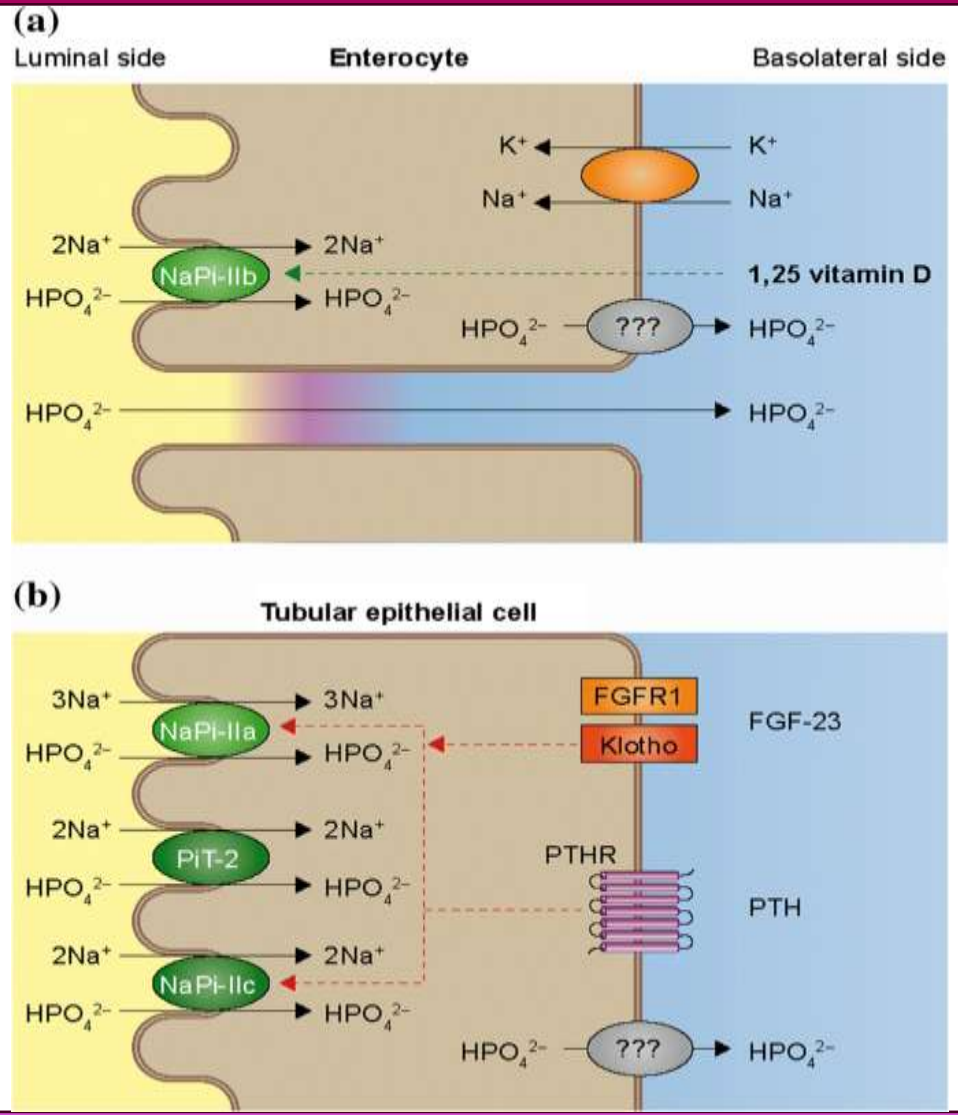
RECEPTORS IN HOMEOSTASIS

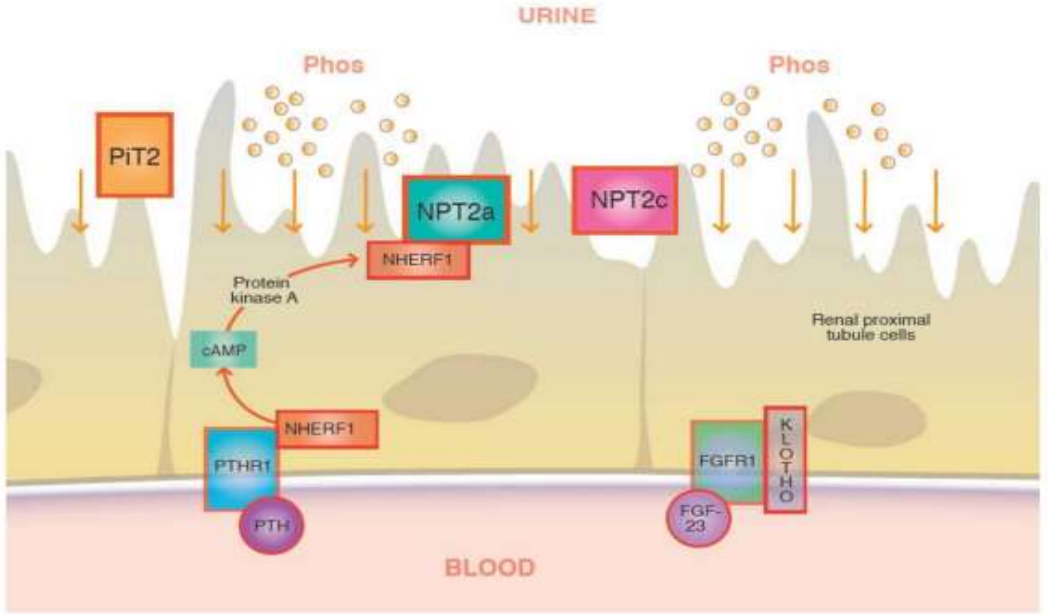






PHOSPHATE METABOLISM





Freely filtered across glomerular capillaries, the reabsorbed in PCT

- 90% is absorbed by NaPi2a in the brush border epithelial PCT

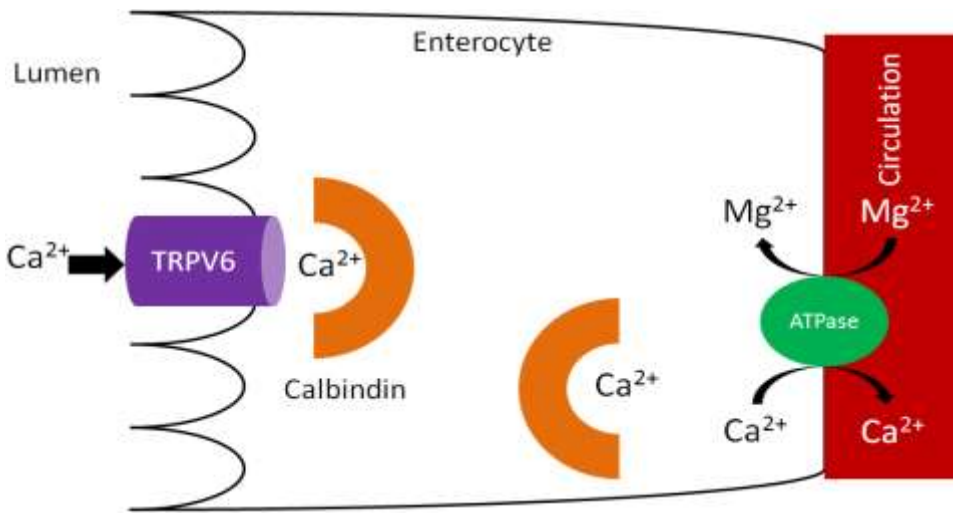
NaPi2a encoded by SLC34A1
NaPi 2b encoded by SLC34 A2
NaPi 2c encoded by SLC34 A3

NaPi 2c –deeper nephrons in PCT

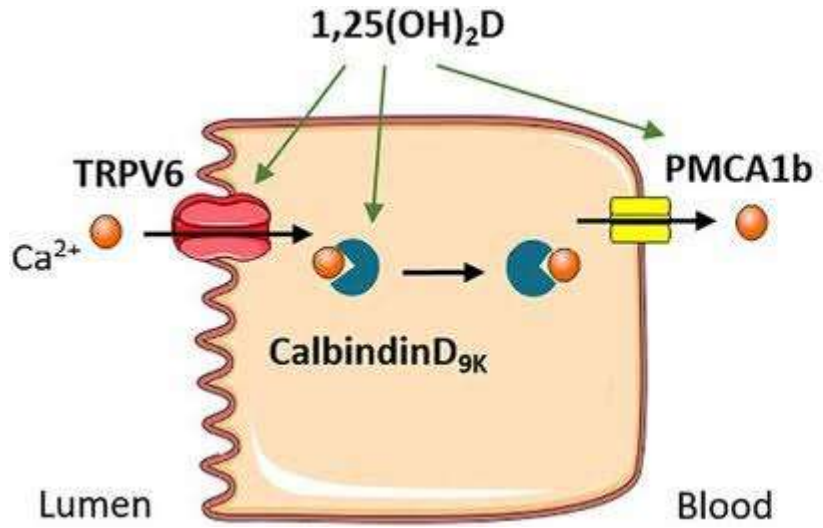
MUTATIONS- PO4 WASTING

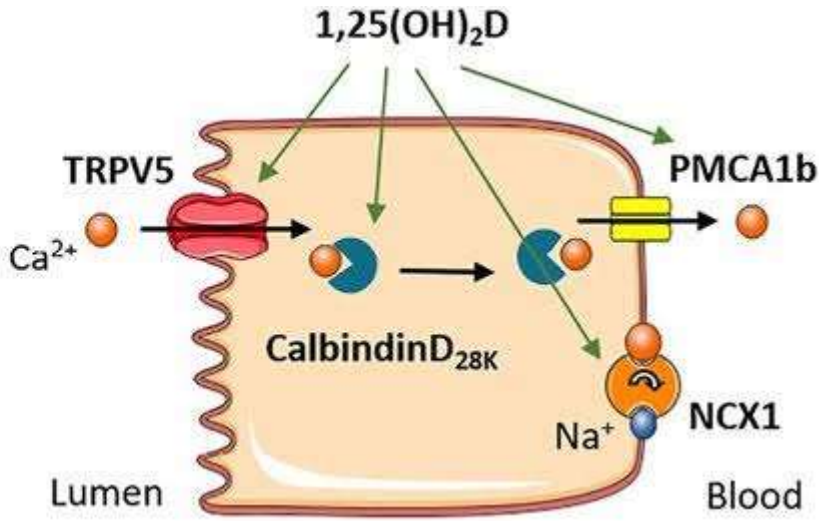
CALCIUM METABOLISM

- Absorption from Intestine via Transepithelial transport through the apical membrane Ca channel TRPV6
- Active extrusion through the basolateral channel PMCA1b

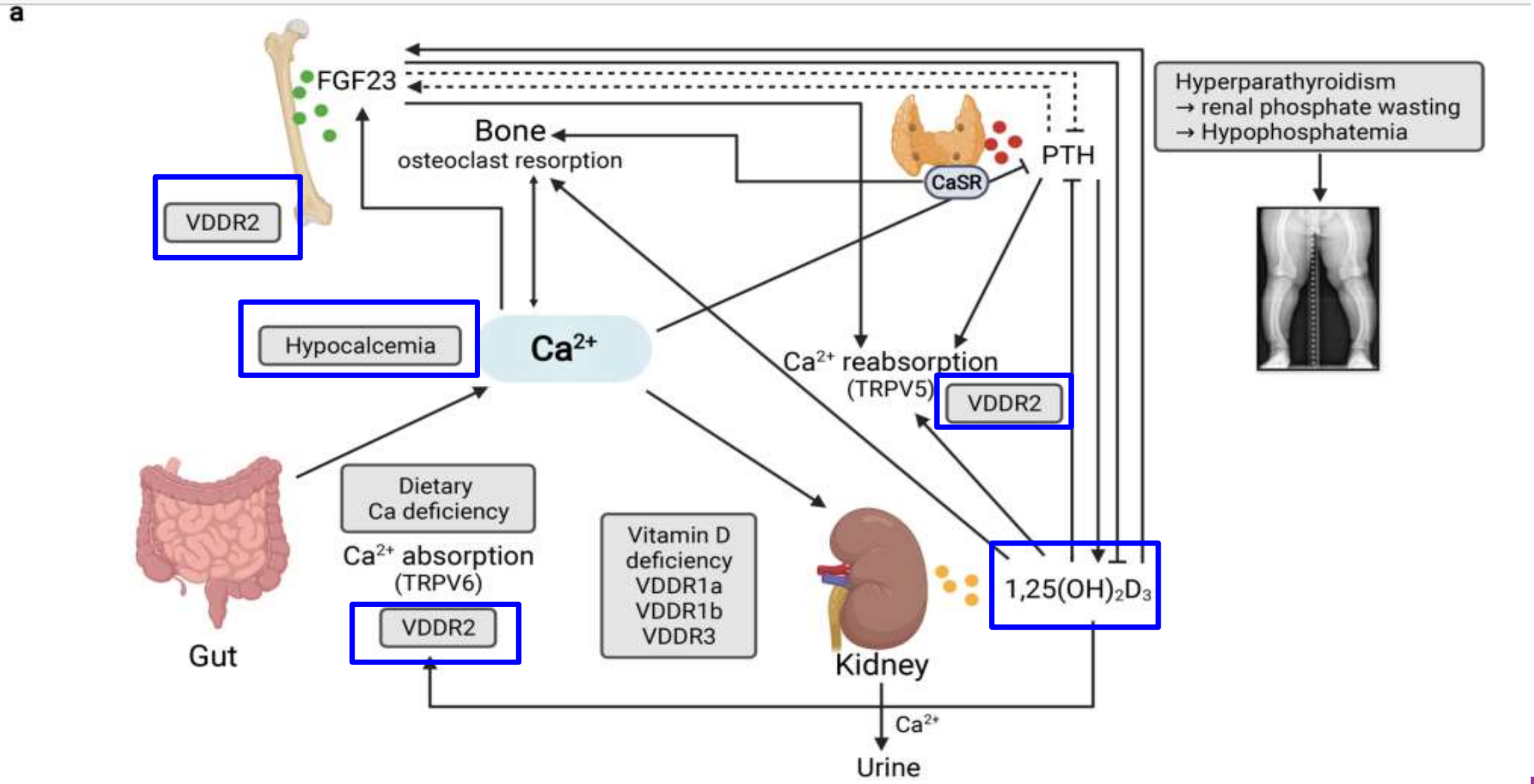


- Calcium enters extracellular fluid – reaches bone-Secreted to Gut or filtered in the kidney through TRPV5channel





VITAMIN D DEPENDANT RICKETS



VDDR

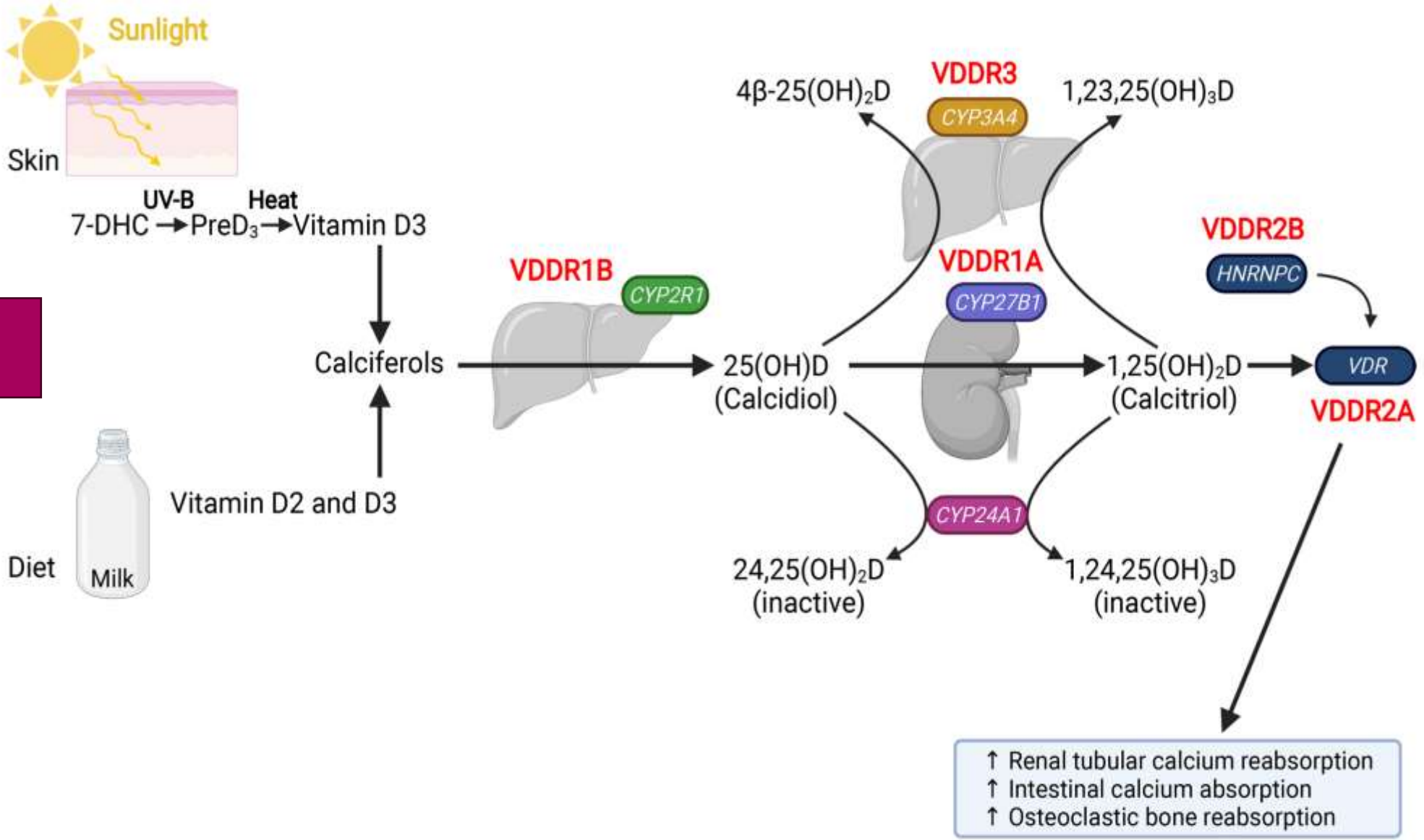

Sunlight
Skin
UV-B
Heat
7-DHC → PreD3 → Vitamin D3
Calciferols
Vitamin D2 and D3
Diet
Milk
VDDR1B
CYP2R1
25(OH)D
(Calcidiol)
VDDR3
CYP3A4
4β-25(OH)2D
1,23,25(OH)3D
VDDR1A
CYP27B1
1,25(OH)2D
(Calcitriol)
VDDR2B
HNRNPC
VDR
VDDR2A
CYP24A1
24,25(OH)2D
(inactive)
1,24,25(OH)3D
(inactive)
↑ Renal tubular calcium reabsorption
↑ Intestinal calcium absorption
↑ Osteoclastic bone reabsorption

Table 1. Genetic mutations in Vitamin D pathway leading to hypocalcemia.

Disease Type of Inheritance	MIM No.	Gene/Protein	Serum 25OHD	Serum 1,25(OH)2D	Serum Ca	Plasma PTH	Serum ALP	TmP/GFR	Serum Phos	Urine Ca Excretion, Urine Ca/Cr
Vitamin D-Dependent rickets type 1A (VDDR1A) AR	264700	CYP271 1α hydroxylase 12q14.1	N	↓↓	↓↓	↑↑↑	↑↑↑	↓	↓	↓
Vitamin D-Dependent rickets type 1B (VDDR1B) AR	600081	CYP2R1 25 hydroxylase 11p15.2	↓↓	↓	↓↓	↑↑↑	↑↑↑	↓	↓	↓
Vitamin D-Dependent rickets type 3 (VDDR3) AD	619073	CYP3A4 7q22.1	↓↓	↓	↓↓	↑↑↑	↑↑↑	↓	↓	↓
Vitamin D-Dependent rickets type 2A (VDDR2A) AR	277440	VDR Vitamin D receptor 12q13.11	N	↑↑↑	↓↓	↑↑↑	↑↑↑	↓	↓	↓
Vitamin D-Dependent rickets type 2B (VDDR2B) AR	164020	HNRNC hormone response element-binding protein	N	↑↑↑	↓↓ or N	↑↑↑	↑↑↑	↓	↓	↓

MIM Mendelian Inheritance in Man, FGF23 = fibroblast growth factor-23, 25OHD = vitaminD25(OH), $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D, urine Ca/Cr = urine calcium /creatinine ratio, Ca = calcium, P = phosphate, ALP = alkaline phosphatase, TmP/GFR renal tubular threshold maximum for phosphate, AR = autosomal recessive, AD = autosomal dominant, ↑ elevated, ↓ reduced, N normal, N/A not available [1,3,34].

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https://doi.org/10.1007/s00467-021-05328-w

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	Pi	ALP	$U_{Ca/Crea}$	$U_{P/Crea}$	TmP/GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	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 $(OH)_2D$
Vitamin D-dependent rickets type 1B (VDDR1B; OMIM#600081)	*CYP2R1* (11p15.2)	↓	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 signaling of the VDR
Vitamin D-dependent rickets type 2B (VDDR2B; OMIM#264700)	*HNRNPC*	↓	N, ↓	↑↑↑	↓	Varies	↓	N	↑↑↑	N	↑↑	Impaired signaling of the VDR
Vitamin D-dependent rickets type 3 (VDDR3; OMIM# pending)	*CYP3A4*	↓	↓	↑↑↑	↓	Varies	↓	?	↑↑↑	↓	↓	↑ inactivation of 1,25 $(OH)_2D$

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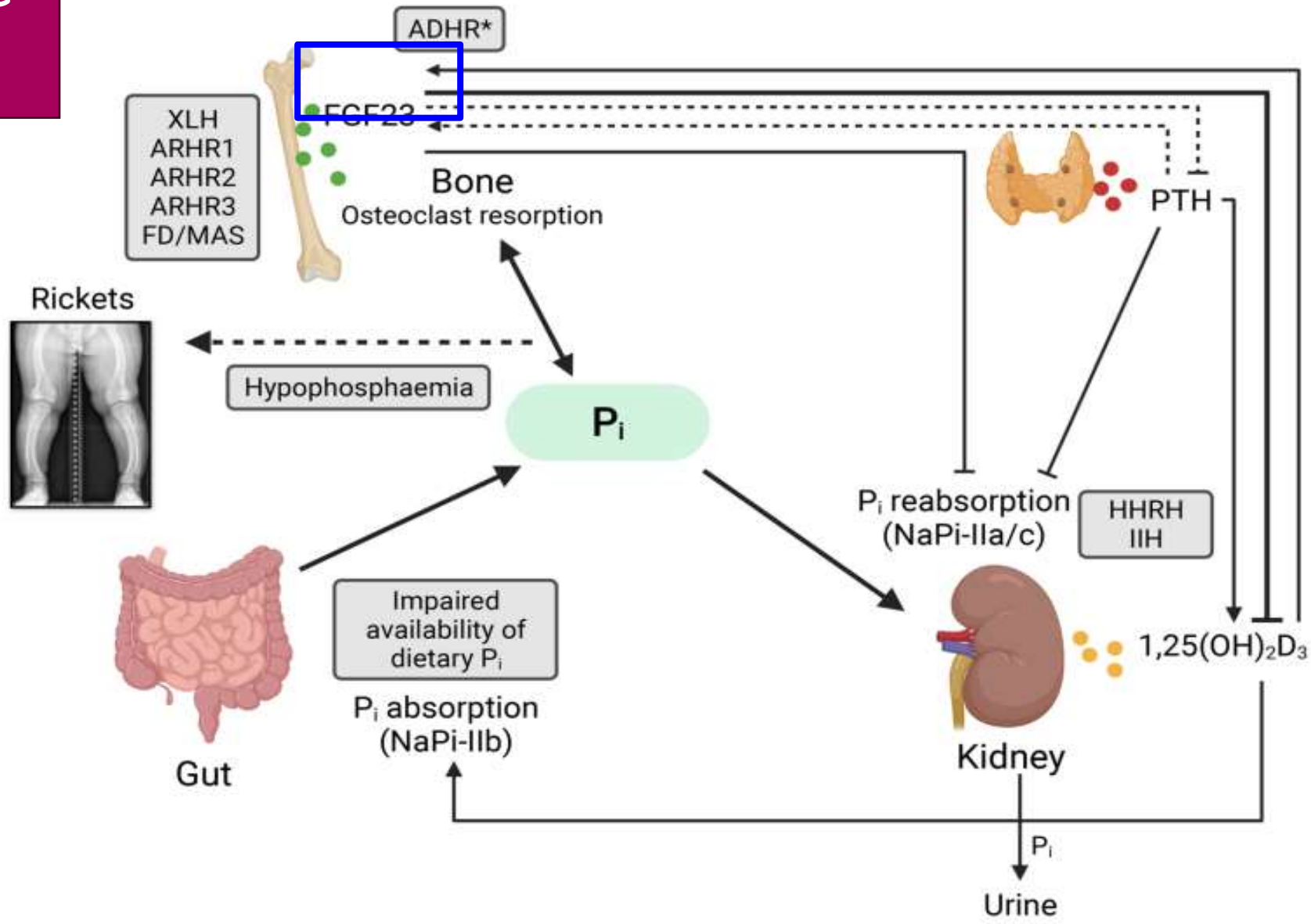
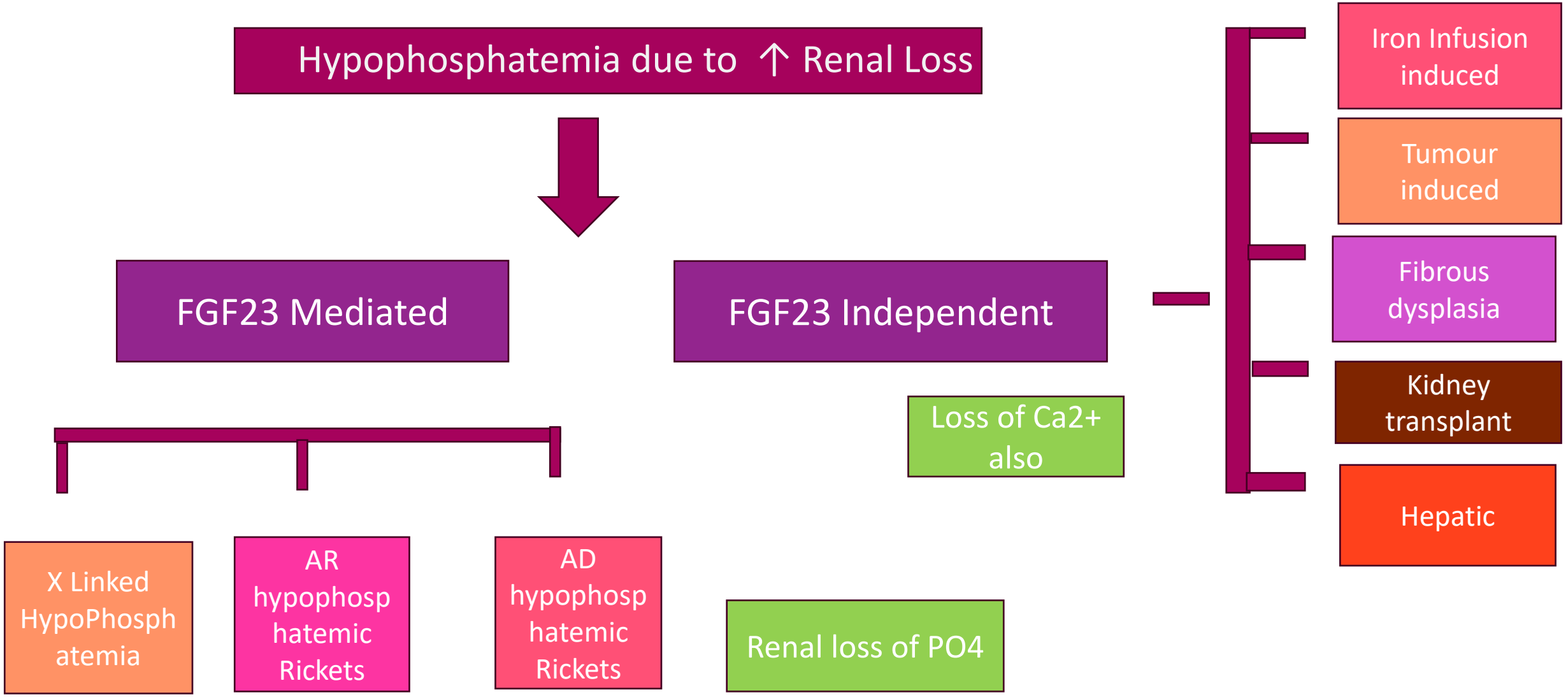
HYPOPHOSPHATEMIC RICKETS



ROLE OF FGF23



NON-FGF23 MEDIATED HYPOPHOSPHATEMIA

- The renal tubule may contain the primary defect
- FGF23 may be inappropriately suppressed
- May be accompanied by hypercalciuria
- Includes Fanconi Syndrome

FANCONI SYNDROME-Genetic renal TUBULOPATHY

- Chloride Channel 5 (Dents)
-Na-PO4 Cotransporter 2a
-Cystinosis:-CTNS causing Nephropathic Cystinosis
-Hereditary Tyrosinemia

HEREDITARY HYPOPHOSPHATEMIC RICKETS with Hypercalciuria- AR SLC34A3 variant

Insufficient renal Na-dependent PO4 transporter 2c
Impaired PO4 reabsorption
Severe Rickets

GENERALISED WASTING OCCURS

Some NaPi2a(SLC34A1) variants cause abnormal processing, intracellular transport of protein and tubular damage

Other cause infantile hypercalcemia due to excess Vit D3 or nephrolithiasis

Table 5. Hypophosphatemic rickets genetic mutations.

Disease Type of Inheritance	MIM No.	Gene Defect Protein	Plasma FGF23	TmP/GFR	Serum Ca	Serum P	Serum ALP	Plasma PTH	Serum 25OHD	Serum 1,25 $(OH)_2D$	Urine Ca Excretion, Urine Ca/Cr
Autosomal dominant hypophosphatemic rickets (ADHR)	193100	*FGF23* 12p13.32	↑	↓	N	↓↓	↑↑	N or ↑	N	N or ↓	N or ↓
X-linked hypophosphatemia (XLH) X-linked dominant	307800	*PHEX* Xp22.11	↑ or N	↓	N	↓↓	↑↑	N or ↑	N	N or ↓	N or ↓
Autosomal recessive hypophosphatemic rickets 1 (ARHR1)	241520	*DMP1* 4q22.1	↑or N	↓	N	↓↓	↑↑	N or ↑	N	N or ↓	N or ↓
Autosomal recessive hypophosphatemic rickets 2 (ARHR2)	613312	*ENPP1* 6q23.2	↑or N	↓	N	↓↓	↑↑	N or ↑	N	N or ↓	N or ↓
Tumour-induced osteomalacia (TIO)	N/A	N/A	↑↑↑	↓	N	↓↓	↑↑	N or ↑	N	N or ↓	N or ↓
Hypophosphatemic rickets with hypercalciuria (HHRH)	241530	*SLC3* 4A39q34.3	↓	↓	N	↓	↑↑	N	N	↑↑	↑

MIM Mendelian Inheritance in Man, FGF23= fibroblast growth factor-23, serum 25OHD=vitaminD25(OH), 1,25(OH)2D =1,25-dihydroxyvitamin D (calcitriol), urine Ca/Cr ratio= urine for calcium or creatinine ratio. Ca = calcium, P = phosphate, ALP =alkaline phosphatase activity, TmP/GFR =renal tubular threshold maximum for phosphate, ↑ elevated, ↓ reduced, N normal, N/A not available [2,60,62–64].

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Disorder (abbreviation; OMIM#)	Gene (location)	Ca	Pi	ALP	$U_{Ca/Crea}$	$U_{P/Crea}$	TmP/GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	Pathogenesis
Phosphopenic rickets												
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
Rickets and/or osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels and/or signaling												
X-linked hypophosphatemia (XLH; OMIM#307800)	*PHEX* (Xp22.1)	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone and impaired FGF23 cleavage
Autosomal dominant hypophosphatemic rickets (ADHR; OMIM#193100)	*FGF23* (12p13.3)	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑[c]	N	N[d]	FGF23 protein resistant to degradation
Autosomal recessive hypophosphatemic rickets 1 (ARHR1; OMIM#241520)	*DMP1* (4q22.1)	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone
Autosomal recessive hypophosphatemic rickets 2 (ARHR2; OMIM#613312)	*ENPP1* (6q23.2)	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone

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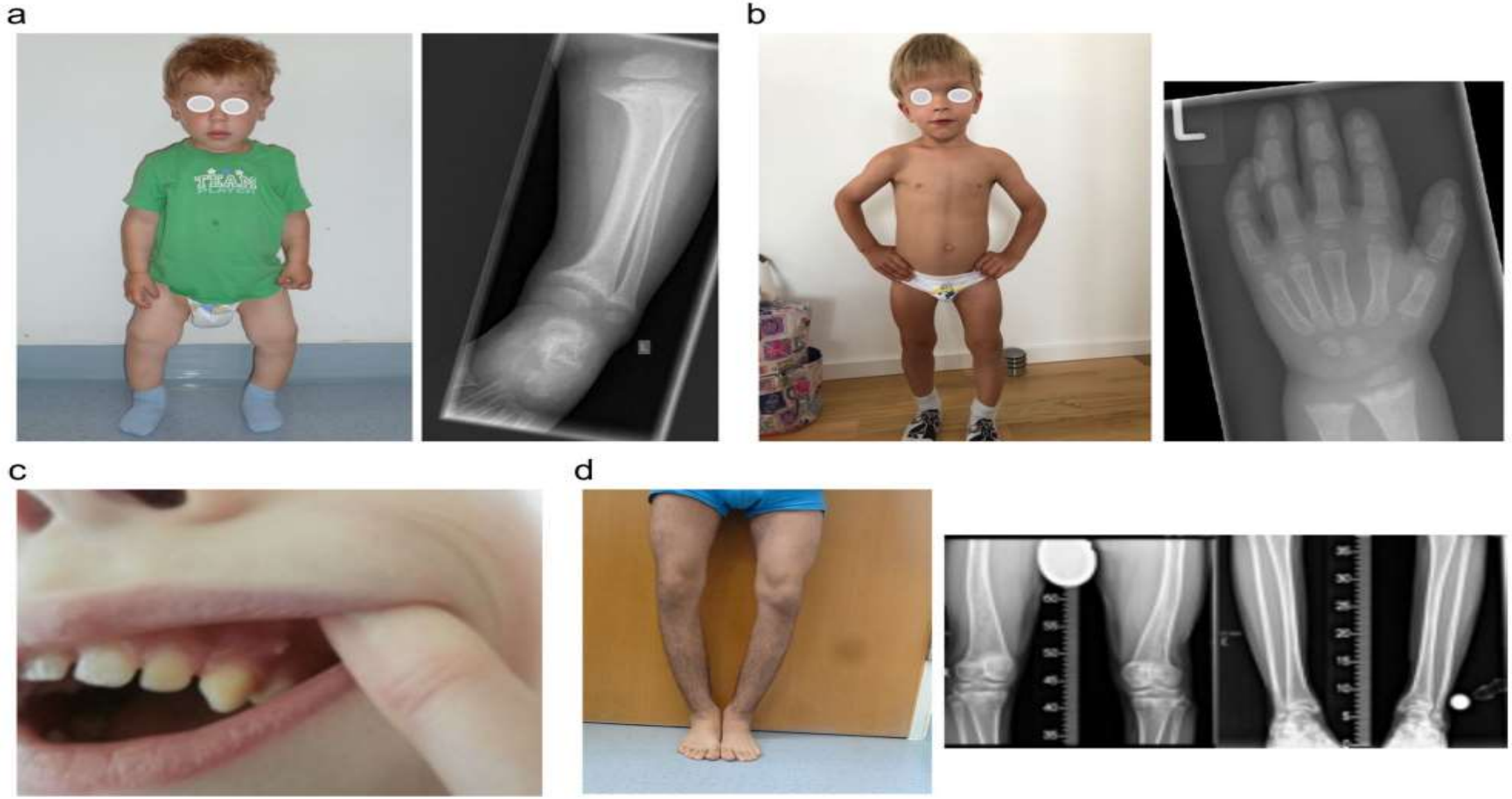

Pediatric Nephrology (2022) 37:2013–2036
https://doi.org/10.1007/s00467-021-05328-w

Table 6. Genetic Mutations leading to Hypophosphatasia.

Disease Type of Inheritance	MIM No.	Gene Defect /Protein	Plasma FGF23	Serum ALP	TmP GFR	Serum Ca	Serum Phos	Plasma PTH	Serum 25OHD	Serum 1,25 $(OH)_2D$	Urine Ca Excretion, Urine Ca/Cr
Infantile severe HypoPhos-phatasia (HPP)	171760	*ALPL* geneTissue nonspecific alkaline phosphatase 1p36.12	↓	N	N/A	↑	↑	↓	↑	↓	↑↑↑

MIM Mendelian Inheritance in Man, FGF23 = fibroblast growth factor-23, 25OHD = vitaminD25(OH), $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D, urine Ca/Cr = urine calcium/creatinine ratio, Ca = calcium, P = phosphate, ALP = alkaline phosphatase, TmP/GFR renal tubular threshold maximum for phosphate, AR = autosomal recessive, AD = autosomal dominant, ↑ elevated, ↓ reduced, N normal, N/A not available [1,3,34].

Endocrines **2022**, *3*(1), 150-167; https://doi.org/10.3390/endocrines3010014

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	Pi	ALP	$U_{Ca/Crea}$	$U_{P/Crea}$	TmP/GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	Pathogenesis
Raine syndrome-associated (ARHR3; OMIM#259,775)	*FAM20C* (7q22.3)	N	↓	↑, ↑↑	?	↑	↓	↑, N	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone
Fibrous dysplasia (FD; OMIM#174800)	*GNAS* (20q13.3)	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone
Tumor-induced osteomalacia (TIO)	NA	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑[c]	N	N[d]	↑ FGF23 expression in tumoral cells
Cutaneous skeletal hypophosphatemia syndrome (SFM; OMIM#163200)	*NRAS (1p13.2)* *HRAS (11p15.5)* *KRAS (12p12.1)*	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑[c]	N	N[d]	↑ FGF23 expression in dysplastic bone lesions
Osteoglophonic dysplasia (OGD) (OMIM#166250)	*FGFR1* (8p11.23)	N	↓	↑, N	N	↑	↓	N	N, ↑[c]	N	N[d]	↑ FGF23 expression in bone
Hypophosphatemic rickets and hyperparathyroidism (OMIM#612089)	*KLOTHO* (13q13.1)	N	↓	↑, ↑↑	↓	↑	↓	↑	↑↑	N	N[d]	Unknown; translocation of the *KLOTHO* promoter
Rickets and/or osteomalacia due to primary renal tubular phosphate wasting												
Hereditary hypophosphatemic 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 hypophosphatemic rickets (Dent disease 1; OMIM#300554)	*CLCN5* (Xp11.23)	N	↓	↑(↑↑)	N, ↑	↑	↓	varies	varies	N	↑	Loss of function of CLCN5 in the proximal tubule
Hypophosphatemia and nephrocalcinosis (NPHLOP1; OMIM#612286) Fanconi reno-tubular syndrome 2 (FRTS2; OMIM#613388)	*SLC34A1* (5q35.3)	N	↓	↑(↑↑)	↑	↑	↓	↓	varies	N	↑	Loss of function of NaPi2a in the proximal tubule

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Table 1 (continued)

Disorder (abbreviation; OMIM#)	Gene (location)	Ca	Pi	ALP	$U_{Ca/Crea}$	$U_{P/Crea}$	TmP/GFR	FGF23	PTH	25 (OH)D[a]	1,25 $(OH)_2D$	Pathogenesis
Cystinosis (OMIM#219800) and other hereditary forms of Fanconi syndrome	*CTNS* (17p13.2)	N, ↓	↓	↑(↑↑)	N, ↑	↑	N, ↓	N, ↑[e]	N, ↑[e]	N	N[d]	Cystine accumulation in the proximal tubule
Iatrogenic proximal tubulopathy	NA	N	↓	↑(↑↑)	varies	↑	↓	↓	varies	N	↑	Drug toxicity

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https://doi.org/10.1007/s00467-021-05328-w

IMPORTANCE OF ALKALINE PHOSPHATASE

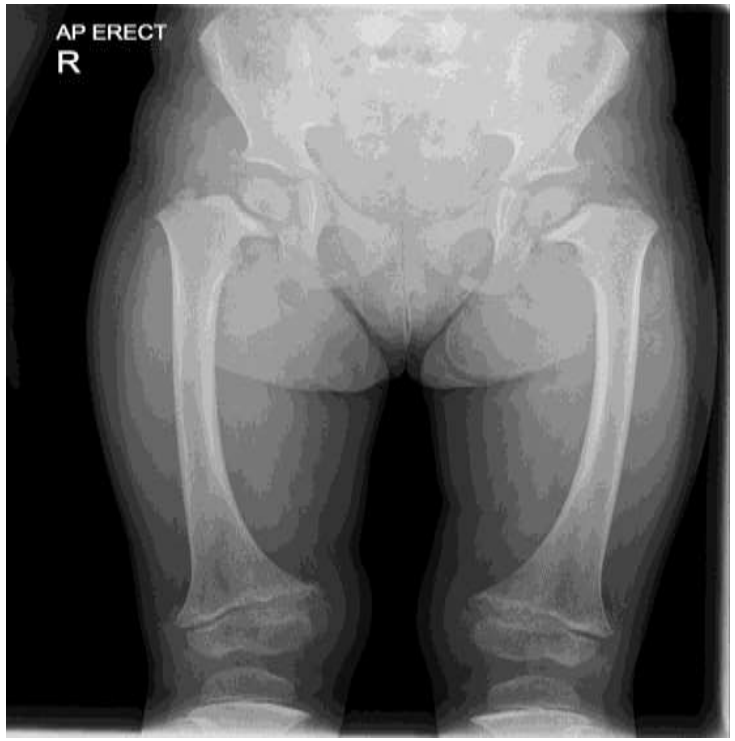
- Marker of osteoblastic activity- elevated in all forms of Rickets
- In children, 80-90% is Bone in origin
- Tetra-phasic increase- highest in Infancy and puberty, Trough in mid-childhood and post-puberty
- Highly elevated in treatment naïve Calcipenic rickets (up to 10-fold->2000U)
- Moderately elevated in Phosphopenic rickets (1-3 times – 400-800U)
- Normal or reduced ALP: Blount's disease

  Metaphyseal dysplasia

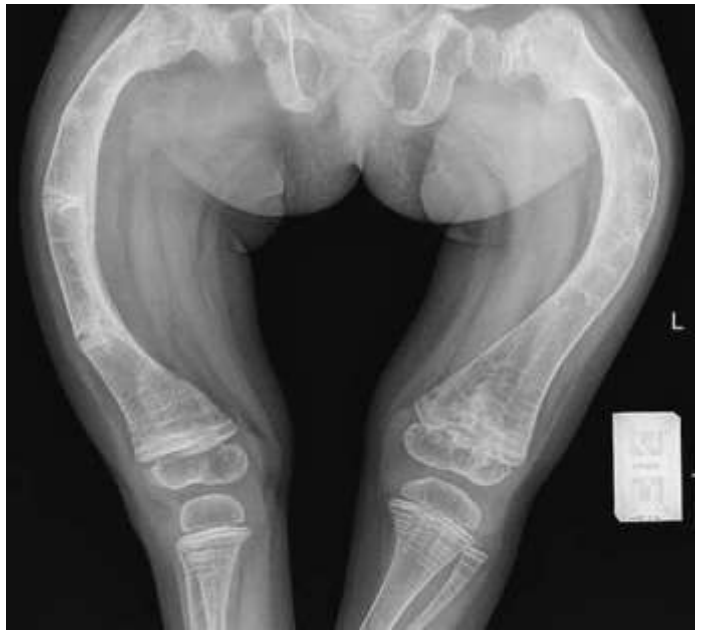
  Hypophosphatasia

Table 3: Radiological mimickers of nutritional rickets.

Signs	Inference
Metaphyseal or epiphyseal flaying without any irregularity or fraying	Metaphyseal-epiphyseal dysplasia
Multiple long bone fractures, healing at variable ages	Osteogenesis imperfecta, child abuse
Osteosclerosis and hyperostosis	Autosomal recessive-hypophosphatemic rickets
Osteosclerosis with tongue of radiolucency within metaphyses	Hypophosphatasia

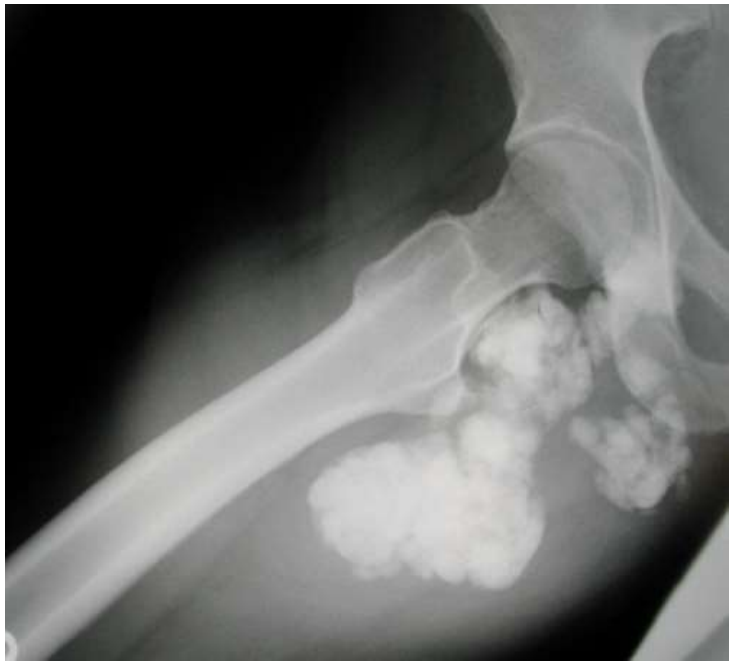


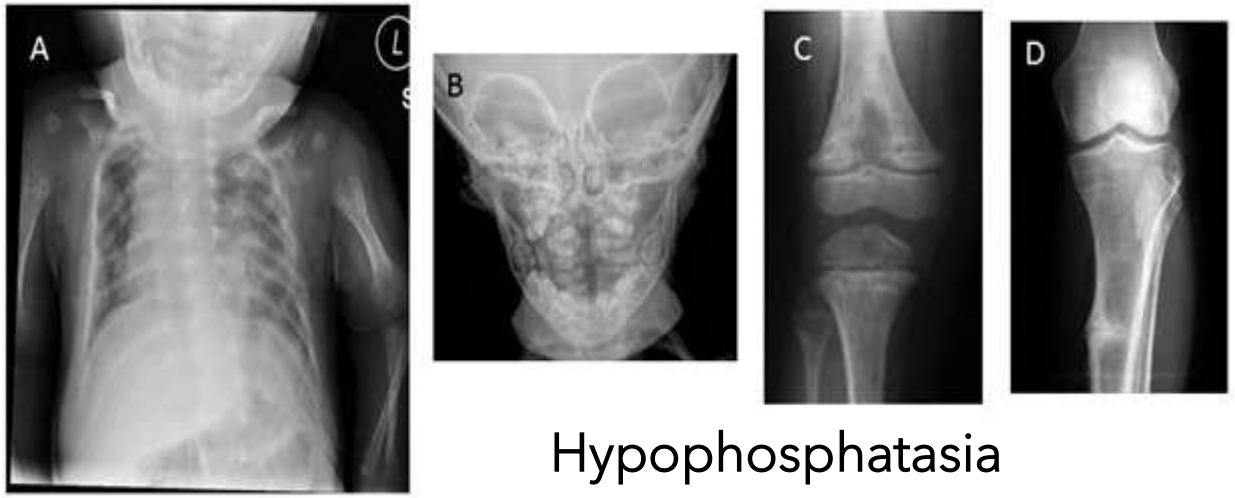
Metaphyseal dysplasia



Osteogenesis imperfecta

Tumoral Calcinosis





Hypophosphatasia

BIOCHEMICAL CHANGES IN RICKETS

	Calcium	Phosphorus	Alkaline Phosphatase	Parathyroid hormone	Vitamin D	Urine phosphorus	Bicarbonate
Nutritional	Low	Low	High	High	Low	Low	Normal
RTA	Low	Low	High	High	Low	High	Low urine pH, <5.3 RTA II and >5.3 type I
VDDR I	Low	Low	High	High	High 25(OH)D low 1,25 (OH)D	Low	Normal
VDDR II	Low	Low	High	High	High 25(OH)D and 1,25(OH)D both		Normal
Hypophosphatemic	Normal	Low	High	Normal	Normal 25(OH)D Low 1,25 (OH)D	High	Normal
Renal failure	Low	High	High	High	Low 25(OH)D and 1,25(OH)D		Low

Aditi Jaiman et al. J Clin Med Kaz 2021; 18(1):7-13

TABLE 1 Main skeletal and dental-periodontal signs in patients with rickets.

Cranium	Thorax and pelvis	Limbs	Total body and spine	Teeth and periodontium
• Frontal bossing • Craniosynostosis • Scaphocephaly • Occipital "bullet deformity" • Delayed anterior fontanel closure • Craniotabes[a] • Mid facial hypoplasia[b]	• Costo-chondral junction enlargement (rachitic rosary)[a] • Harrison sulcus[a] • Costal pathological fractures[a] • Pigeon chest • Chest wall asymmetry • Depressed ribs • Narrowed pelvic outlet	• Widened wrists, knees, and ankles • Genu-varum • Genu-valgum • Combined genu-varum/valgum • Short humerus[b] • Short femur[b] • Tibial torsion[c] • Coxa-vara	• Stunted growth • "Taylorwise" posture[a] • Disproportionate short stature (short limbs)[b] • Spinal curvature • Kyphosis	• Multiple dental decay[a] • Dyschromic enamel • Enamel hypoplasia • Delayed dentition • Abscesses with gingival fistulae[d]

[a]Mainly in patients with nutritional vitamin D deficiency rickets or vitamin D-dependent rickets; [b]mainly in patients with XLH; [c]intoeing or extoeing; [d]typical of patients with XLH: mainly in incisors and canines, without evidence of trauma or dental decay.

Baroncelli G et al.Frontiers of Endocrinol 2024Vol 15- 2024

Table 2. Dental abnormalities in different forms of ricket

Disease	Dental manifestations
Calciopenic rickets	Thin hypoplastic enamel Dental caries Delayed dentition (both deciduous and permanent teeth)
XLHR, ARHR-1	Periradicular abscess in teeth without caries (deciduous teeth are more affected) Increased frequency of caries Taurodontism and wide pulp chamber and high apical horns Delayed dentition Early loss of permanent teeth
ARHR-3	Amelogenesis imperfecta (hypoplastic) Delayed dental eruption
Hypophosphatasia	Premature loss of deciduous teeth (without appearance of permanent teeth) Early loss of permanent teeth Periodontitis Ankylosis involving the posterior teeth
dRTA due to *WDR72* mutation	Amelogenesis imperfecta (hypomaturation)

ARHR-1, autosomal recessive hypophosphatemic rickets type 1; ARHR-3, autosomal recessive hypophosphatemic rickets type 3; dRTA, distal renal tubular acidosis; XLHR, X-linked hypophosphatemic rickets.

Etiology, clinical characteristics, genetic profile and outcomes of children with refractory rickets at a referral center in India: A cohort study

Original Article

AIM: To evaluate the etiology, clinical features, genetic profile, and outcomes of refractory rickets with normal kidney function at presentation

DESIGN & OUTCOMES

Single centre in south India

72 patients from 65 families

Refractory rickets with normal eGFR at presentation

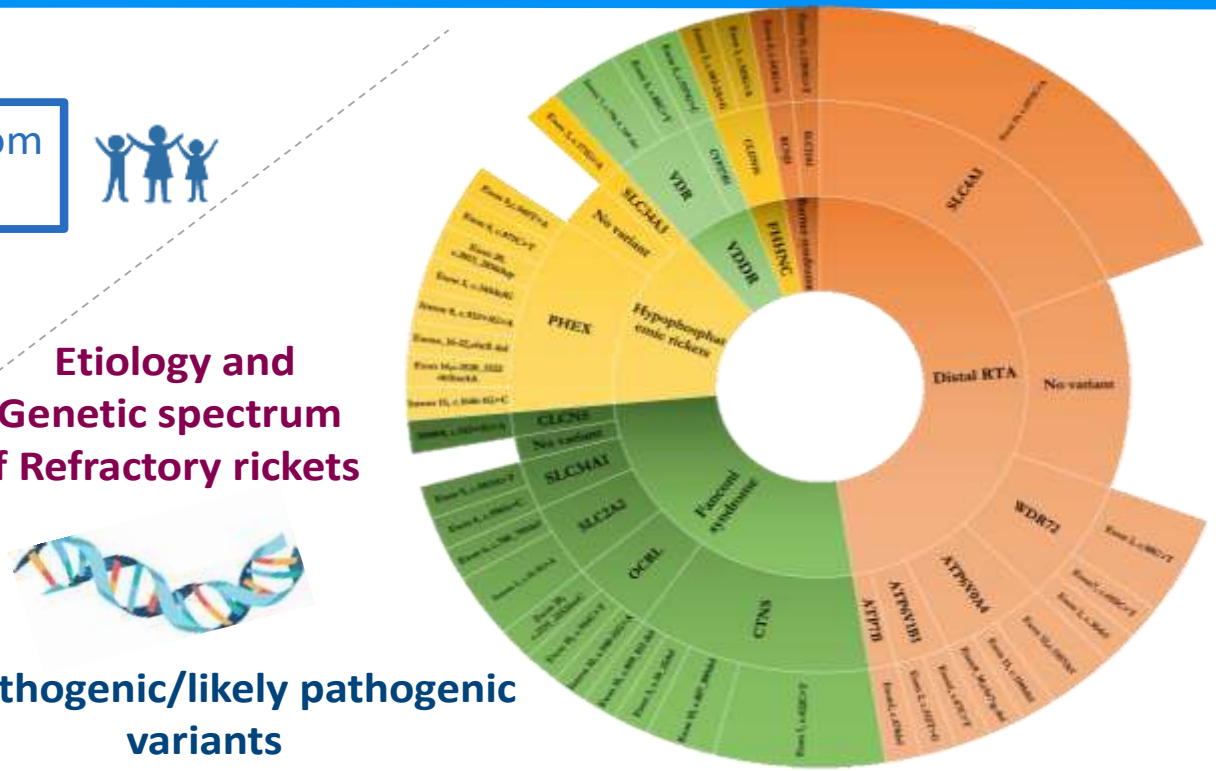
Age at presentation- 2 [1, 4] years

Failure to thrive- 68.1%

Polyuria- 51.4 %

Nephrocalcinosis- 45.8%

Etiology and Genetic spectrum of Refractory rickets



56 Pathogenic/likely pathogenic variants

Progression to CKD stage 2 or greater on follow-up:

- Cystinosis- 5 cases
- *SLC4A1*-dRTA- 2 cases
- *WDR72*-dRTA- 2 cases
- Bartter syndrome- 2 cases

❖ Total- 11 patients

CONCLUSION: Distal RTA, X-linked hypophosphatemic rickets and cystinosis were the commonest cause of refractory rickets. The c.2573C>A variant in exon 19 was a recurrent mutation in *SLC4A1*-dRTA.

Mathew V, Deepthi B, et al. 2025

Pediatric Nephrology
Journal of the
International Pediatric Nephrology Association

ORIGINAL ARTICLE

Etiology, clinical characteristics, genetic profile, and outcomes of children with refractory rickets at a referral center in India: a cohort study

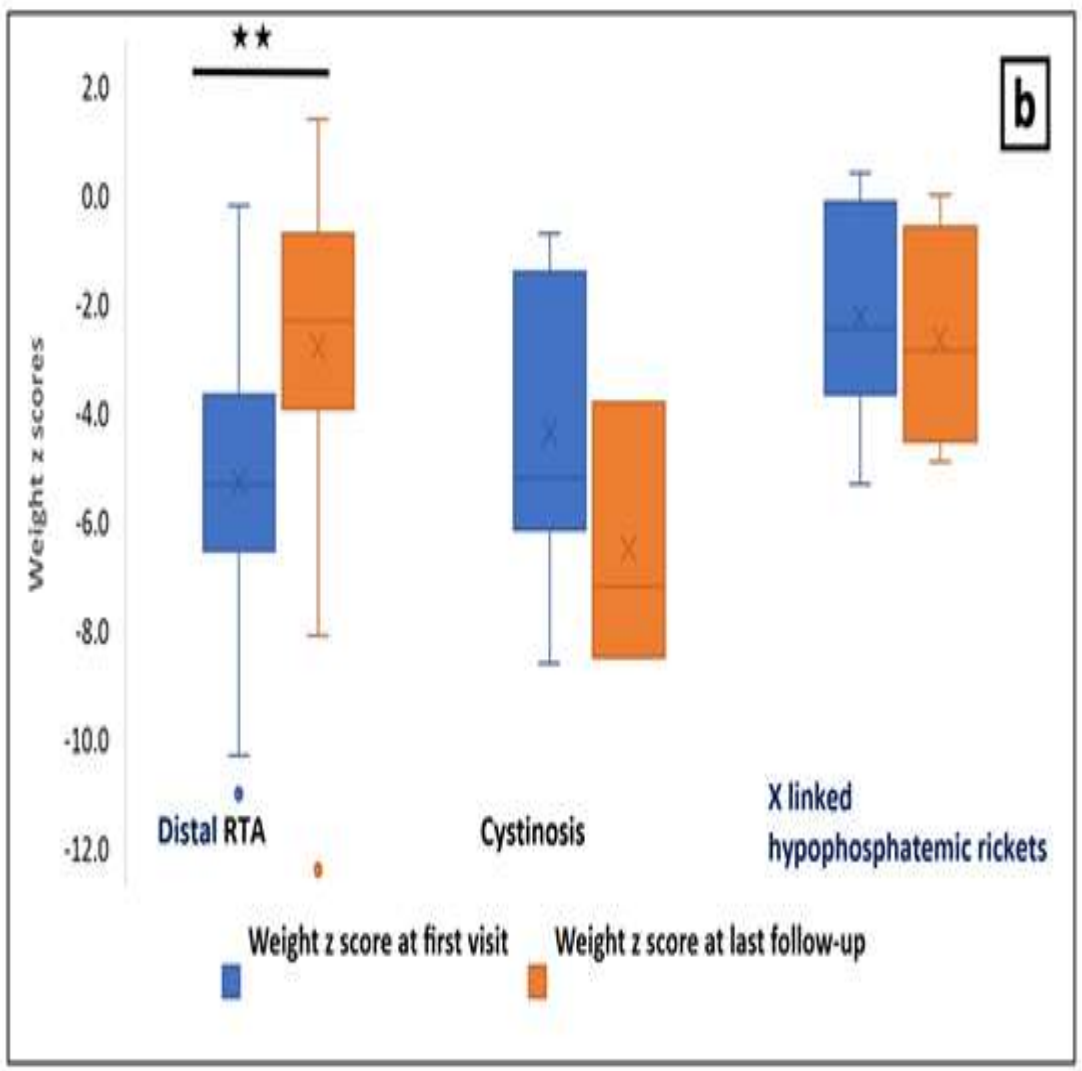
Varna Mathew[1] · Bobbity Deepthi[1] · Sudarsan Krishnasamy[1] · Prabhaker Yadav[2] · Madhileti Sravani[1] · Gopalan Suresh Ramprabhu[1] · Girish Chandra Bhatt[3] · Kausik Mandal[4] · Sriram Krishnamurthy[1]

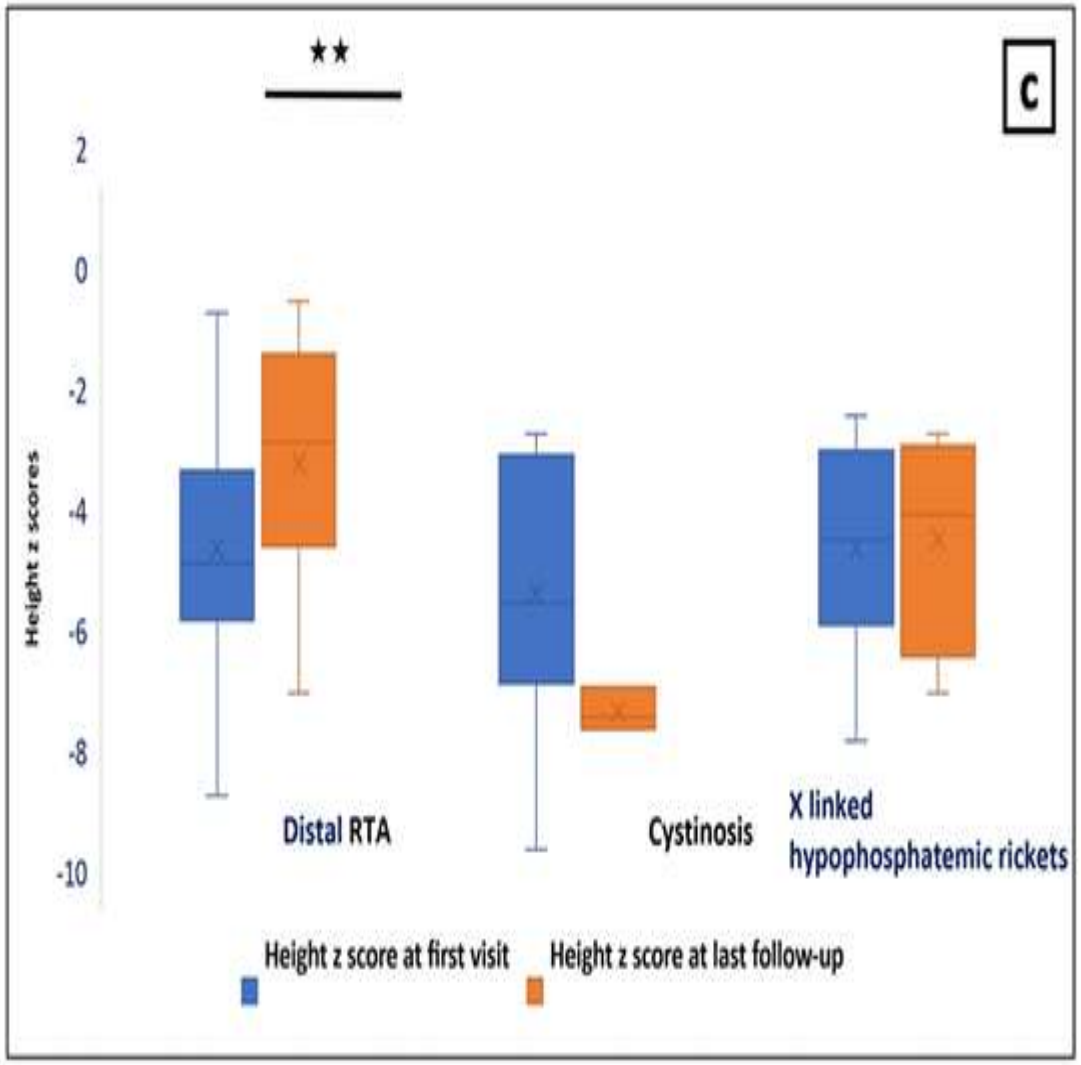
Table 3 Patterns of clinical presentation and complications in children with refractory rickets ($n=72$)

Etiology Clinical features	Distal RTA $n=34$; 47.2%	Fanconi syndrome $n=19$; 26.4%	HHR $n=11$; 15.3%	VDDR $n=4$; 5.5%	Bartter syndrome $n=2$; 2.8%	FHHNC $n=2$; 2.8%
Age at onset of symptoms (years)	3 (1, 4)	2 (0.75, 4)	1 (1, 4.75)	2 (1, 7)	1.5	6
Failure to thrive	22 (64.7)	18 (94.7)	4 (36.4)	2 (50)	2 (100)	1 (50)
Polyuria	21 (61.8)	12 (63.2)	-	-	2 (100)	2 (100)
Nephrocalcinosis	24 (70.6)	6 (31.6)	-	-	1 (50)	2 (100)
Pathological fractures	3 (8.8)	2 (10.5)	1 (9.1)	2 (50)	2 (100)	-
Hypokalemic paralysis	3 (8.8)	1 (5.3)	-	-	-	-
Hypokalemic myopathy	3 (8.8)	-	-	-	-	-
Consanguinity	19 (55.9)	8 (42.2)	3 (27.3)	2 (50)	2 (100)	1 (50)

V Mathew et al Pediatric Nephrology (2025) 40:1915–192

Etiology	*n* (%)
Distal renal tubular acidosis (dRTA)	34 (47.2)
• dRTA-4 with hemolytic anemia (*SLC4A1* homozygous mutation)	14 (41.2)
• dRTA-3 with or without sensorineural hearing loss (*ATP6V0A4* mutation)	3 (8.8)
• dRTA-2 with progressive sensorineural hearing loss (*ATP6V1B1* mutation)	2 (5.9)
• Amelogenesis imperfecta (*WDR72* mutations)	5 (14.7)
• Wilson disease	1 (2.9)
• No mutations identified	9(26.5)
Fanconi syndrome	19 (26.4)
• Cystinosis	9 (47.3)
• Lowe syndrome	3 (15.8)
• Fanconi–Bickel syndrome	3 (15.8)
• Dent disease type 1	1 (5.3)
• Dent disease- negative for mutations	1 (5.3)
• Tyrosinemia type 1	1 (5.3)
• Fanconi renotubular syndrome-2 (*SLC34A1* mutation)	1 (5.3)
Hypophosphatemic rickets	11 (15.3)
• X-linked hypophosphatemic rickets	8 (72.7)
• Hypophosphatemic rickets with hypercalciuria (HHRH)	1 (9.1)
• Hypophosphatemic rickets associated with epidermal nevus syndrome	1 (9.1)
• McCune Albright syndrome	1 (9.1)
Vitamin D-dependent rickets (VDDR)	4 (5.5)
• VDDR type 1	1 (25)
• VDDR type 2	3 (75)
Bartter syndrome	2 (2.8)
• Type 1	1 (50)
• Type 2	1 (50)
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)	2 (2.8)





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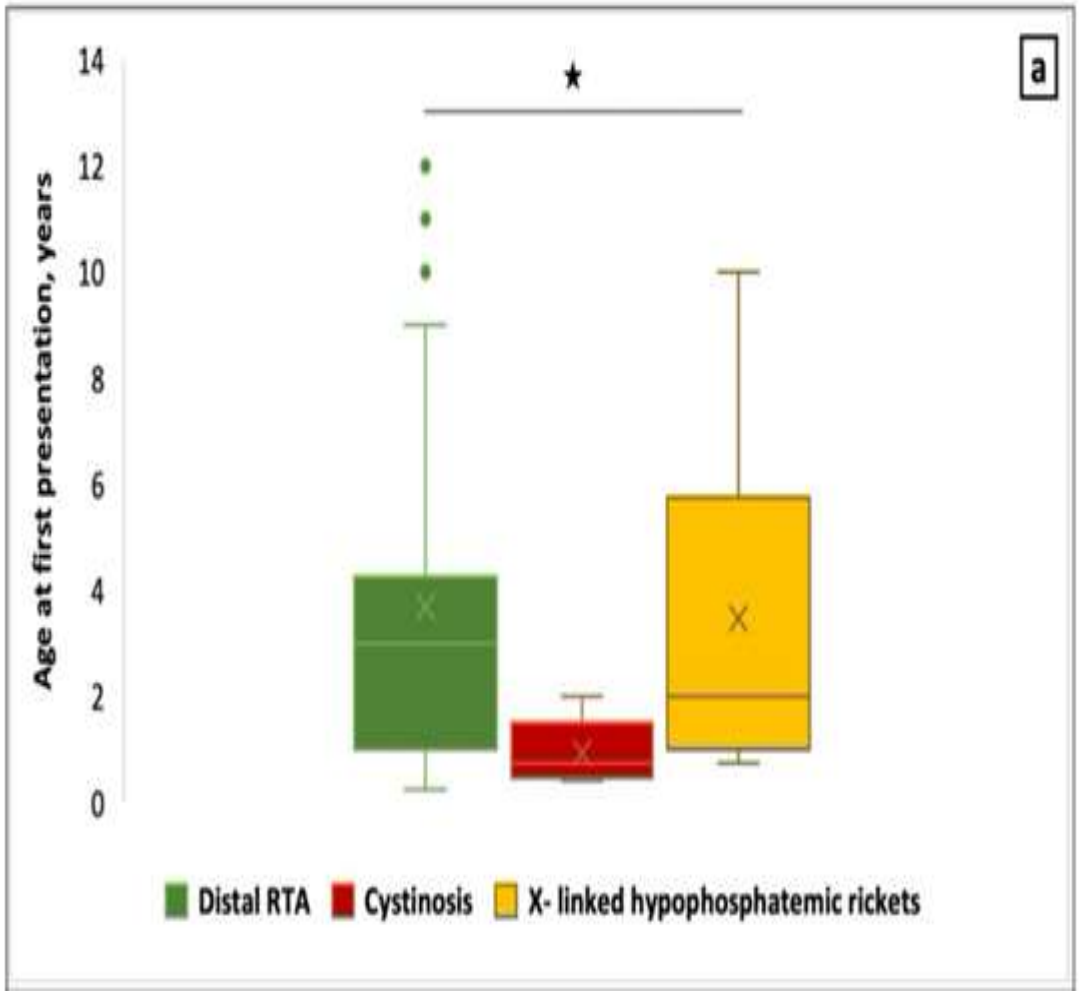

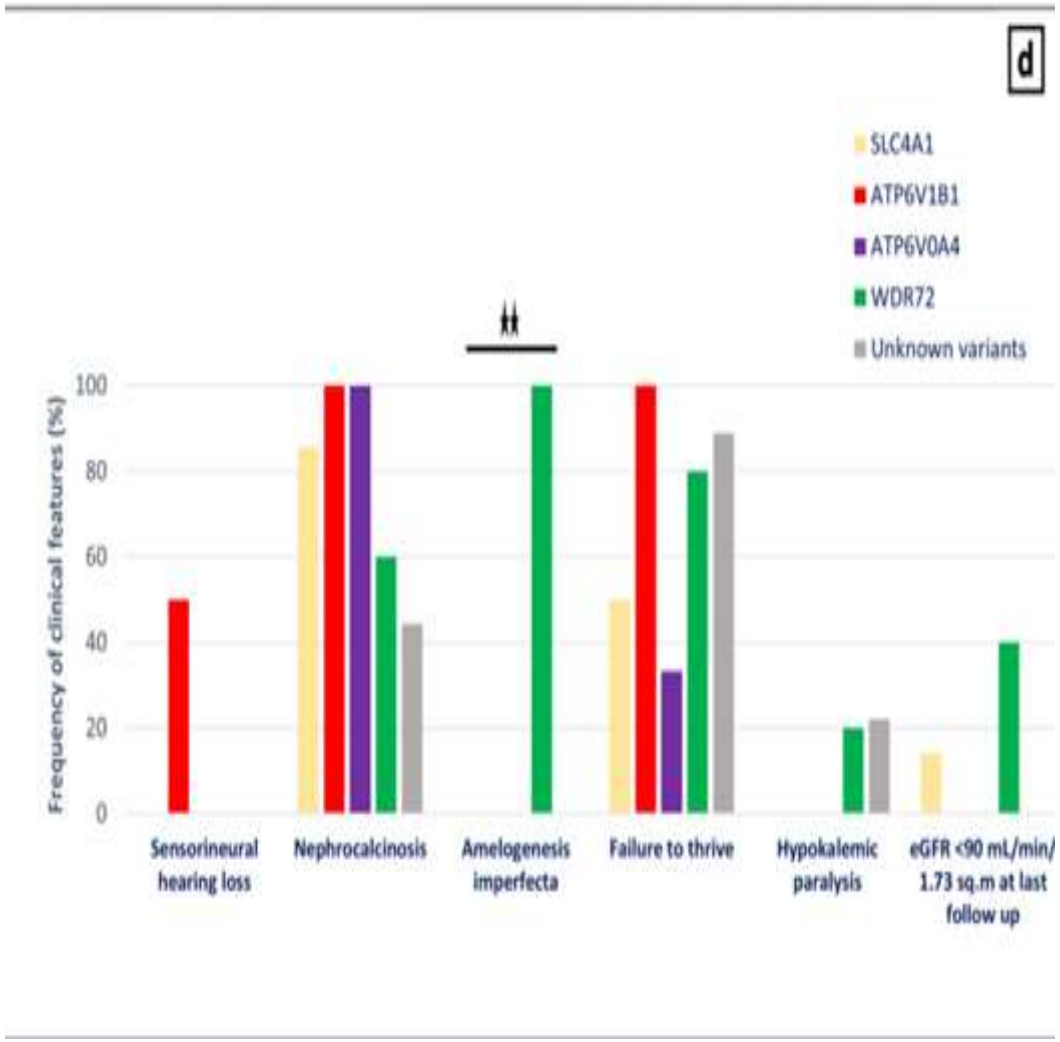

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HYPOPHOSPHATEMIC RICKETS(HPR)

- In infancy or early childhood with skeletal deformities and growth plate abnormalities
- Most common causes are genetic (XLHPR)resulting in lifelong hypophosphatemia and osteomalacia
- Good clinical evaluation required
- Treatment includes the active form of vit D along with PO4 salts
- **Newest modality available- BURSOSUMAB - XLHPR**

  (anti-FGF23 antibody treatment)

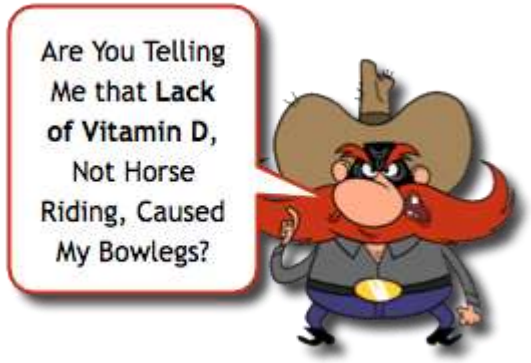
CLINICAL FEATURES- HPR

Presents similar to nutritional Rickets

- Poor growth
- Deformities of weight-bearing joints (Genu valgum or varus)
- Rachitic rosary, frontal bossing, enlargement of knees, wrists, ankles
- May have hypotonia, delayed motor development, myopathy, bone pain
- Waddling gait with in-toeing
- Short stature with disproportionately short lower limbs, typically after 1 year
- Dental abscesses are common
- Family history may be present

APPROACH TO DIAGNOSIS-RICKETS

Wrong and delayed diagnosis may result in inappropriate treatment of rickets and poor outcome



- Good medical history
- Biochemical tests
- Radiography
- Genetic tests

(especially in those with no family history but genetic form suspected)

Table 4 Biochemical workup in rickets

Serum/plasma	• Phosphate (Pi), calcium, ionized calcium, albumin • Creatinine, bicarbonate • Alkaline phosphatase (ALP) • Alanine transaminase (ALT) • Aspartate transaminase (AST) • Bone specific ALP (in cases of elevated ALT/AST) • Parathyroid hormone (PTH) • 25(OH)D, and $1,25(OH)_2D$ • Intact and/or c-terminal fibroblast growth factor 23 (FGF23)
Spot urine	• Dipstick: glucose, protein, pH • Potassium, sodium, calcium, phosphate, creatinine, glucose, amino-acids • ß2-microglobuline (or other low molecular weight proteins)
Calculations	• Estimated glomerular filtration rate (GFR) [96] • Urine: calcium/ creatinine ratio • Urine: phosphate/ creatinine ratio • Tubular maximum reabsorption of Pi per GFR (TmP/GFR)[a] • Fractional tubular reabsorption of Pi (TRP)[a]

[a]Calculations are given in Table 5

Pediatric Nephrology (2022) 37:2013–2036
https://doi.org/10.1007/s00467-021-05328-w

TUBULAR ABSORPTION OF PO4

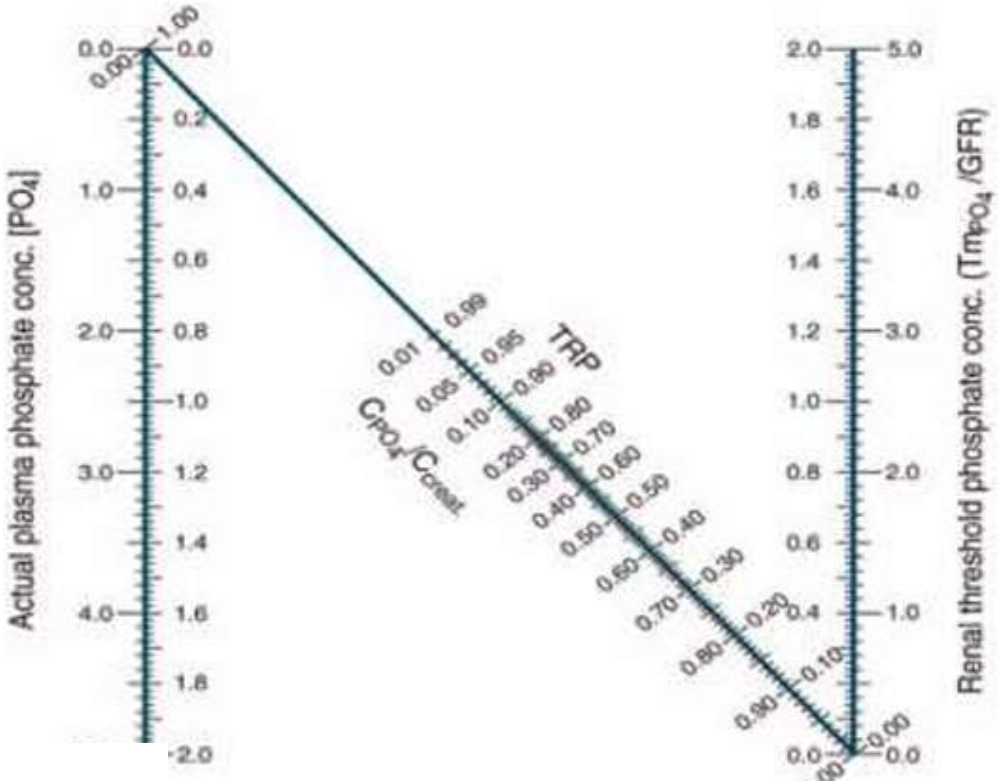
$$C_P/C_{Cr} = \frac{\text{serum creatinine} \times \text{Urine phosphate}}{\text{Urine creatinine} \times \text{Serum phosphate}}$$

$$TRP = 1 - \frac{\text{serum creatinine} \times \text{Urine phosphate}}{\text{Urine creatinine} \times \text{Serum phosphate}}$$

Age-related reference ranges for TmP/GFR

Paediatric Ranges

Age	Range (mmol/L)	n
Birth	1.43-3.43	20
3 months	1.48-3.30	20
6 months	1.15-2.60	20
2-15 years	1.15-2.44	101

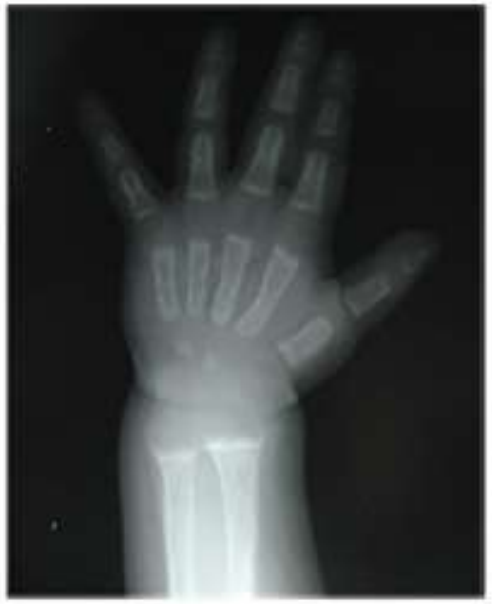


Bijvoet normogram for TmP/GFR

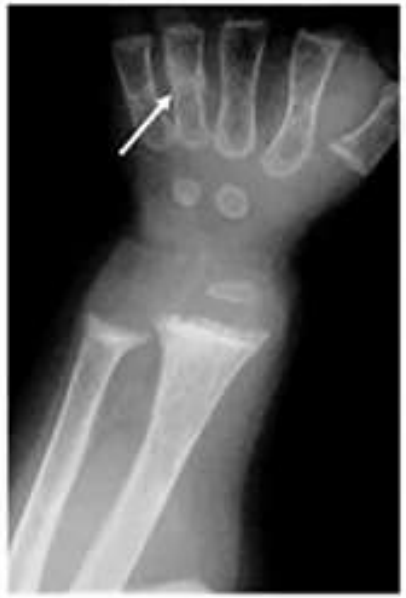
If TRP<0.86, reabsorption is Maximal

Renal Tubular reabsorption of phosphate, (TmP/GFR): indications and interpretation. Payne RB Ann. Clin. Biochem. 1998; 35: 201-206

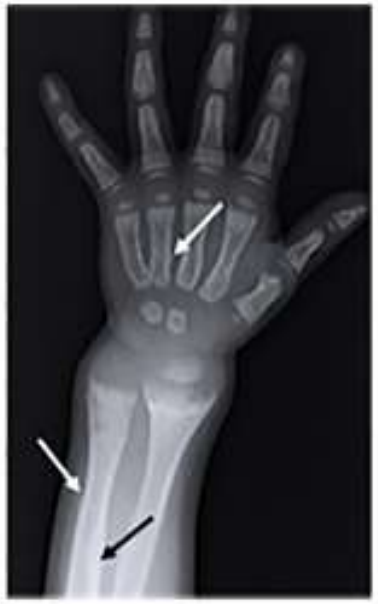
RADIOLOGICAL FEATURES OF RICKETS



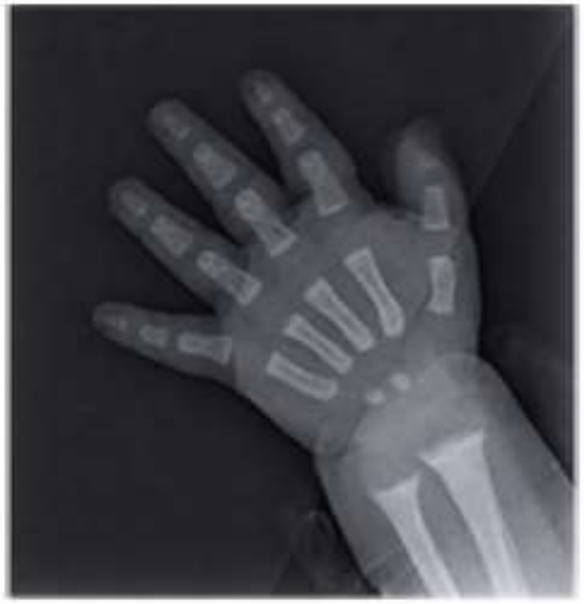
Nutritional vitamin D deficiency rickets
Male 3.5 mo



Vitamin D-dependent rickets type 1A
Female 16 mo



Vitamin D-dependent rickets type 2A with alopecia
Female 2.3 yr



X-linked hypophosphatemic rickets
Male 4 mo

Best assessed at the growth plates of rapidly growing bones

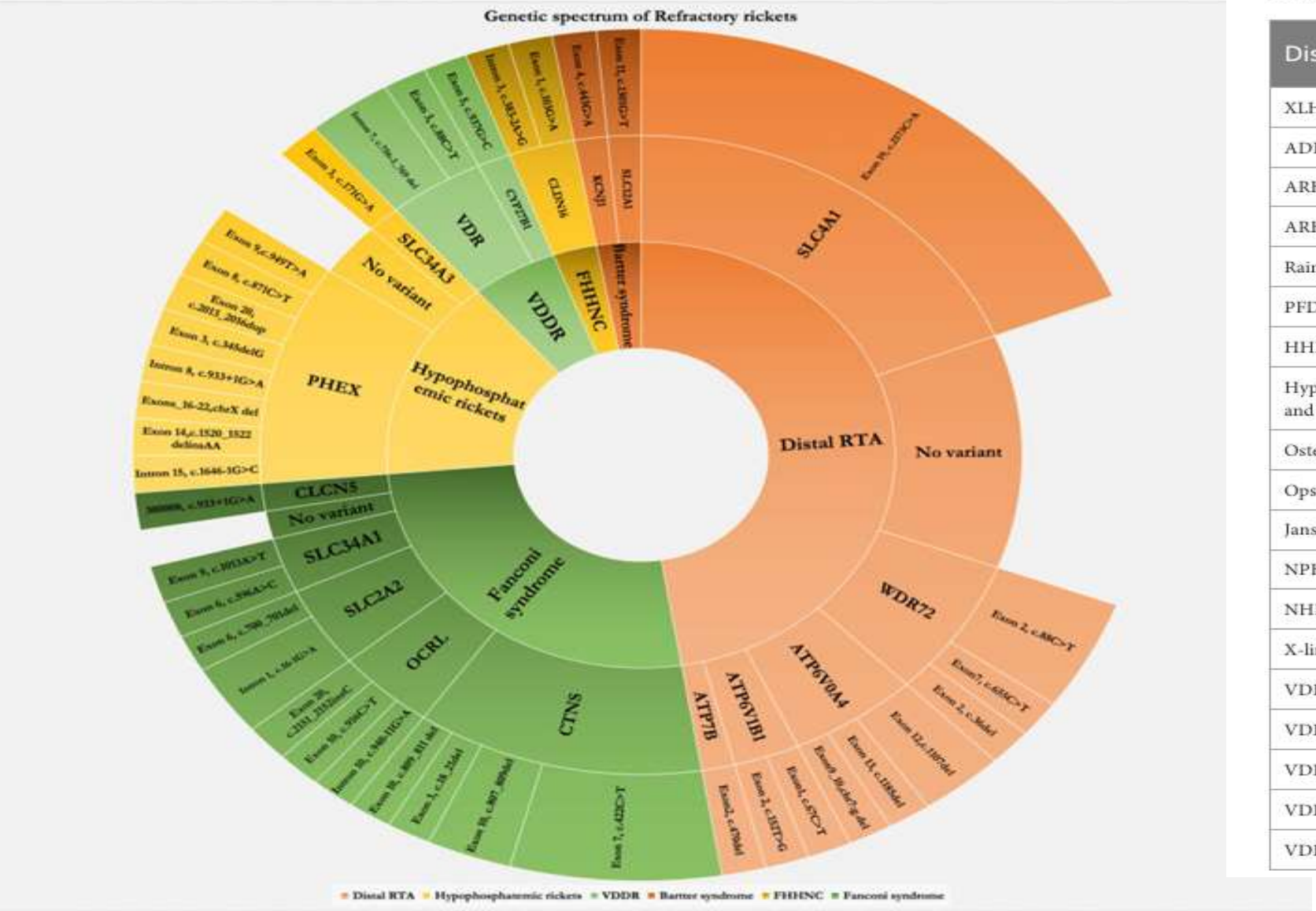
Rickets Severity Score (Thacher)

Baroncelli G et al.Frontiers of Endocrinol 2024Vol 15- 2024

GENETIC TESTING

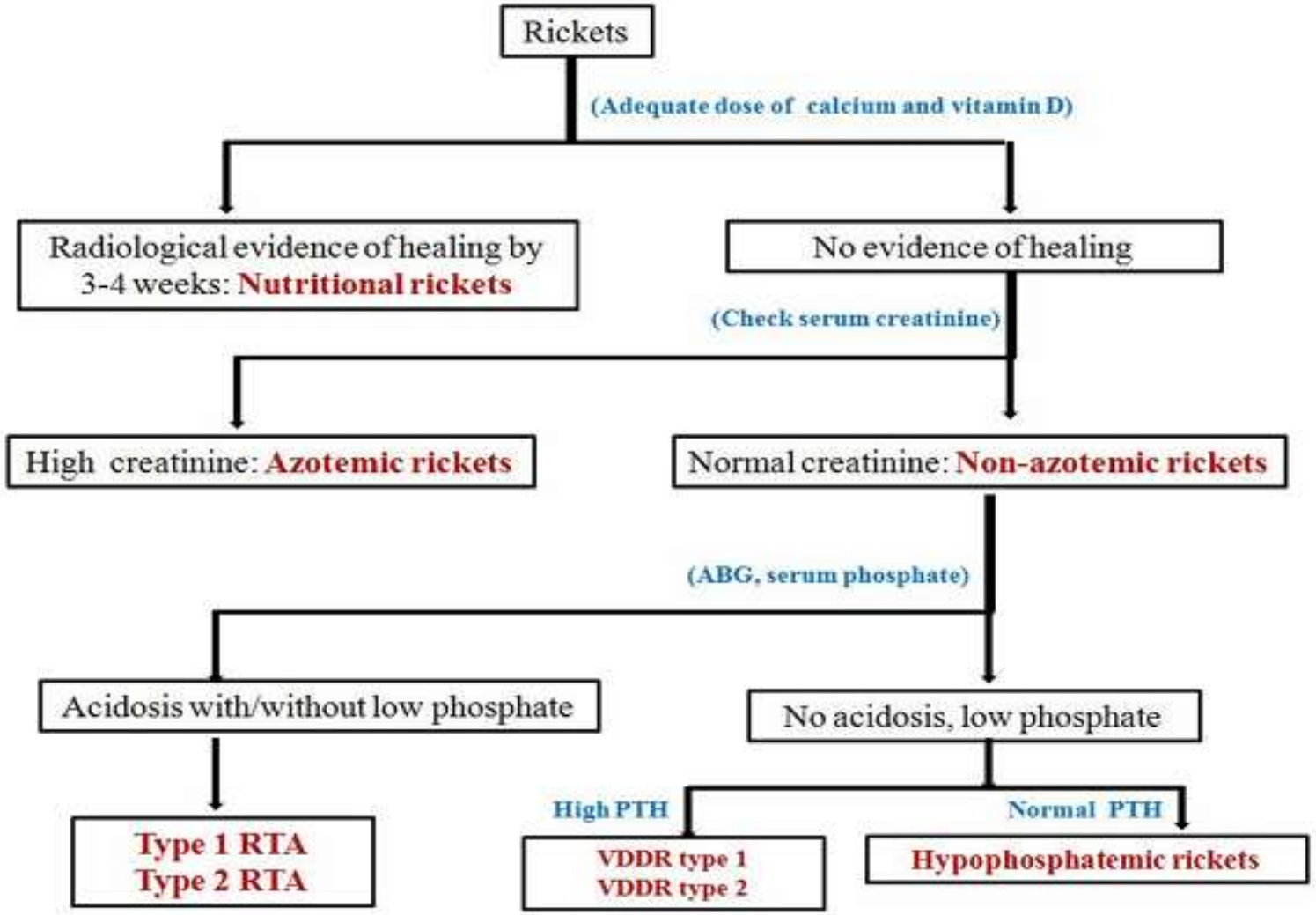
- Consider Genetic testing whenever available
- If family history present- **TARGETED SEQUENCING**
- **MULTIGENE** hypophosphatemia panels are also available

Sunburst chart showing the etiologies of children with refractory rickets ($n=71$) in relation to their genetic profile



Disorder	Gene	OMIMM #
XLH	*PHEX*	307800
ADHR	*FGF23*	193100
ARHR1	*DMP1*	241520
ARHR2	*ENPP1*	613312
Raine syndrome	*FAM20C*	259775
PFD	*GNAS*	174800
HHRH	*SLC34A3*	241530
Hypophosphatemic rickets and hyperparathyroidism	*13q13.1*	612089
Osteoglophonic dysplasia	*FGFR1*	166250
Opsismodysplasia	*INPPL1*	258480
Jansen-type metaphyseal chondrodysplasia	*PTH1R*	156400
NPHLOP1	*SLC34A1*	612286
NHERF1	*SLC9A3*	604990
X-linked recessive hypophosphatemic rickets	*CLCN5*	300554
VDDR1A	*CYP27B1*	264700
VDDR1B	*CYP2R1*	600081
VDDR2A	*VDR*	277440
VDDR2B	*VDR*	600785
VDDR3	*CYP3A4*	619073

APPROACH TO DIAGNOSIS



Agrawal C, Chakraborty PP. Rickets in renal tubular acidosis: A clinical appraisal. J Exp Nephrol 2020; 1(1):17-24.

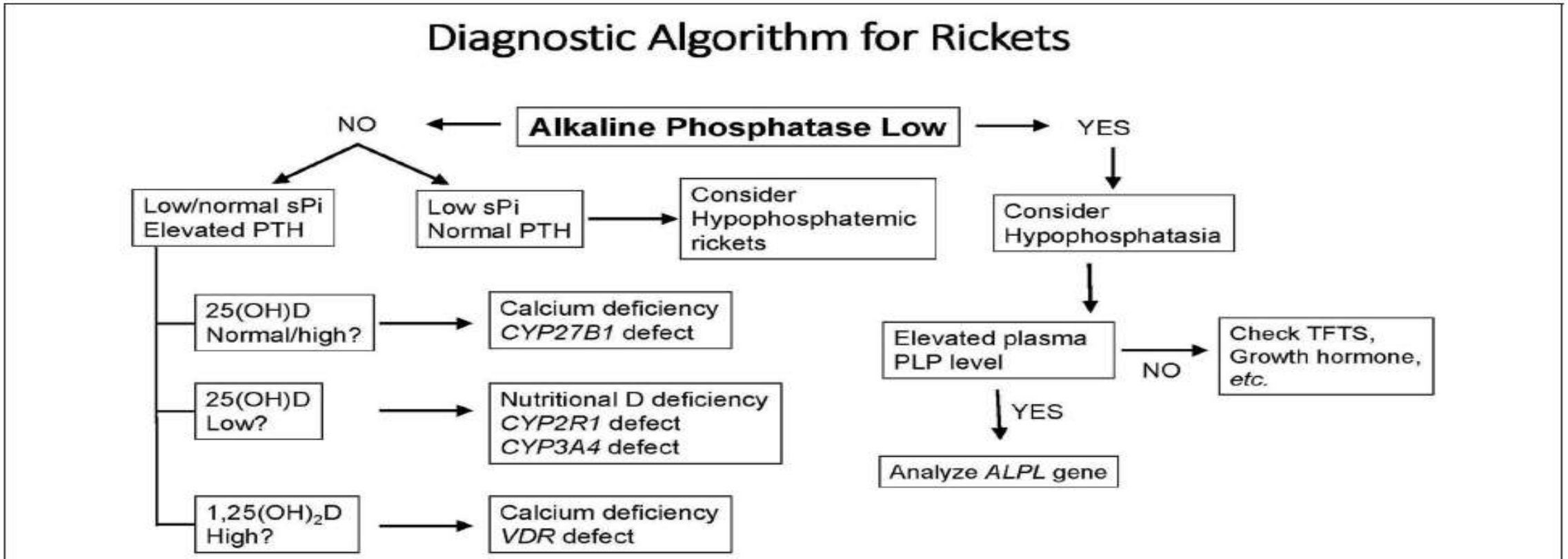


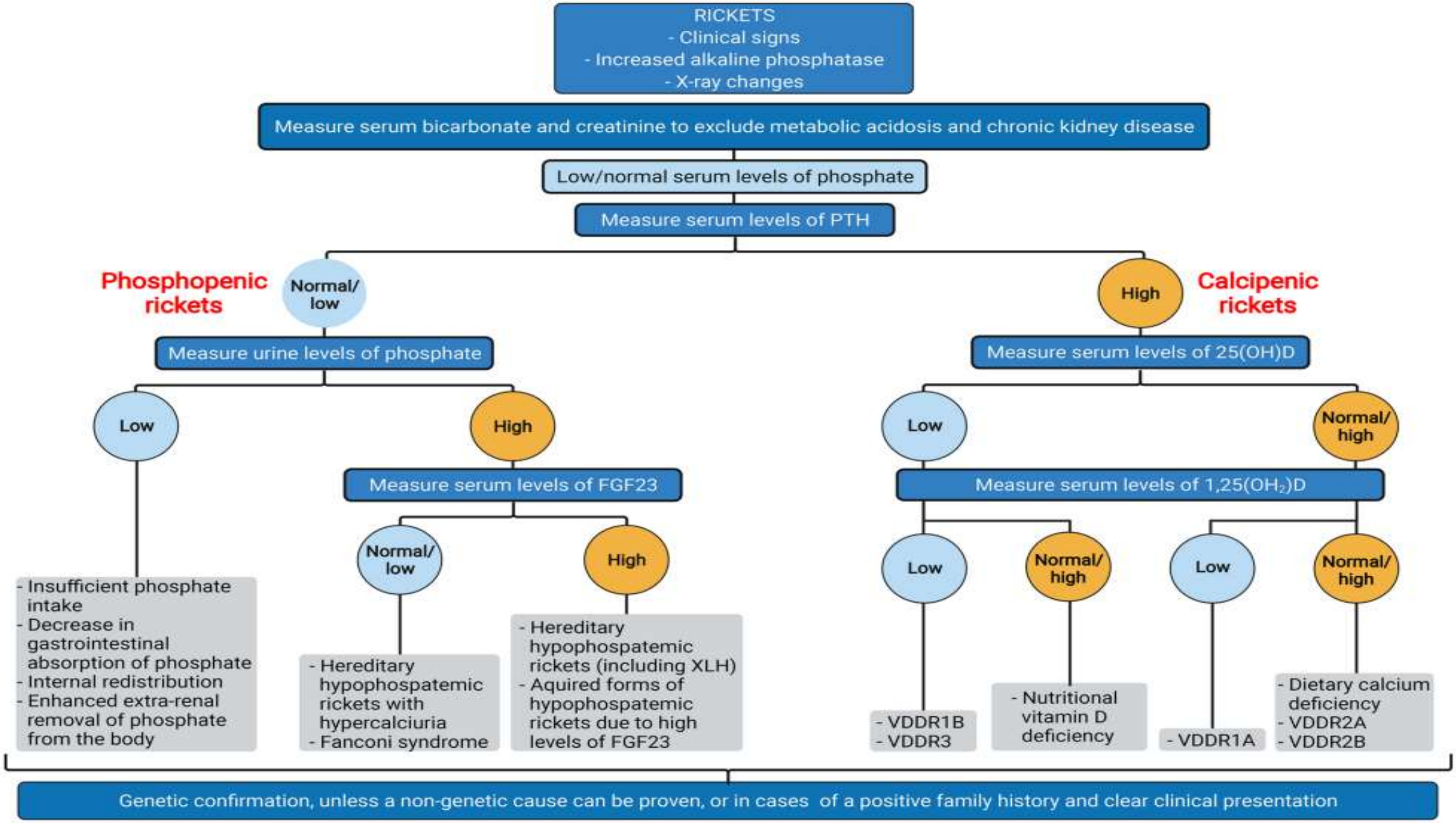
FIGURE 2 | A diagnostic algorithm for evaluation of a child with radiological or clinical features of rickets. See text for complete description of biochemical and clinical features of each form of rickets. PLP, Pyridoxal 5′-phosphate, the metabolically active form of vitamin B6; sPi, serum phosphorus; TFTs, thyroid function tests; PLP, pyridoxal 5′ phosphate (vitamin B6); ALPL, the gene for tissue non-specific alkaline phosphatase.

TABLE 1 | Vitamin D-dependent rickets.

Type	25(OH)D	$1,25(OH)_2D$	PTH	Inheritance	Gene defect (OMIM)
VDDR1A	N/I	D	I	A.R.	CYP27B1 (264700)
VDDR1B	D	D	I	A.R.	CYP2R1 (600081)
VDDR2A	N/I	N/I	I	A.R.	VDR (277440)
VDDR2B	N/I	N/I	I	A.R.	Unknown (600785)
VDDR3	D	D	I	A.D.	CYP3A4 (124010)

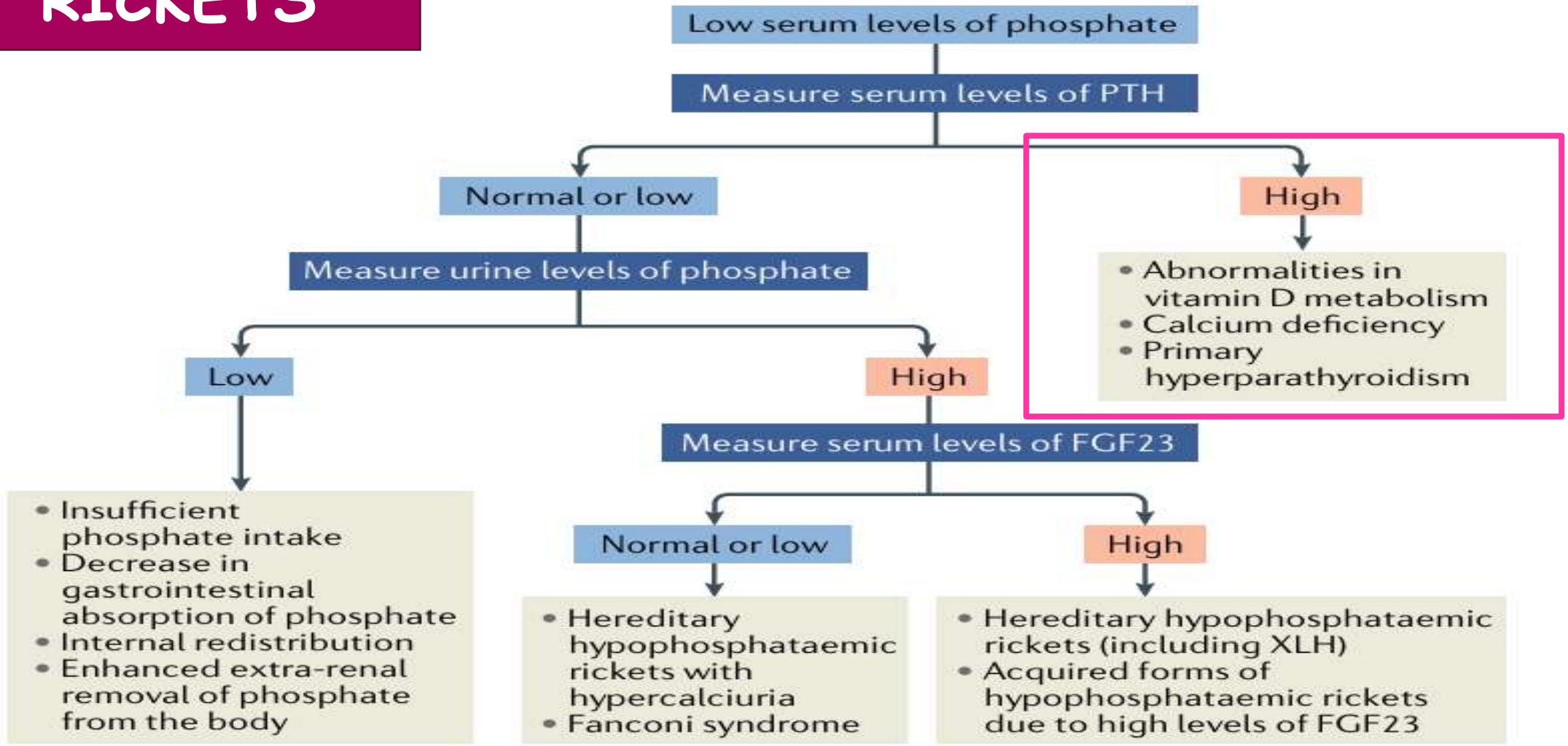
VDDR, vitamin D-dependent rickets, N, normal; I, increased, D, decreased; PTH, parathyroid hormone.

Michael Levine. Frontiers in Pediatrics. 2020

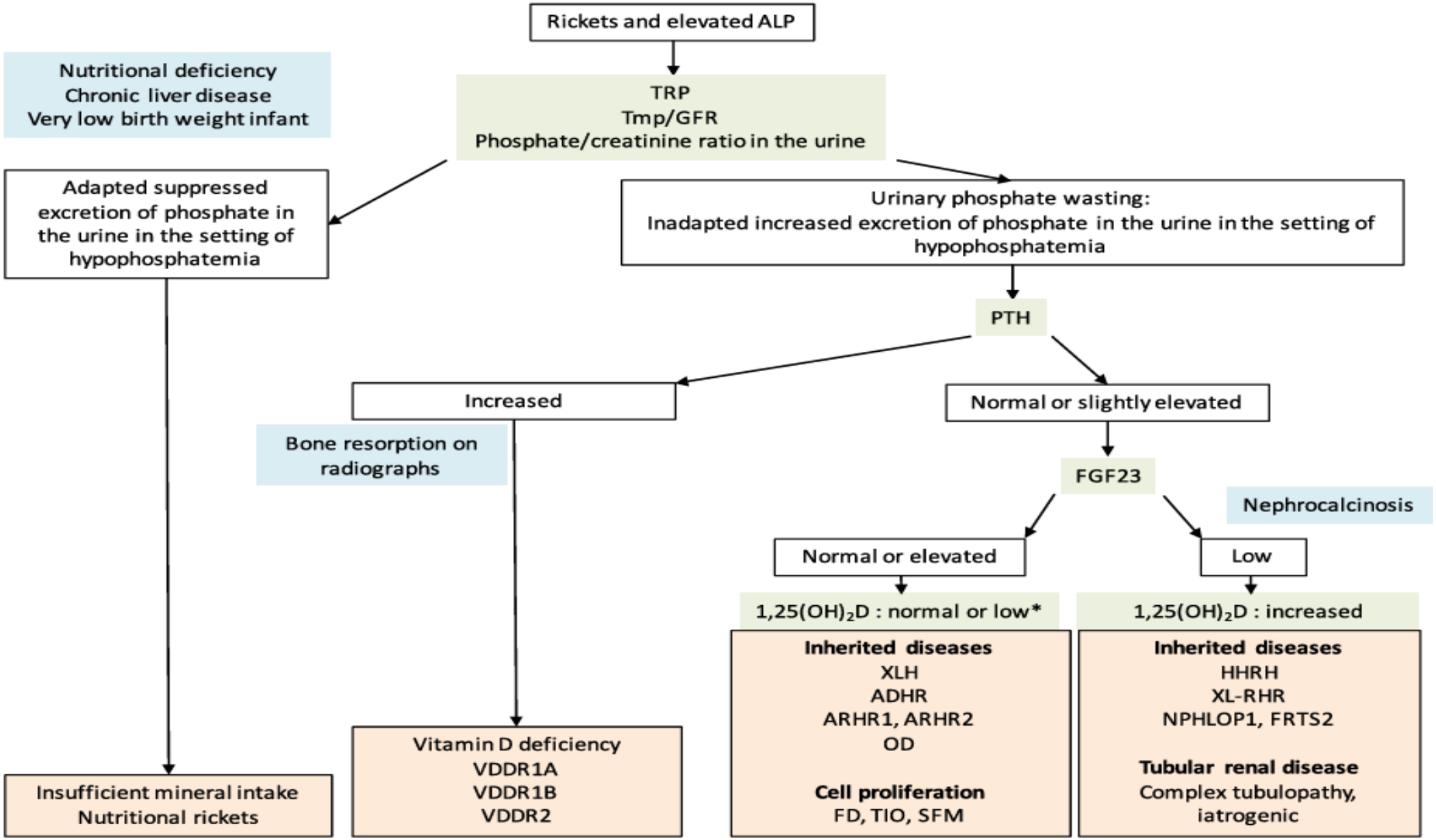


Dieter Haffner. Natures Review Nephrology 2019

RICKETS

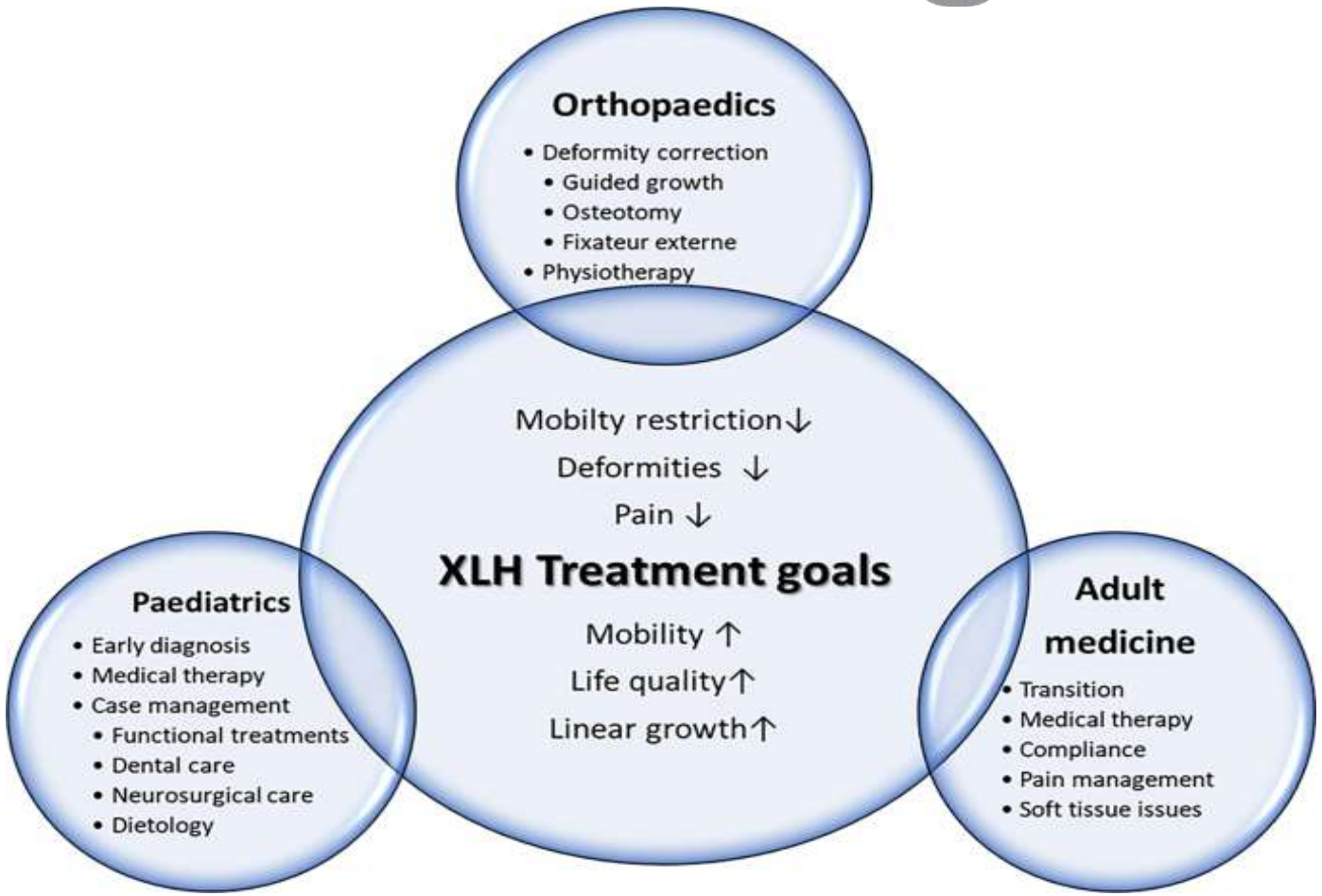


Haffner D, Emma F, Eastwood DM, et al Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019 Jul;15(7):435-455.


Rickets and elevated ALP
Nutritional deficiency
Chronic liver disease
Very low birth weight infant
TRP
Tmp/GFR
Phosphate/creatinine ratio in the urine
Adapted suppressed excretion of phosphate in the urine in the setting of hypophosphatemia
Urinary phosphate wasting:
Inadapted increased excretion of phosphate in the urine in the setting of hypophosphatemia
PTH
Increased
Normal or slightly elevated
Bone resorption on radiographs
FGF23
Nephrocalcinosis
Normal or elevated
Low
1,25(OH)2D : normal or low*
1,25(OH)2D : increased
Inherited diseases
XLH
ADHR
ARHR1, ARHR2
OD
Cell proliferation
FD, TIO, SFM
Inherited diseases
HHRH
XL-RHR
NPHLOP1, FRTS2
Tubular renal disease
Complex tubulopathy, iatrogenic
Insufficient mineral intake
Nutritional rickets
Vitamin D deficiency
VDDR1A
VDDR1B
VDDR2

TREATMENT GOALS

- Improve Growth
- Treat Rickets
- Decrease SKELETAL deformity
- Decrease Bone Pain
- Improve muscle strength and ambulation



TREATMENT of VDDR

TABLE 2 | Suggested calciferol doses for maintenance treatment of patients with VDDR.

	VDDR1A (μg per day)	VDDR1B (μg per day)	VDDR2 (μg per day)	VDDR3 (μg per day)
Vitamin D3 or D2	NI	100–200	125–1,000?*	**1,000 to?**
Calcifediol	NI	**20–50**	20–200*	50 to?
Calcitriol	**0.3–2**	0.3–2	**5–60**†	1 to?
1α (OH)D	**0.5–3**	0.5–3	**5–60**†	2 to?

Michael Levine. Frontiers in Pediatrics. 2020

X-LINKED HYPOPHATEMIC RICKETS

- **High Dose Calcitriol**

  Without this can develop severe hyperparathyroidism

  Helps to increase PO4 absorption and helps in healing

  Dose: 20-30 ng/day, alpha calcidiol 40-60 ng/day

  Multiple doses- due to short half-life and ongoing losses

  Dose titrated based on response- improvement in symptoms and ALP normalizing

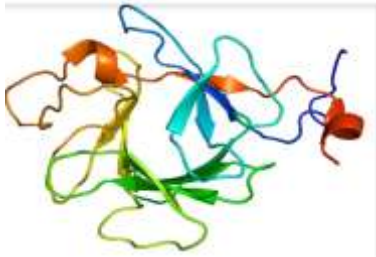
In Non FGF23 Rickets: only PO4 supplements
Vit D is already high

- **Oral PO4:**
- 20-60 mg/day (divided into 3 to 5 doses)

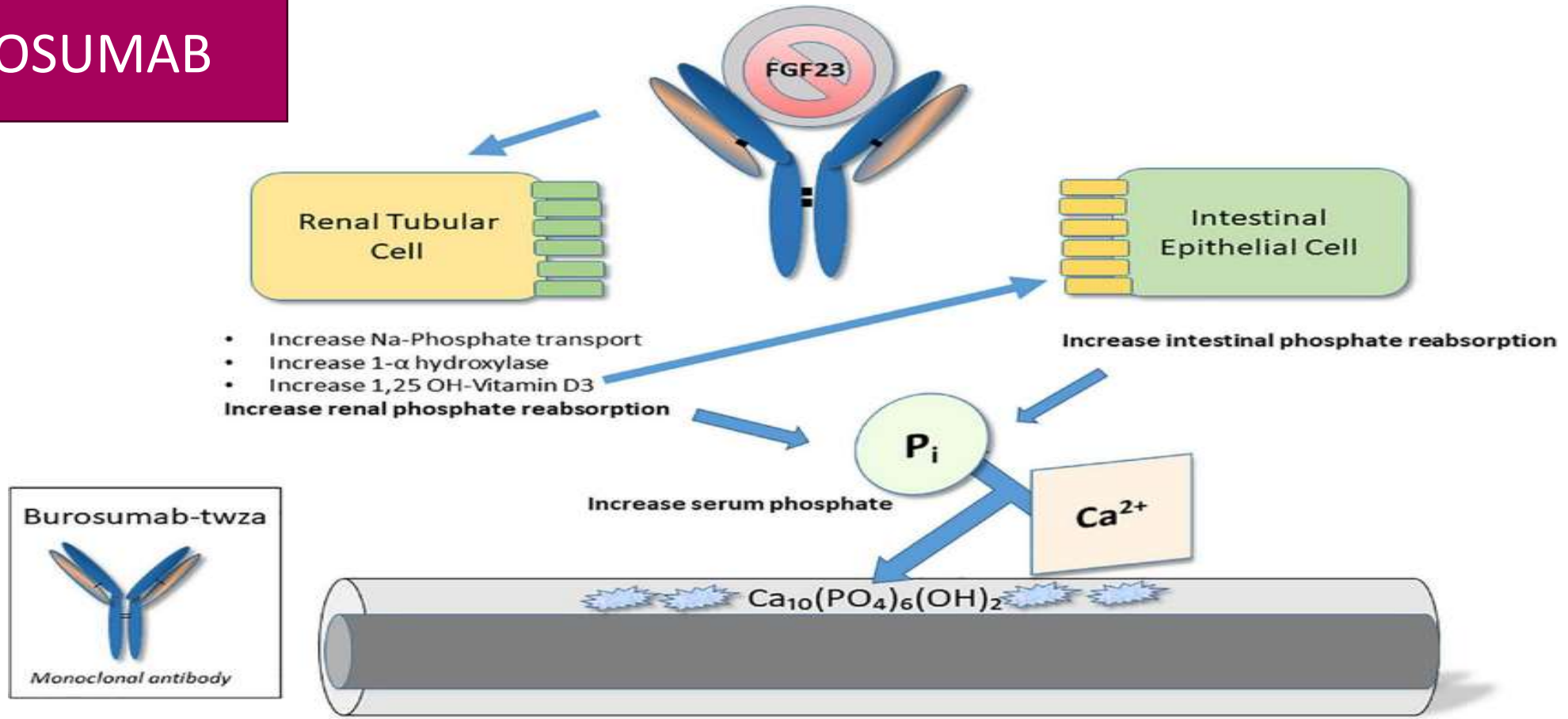
TARGETED THERAPY - BUROSUMAB

- Human Monoclonal Antibody that binds to FGF23 and inhibits it activity
- FDA approved as monotherapy in children and adults with XL HPR and TIO
- Further studies are needed for FGF-mediated disorders
- It is mechanistically inappropriate if FGF23 levels are low
- CI in moderate to severe kidney disease

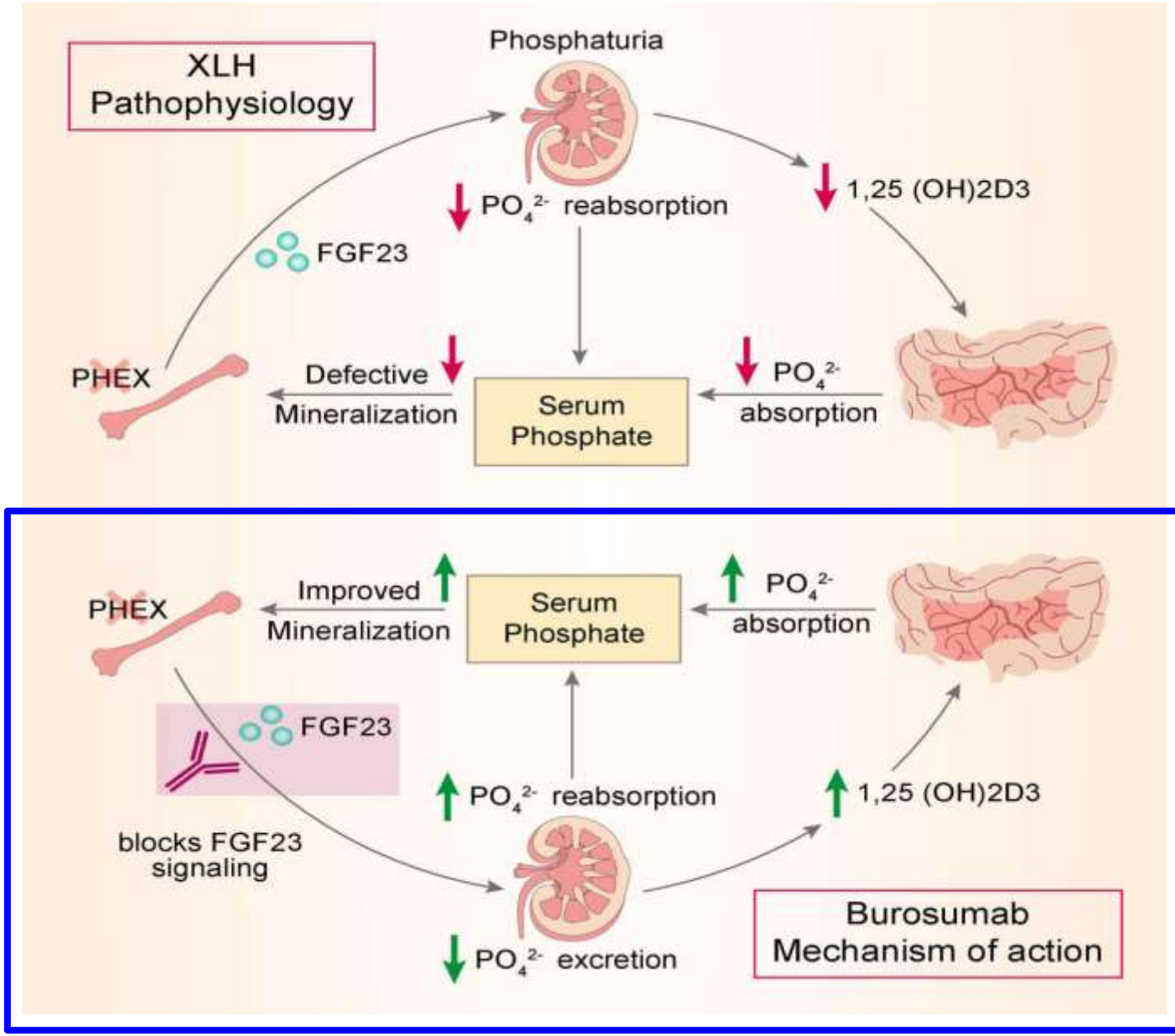
Fibroblast growth factor 23 (FGF23)



BUROSUMAB



Molecular mechanism of action – Burosumab-twza. Burosumab-twsa is a human IgG1 monoclonal antibody that inhibits fibroblast growth factor (FGF)-23 action in the kidney. In so doing, it directly enhances phosphate (Pi) resorption from the kidney. In addition, through effects on vitamin D metabolism it indirectly enhances Pi reabsorption from the intestine. The resulting increase in serum Pi promotes improved bone quality and mineralization.


XLH
Pathophysiology
Phosphaturia
PO_4^{2-} reabsorption
1,25 (OH)2D3
FGF23
PHEX
Defective
Mineralization
Serum
Phosphate
PO_4^{2-}
absorption
Improved
Mineralization
Serum
Phosphate
PO_4^{2-}
absorption
PHEX
FGF23
PO_4^{2-} reabsorption
1,25 (OH)2D3
blocks FGF23
signaling
PO_4^{2-} excretion
Burosumab
Mechanism of action


NDC 69794-304-01
CRYSVITA®
(burosumab-twza)
Injection
30 mg/mL
For Subcutaneous Use Only
Single-Dose Vial
Discard Unused Portion
Rx only
1 vial
CRYSVITA
30 mg/mL
© 2018 GS

SITUATIONS INDICATED

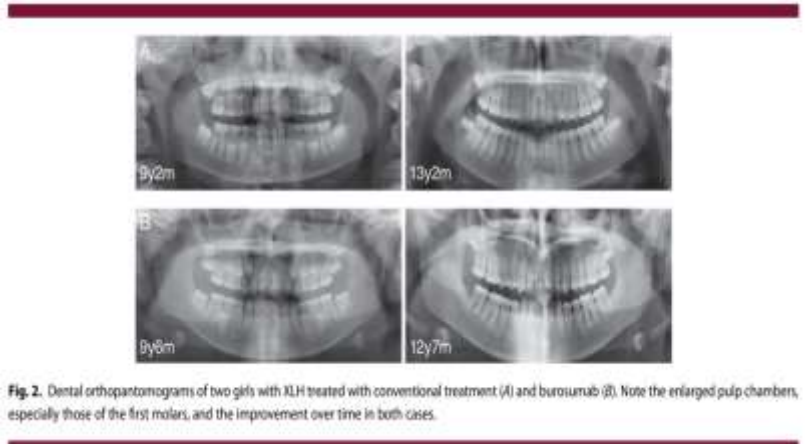


Fig. 2. Dental orthopantomograms of two girls with XLH treated with conventional treatment (A) and burosumab (B). Note the enlarged pulp chambers, especially those of the first molars, and the improvement over time in both cases.

- Failure of conventional therapy
- Severe Rickets, deformities, short stature- start early
- Development of hyperparathyroidism
- Persistent rickets, bone pain, failure to correct ALP- worsening growth deficit
- Non-compliance with Conventional treatment, multiple dosing

DOSE: 0.8mg/kg- every 2 weeks
Given Subcut, titrated to 2 mg/kg
Half life 13-19 days
Target- low to mid normal PO4

Peak increase in TMP GFR- 7 days
Increase in PO4 and 125 (OH)2 D3 in 3d
Rise to supraphysiological levels initially

CONCLUSIONS- EFFICACY

Burosumab has several advantages over conventional treatment

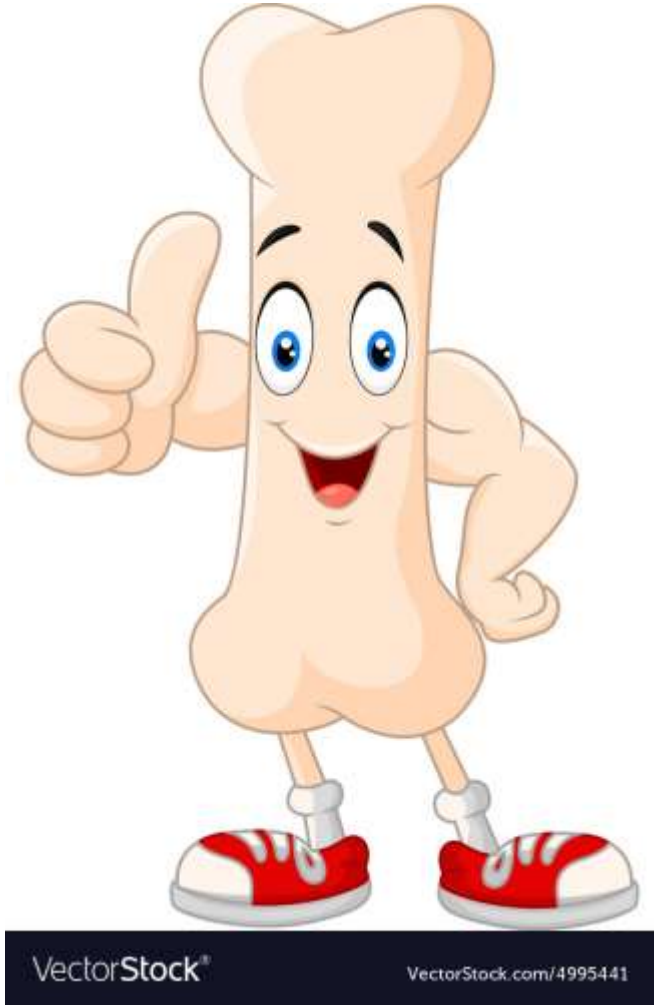
- It removes the burden of medicating several times per day as with conventional treatment which hampers adherence
- It was shown to be more effective in healing rickets
- It has good safety profile compared to Conventional- which is known for GI discomfort, hypercalciuria, secondary hyperparathyroidism, diarrhoea and nephrocalcinosis

Is Expensive Not freely available	Not licensed below 12 months of age	Some milder cases may not require it

Pediatric Nephrology (2022) 37:2289–2302
https://doi.org/10.1007/s00467-022-05505-5

TAKE HOME MESSAGE

- The diagnosis of Rickets is based on typical clinical symptoms and radiological findings
- Nutritional Rickets due to Vit D deficiency or Ca deficiency is commonest
- Hereditary causes of Rickets is due to mutation in genes involved in Vitamin D metabolism or action, renal PO4 reabsorption or synthesis/degradation of Phosphaturic hormone FGF23
- Genetic confirmation of diagnosis is helpful in planning therapy
- Conventional treatment of X-linked HPR may be beneficial but not always successful
- Burosumab has been proven to be highly successful in treating XL HPR and TIO
- Its role in other FGF23-driven forms of Phosphopenic rickets needs study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THANK YOU!