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Genetic basis of hereditary hypophosphataemic rickets and phenotype presentation in children and adults

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Abstract

Hypophosphataemic rickets (HR) is a genetic disorder causing defects in the renal handling of phosphorus, resulting in rickets. HR can be classified into two groups. First — with excess fibroblast growth factor 23 (FGF23) levels, which are due to gene mutations in extrarenal factors and include X-linked dominant hypophosphataemic rickets (XLHR), autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hypophosphataemic rickets with hyperparathyroidism. Second — with normal or low FGF23, which are caused by gene mutations in renal tubular phosphate transporters and include hereditary hypophosphataemic rickets with hypercalciuria (HHRH) and X-linked recessive hypophosphataemic rickets. The radiographical changes and clinical features of rickets in various types of HR are similar but not identical. Short stature, bone deformities mainly in the lower limbs, and dental problems are typical characteristics of HR. Although the initial diagnosis of HR is usually based on physical, radiological, and biochemical features, molecular genetic analysis is important to confirm the diagnosis and differentiate the type of HR. In this review, we describe clinical and biochemical features as well as genetic causes of different types of HR. The clinical and biochemical characteristics presented in this review can help in the diagnosis of different types of HR and, therefore, direct genetic analysis to look for the specific gene mutation. **(Endokrynol Pol 2021; 72 (4): 366–394)**

Key words: *hypophosphatemia; hypophosphataemic rickets; phenotype; PHEX; FGF23; clinical features; mutation; XLHR*

Introduction

Rickets is a childhood bone disorder characterized by defective growth plate mineralization leading to deformity in the growing skeleton. Adults are also vulnerable to a similar condition of rickets, known as osteomalacia, which causes softening of the bone. Osteomalacia occurs after the closure of the epiphyses, the end part of bones that is the most active in osteogenesis [1–3]. Deficiency of calcium, phosphorous, or vitamin D are known causes of rickets [3]. Chronic phosphate deficiency causes poor bone mineralization leading to rickets and osteomalacia [4].

Hypophosphataemic rickets (HR) was first described as vitamin D-resistant rickets by Fuller Albright because a patient did not respond to vitamin D treatment [5], although vitamin D deficiency was then the most common cause of rickets. Unlike vitamin D deficiency rickets, HR is due to mutations in genes involved in phosphate regulation and is characterized by low serum phosphate levels due to renal phosphate loss [2, 6, 7].

Serum levels of phosphate are mainly regulated by 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). The action of 1,25$(OH)_2$D is to increase the absorption of phosphate from the intestine and reduce the synthesis and secretion of PTH. In the kidney, both PTH and FGF23 contribute to renal reabsorption of phosphate by suppressing the expression of type 2 co-transporters of sodium/phosphate (NaPi2a and NaPi2c). In addition, FGF23 decreased the production of 1,25$(OH)_2$D by inhibiting 25-OH vitamin D 1-α hydroxylase, resulting in reduced phosphate absorption from the intestine. FGF23 plays its role in the presence of Klotho, which is a transmembrane protein. The FGF receptor is activated by intact FGF23 when the co-receptor Klotho is present [1,7]. Depending on whether FGF23 is involved, HR can be classified into two groups: HR with excess FGF23 levels due to mutations in genes not predominantly expressed in the kidneys, and

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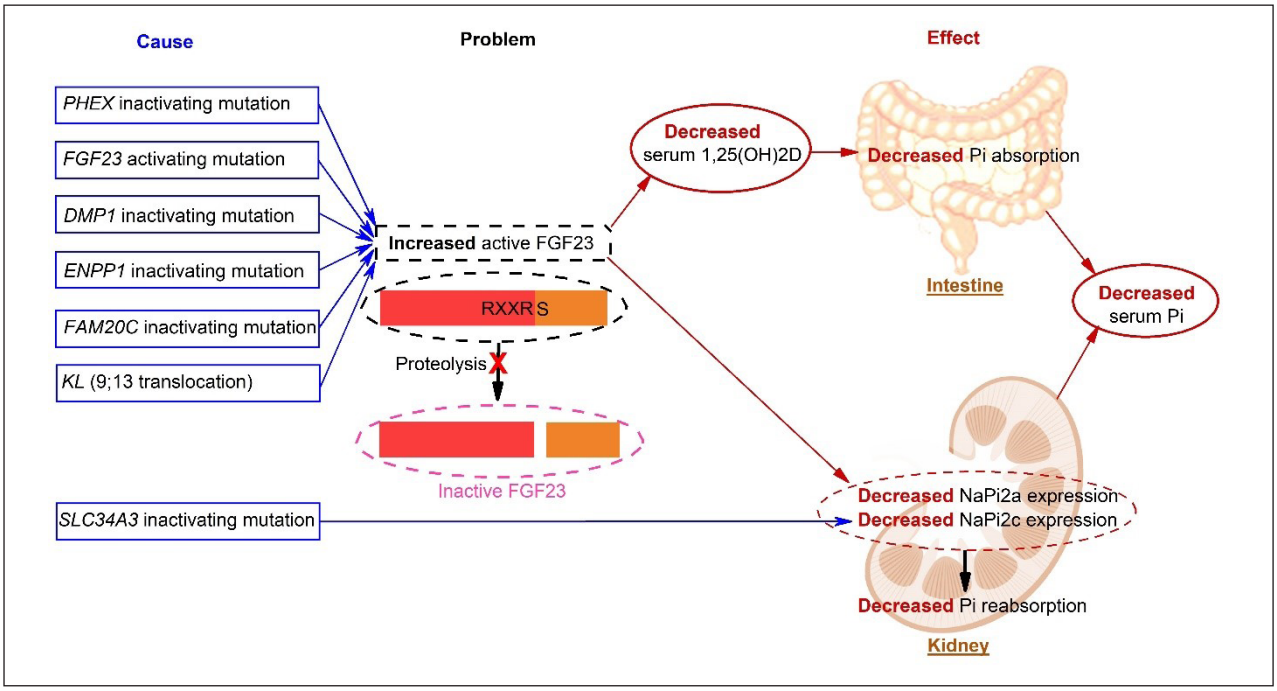

Figure 1. *Summary of HR pathogenesis. Mutations in PHEX (phosphate regulating endopeptidase homologue, X-linked), FGF23 (fibroblast-growth-factor 23), DMP1 (dentin matrix acidic phosphoprotein 1), ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1), FAM20C (family with sequence similarity 20, member C), and KL (Klotho) increase active form of FGF23 in serum. Activating mutations in FGF23 and inactivating mutations in PHEX and FAM20C lead to the prevention of proteolytic cleavage of FGF23 between R (Arg179) and S (Ser180). Elevated FGF23 results in decreased serum Pi (phosphate) through the intestine and kidney. Mutations in SLC34A3 (solute carrier family 34) cause decreased reabsorption of phosphate in the kidney and thus decreased serum Pi without the mediation of FGF23*

HR with normal or low FGF23 caused by gene mutations in renal tubular phosphate transporters [7, 8] (see Fig. 1).

Normally, individuals at different ages show different levels of serum phosphate. The concentration of phosphate is higher in infants compared to adolescents [2]. For instance, normal levels of serum phosphate for 1–3 and 16–19 years of age range from 3.8 to 6.5 mg/dL and from 2.7 to 4.7 mg/dL, respectively [7]. The best method of estimating renal phosphate wasting is the ratio of the tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR). In the presence of hypophosphataemia, low TmP/GFR indicates renal phosphate loss [7]. Other typical biochemical findings in HR include increased serum alkaline phosphatase (ALP) levels and normal or slightly increased PTH levels. Nevertheless, PTH levels are markedly elevated in HR with hyperparathyroidism (Klotho translocation) [1].

The clinical manifestations of HR change at different stages of life in the same individual and vary between different individuals with the same gene mutation, even within the same family. The radiographical changes and clinical features of rickets in various types of HR are similar. Short stature, bone deformities mainly in the lower limbs, and dental problems are typical characteristics of HR [2, 6, 8]. A review of different types of HR, as well as the genetic causes, physical characteristics, and biochemical findings of each type is presented.

Hypophosphataemic rickets with increased FGF23 levels

X-linked dominant hypophosphataemic rickets

X-linked dominant hypophosphataemic rickets (XLHR; MIM#307800) is the most common inherited form of HR, which accounts for more than 80% of familial hypophosphataemic rickets [9]. It is a rare disease with a prevalence of 1 per 20,000 live births [8]. Inactivating mutations in the phosphate regulating endopeptidase homologue, X-linked (*PHEX*; MIM#300550) gene lead to XLHR. Osteocytes produce more FGF23 due to inactivity or decreased activity of PHEX, leading to increased FGF23 circulating levels [10]. Elevated FGF23 levels decrease renal reabsorption of phosphate and absorption of phosphate from the gut into the bloodstream, leading to hypophosphataemia (see Fig. 1).

The *PHEX* gene mutation was first described in 1995 [11]. Subsequent studies of HR patients, as shown in Table 1, have reported several mutations in *PHEX* using

Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[102]	NA	Country: UK & USA northern European African American Saudi Arabian Indian subcontinent Southeast Asian (n = 68) (46 familial and 22 sporadic)	68/68	31	2	31 *PHEX* mutations: Nonsense, deletions, deletional insertions, duplication, insertions, splice site, missense, 5′ UTR	1. SSCP analysis of *PHEX* 2. DNA sequence of *PHEX*	Rachitic disease, 68/68	P ↓, 68/68
[103]	NA	Country: Finland Finnish (n = 23) (5 familial and 15 sporadic)	20/23	15	9	18 *PHEX* mutations in 19 patients: Nonsense, splice site, missense, small deletion	1. SSCP of *PHEX* 2. DNA sequencing of *PHEX*	Rickets	P ↓
[17]	Birth–37 y	Country: NA (n = 50) (35 familial and 15 sporadic)	22/50	15	1	20 *PHEX* mutations in 22 patients: Nonsense, deletion, insertion, splice site, missense	1. SSCP of *PHEX* 2. DNA sequencing of *PHEX*	Bowing of legs, 50/50 Knock-knee, 3/50 Dental abscess, 21/50 Bad teeth, 4/50	P ↓, 50/50
[20]	10 m–60 m	Country: Korea Korean (n = 17) (5 familial and 12 sporadic)	8/17	3	5	7 *PHEX* mutations in 8 patients: Missense, nonsense, deletions	1. Sequencing of *PHEX* cDNA by nested PCR 2. DNA sequencing of *FGF23*	Bow legs, 17/17 Gait disturbance, 3/17 Lordosis, 1/17 Dental abscess/caries, 6/17	P ↓ ALP ↑ Ca, N 25(OH)D3, N $1,25(OH)_2D3$, N iPTH, N GFR ↓ Osteocalcin ↑ Renal glycosuria
[104]	4 y and 35 y	Country: Japan Japanese (n = 2) (one family)	2/2	0	0	One *PHEX* mutation: Nonsense (Father was mosaic)	1. Direct nucleotide sequencing of *FGF23* and *PHEX* 2. Single nucleotide primer extension and dHPLC analysis of father's DNA 3. Confirmation by Haplotype analysis	Lower extremity bowing, 1/2 Severe rickets, 1/2 Short stature, 1/2	P ↓, 2/2 ALP ↑, 2/2 iPTH, N Ca, N $1,25(OH)_2D3$, N

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[23]	20 m–60 y	Country: Korea Korean (n = 15) (15 probands + 5 family members) (5 familial, 4 sporadic, 6 unknown)	9/15	5	NA	8 *PHEX* mutations: Nonsense, missense, insertion (frameshift), splice acceptor/donor site	Sanger of *PHEX*	Bowing of legs, 15/15 Dental abscess, 13/15	P ↓, 10/10 Ca, N, 10/10
[105]	1 y–53 y	Country: China Chinese (Han ethnic) (n = 8) (3 families)	8/8	3	1	*PHEX* mutations in 8 patients: Missense, nonsense, deletion (frameshift-premature stop codon)	Sanger of *PHEX* and *FGF23*	NA	P ↓, 8/8 ALP ↑, 4/8 TmP/GFR, 8/8 FGF23 ↑, 8/8 1,25(OH)D3 ↓, 4/8 iPTH ↑, 2/8 Ca, N, 8/8
[106]	NA	Country: USA (n = 34) (26 families)	34/34	13	NA	PHEX mutations: Deletions, splice site, missense, nonsense, 3′-UTR, synonymous (polymorphism?)	Sanger of *PHEX*	NA	P ↓, 34/34 Urinary phosphate excretion ↑, 34/34
[27]	16 d	Country: USA (n = 1)	1/1	NA	0	*PHEX* mutation: Nonsense	Sanger of *PHEX*	Normocephalic head with open sutures Astigmatism Amblyopia Bilateral chronic papilledema Bitemporal narrowing Closure of the sagittal suture	P ↓ TRP ↓ ALP, N PTH, N
[107]	37 y–39 y	Country: Japan Japanese (n = 2) (one family)	2/2	NA	0	One *PHEX* mutation in 2 patients: Deletion of 3 exons (Mother was somatic mosaic and phenotypically normal)	1.Sanger of *DMP1*, *FGF23*, and *PHEX* 2. Analysis of 5′ region of *PHEX* 3. Semi-quantitative PCR (To compare the amount of wild-type and mutant *PHEX* alleles in mother) 3. SNP analysis of mother's DNA	Bowing of legs, 2/2	P ↓, 2/2 FGF23 ↑, 2/2 Ca, N, 2/2 iPTH, N, 2/2 $1,25(OH)_2D$, N, 2/2

Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n[2]	Biochemical features, n_2
			n[1]	Novel	*De novo*	Type			
[108]	NA	Country: France European (n = 106) North African (n = 10) Caribbean (n = 2) Asian (n = 1) (n = 118) (56 familial and 62 sporadic)	93/118	60	12	78 *PHEX* mutations in 93 patients: Nonsense, frameshift, inframe ins/del, disrupted splice sites, missense (2 mosaicism)	1. Sanger and HRM analysis of *PHEX*	Bone deformities, 118/118 Rickets, 118/118	P ↓, 118/118 TmP/GFR ↓, 118/118
[109]	< 18 y	Country: Denmark Danish (n = 38) (11 familial and 6 sporadic)	25/38	NA	NA	*PHEX* mutations in 25 patients	1. dHPLC analysis of *PHEX*, *FGF23*, *DMP1*, *SCL34A3*, and *CLCN5* 2. Sequencing of samples with deviating chromatographic profiles 3. MLPA analysis of *PHEX* and *FGF23* to detect larger deletions	Short stature Bone Pain Arthrosis, 22/38 Enthesopathies and calcification of the collateral ligaments between the vertebrae, 16/38 Fracture, 7/38 Spinal stenosis, 2/38 Endodontic problems, 26/38	P ↓ FGF23 ↑
[13]	Children	Country: USA non-Hispanic Whites (22 families) Hispanic (21 families) African American (2 families) Asian American (1 family) (n =76) (46 families: 20 familial and 26 sporadic)	43/76	16	NA	*PHEX* mutations in 42 patients: Nonsense, missense, frameshift, splice site, deletion, frameshift-nonsense *FGF23* mutation in 1 patient: missense	Sanger of *PHEX*, *FGF23*, and *DMP1*	NA (Patients were included based on laboratory parameters)	P ↓, 76/76 TmP/GFR ↓, 76/76 Calcitriol, N, 76/76 Urinary Ca, N, 76/76

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n[2]	Biochemical features, n_2
			n[1]	Novel	*De novo*	Type			
[110]	4 m–14 y	Country: Spain (n = 43) (36 probands)	43/43	25	21	*PHEX* mutations: Missense, nonsense, deletion, duplication, splicing	1. Sanger of *PHEX* 2. mRNA Sequencing of *PHEX* 3. MLPA of *PHEX*	Genu varum and/or femur deformities, 26/36 probands Null or subtle genu varum, 10/36 probands	P ↓ ALP ↑ TRP ↓ 25(OH)D, N $1,25(OH)_2D$, N PTH ↑
[111]	NA	Country: Denmark Danish (n = 23) Lebanon (n = 1) (12 familial and 12 sporadic)	21/24	13	11	*PHEX* mutations in 20 patients: Frameshift, nonsense, missense, abnormal splicing, deletion, duplication *DMP1* mutation in 1 patient: Frameshift	1. dHPLC & Sanger of *PHEX*, *FGF23*, and *CLCN5* 2. Sanger of *DMP1* and *SLC34A3* 3. MLPA analysis of *PHEX* and *FGF23* to detect larger deletions/duplications	Inclusion criteria: history of childhood rickets or spontaneous dental abscesses	P ↓ FGF23 ↑, 19/24 TPO4/GFR ↓
[112]	0 y–51 y	Country: Japan Japanese (n = 27) (14 familial and 13 sporadic)	27/27	11	NA	*PHEX* mutations in 26 patients: Missense, nonsense, base deletion, large deletion, balance translocation between X and 4 chromosomes (aberrant *PHEX* mRNA) *ENPP1* mutation in 1 patient: Splice donor site	1.Sanger of *PHEX*, *FGF23*, *DMP1*, and *ENPP1* 2.MLPA analysis of *PHEX* 3. Analysis of *PHEX* mRNA	Congenital rickets, 27/27	P ↓, 23/27 (Not low in 4 patients due to treatment with neutral phosphate and/or active vitamin D3) FGF23 ↑ (> 30 pg/ml), 27/27
[113]	2 y–40 y	Country: Turkey and Saudi Arabia Turkish (n = 10) (6 familial and 4 sporadic)	10/10	4	4	*6 PHEX* mutations: Missense, Splice donor/acceptor site	Sanger of *PHEX*	Failure to walk, 10/10 Bowing of legs, 10/10	P ↓, 10/10 ALP ↑, 7/10 PTH ↑, 1/9 Ca, N, 10/10

Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[114]	4 y	Country: India Indian (n = 1) (sporadic)	1/1	1	NA	*PHEX* mutation: Missense	Sanger of *PHEX*	Anterolateral bowing of thighs Genu varum Metaphyseal cupping and fraying Generalized osteopenia Reduced mean bone mineral density in the lumbar spine	P ↓ ALP ↑ PTH, N Ca, N 25(OH)D, N $1,25(OH)_2D$ ↓ (Slightly low) TmP/GFR ↓ Urine Ca/Cr, N
[115]	43 y	Country: Finland (n = 1)	1/1	1	NA	*PHEX* mutation: Complex re-arrangement involving gross deletions, insertions, and inversion	1. Sanger of *PHEX* 2. quantitative MLPA of *PHEX* 3. long-range PCR (generated a specific junction fragment)	Short stature Painful leg deformities Poor dentition	P ↓ TRP ↓ PTH, N Ca, N FGF23 ↑ ALP, N
[116]	2.2 y	Country: Serbia (n = 1)	1/1	0	1	One *PHEX* mutation	Analysis of *PHEX*	Short stature Coxa vara Genu varum Waddling gait	P ↓ ALP ↑ Hyperphosphaturia Ca, N 25(OH)D, N PTH, N
[117]	1–12 y	Country: USA American (n = 41) (All sporadic)	6/41	0	NA	*PHEX* mutation: 3′-UTR	1. Sequencing of 3′-UTR region of *PHEX* to investigate a previously identified mutation (c.231A > G) 2. Haplotyping	Rickets, 41/41	P ↓ TMP/GFR ↓

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[30]	6 m–36 y	Country: Italy Italian (n = 26)	23/26	16	11	*PHEX* mutations in 22 patients: Missense, nonsense, frameshift, splice site, large deletion/duplication *ENPP1* mutation in 1 patient: Splice site	1. Sanger of *PHEX* and *FGF23* 2. MLPA analysis of *PHEX* and *FGF23* 3. Sanger of *DMP1*, MEPE and *ENPP1*	Bowing of legs, 24/26 Swelling of wrist, 3/26 Poor growing, 4/26 Delayed dentition, 1/26 Osteoporosis, 3/26	P ↓, 22/24 ALP ↑, 23/24 PTH ↑, 6/23 TRP ↓, 12/20 25(OH)D ↓, 8/18
[118]	8 y–35 y	Country: NA Indian (n = 4) (2 families)	4/4	2	1	*PHEX* mutation: Splice site, frameshift	WES (3 subjects) & Sanger of *PHEX* (1 subject)	Growth retardation, 4/4 Dental hypoplasia, 3/4 Genu valgum, 3/4 Genu varum, 1/4	P ↓, 4/4 TmPO4/GFR ↓, 4/4 Ca, N, 4/4
[119]	< 18 y	Country: Norway Norwegian (n = 28) (22 familial and 6 sporadic)	24/28	10	NA	*PHEX* mutation in 21 patients: Frameshift (premature stop codons), inframe deletion, missense, nonsense, splice site, *SLC34A3* mutation in 1 patient: Splice site & intronic deletion (compound heterozygous) (*FAM20C* compound heterozygous mutations in 2 patients: Missense & nonsense [75])	1.Sanger of *PHEX* 2. MLPA of *PHEX* 3.Sanger of *FGF23*, *DMP1*, *ENPP1*, *KL*, *FAM20C*, and *SLC34A3* (WES & Sanger of *FAM20C* [75])	Skeletal involvement, 13/28 (There were no differences between the mutation status groups in growth, dental involvement, persistent bowing, or development of nephrocalcinosis)	P ↓, 28/28 ALP ↑
[35]	6 y–62 y	Country: China Chinese (Han ethnicity) (n = 4) (one family)	4/4	1	0	*PHEX* mutation: Frameshift	1. WES 2. Sanger of *PHEX* (Validation of *PHEX* mutation)	Growth retardation, 4/4 Bowing of legs, 4/4 Disabilities in walking, 4/4 Bone pain, 3/4 Skeletal deformities, 4/4 Dental abnormalities, 4/4 Hearing impairment, 2/3	P ↓, 4/4 ALP ↑, 4/4 Ca, N, 4/4 PTH ↑, 4/4 Urine P ↑, 4/4 Urine Ca ↓, 4/4
[120]	4.5 y	Country: China Chinese (n = 1)	1/1	1	1	*PHEX* mutation: Splice site (mosaic)	1. Direct sequencing of *PHEX* 2. TA clone assay 3. Real-time PCR for copy number analysis of *PHEX*	Gait abnormalities Bone pain Short stature Caput quadratum	P ↓ ALP ↑ Ca, N

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n[2]	Biochemical features, n_2
			n[1]	Novel	*De novo*	Type			
[12]	2 y–50 y	Country: Turkey (n = 14) (9 families)	14/14	7	3	*PHEX* mutations in 12 patients: Missense, nonsense, frameshift, insertion, large deletion, splice site *FGF23* mutation in 1 patient: Missense *CLCN5* mutation in 2 patients: Missense	1. Sanger of *PHEX*, *FGF23*, *DMP1*, *ENPP1*, *CLCN5* or *SLC34A3* 2. Copy number analysis	Bowed legs, 14/14 Bone pain, 1/14	P ↓, 14/14 ALP ↑, 11/14 Ca, N, 14/14 25OH D, N, 14/14 1,25(OH)$_2$D, N, 11/11 PTH ↑, 6/14 TRP ↓, 9/10
[121]	3 y–70 y	Country: China Chinese (n = 86)	17/86	3	NA	7 *PHEX* mutations in 16 patients: Missense, nonsense DMP1 mutation in 1 patient: Nonsense 14 heterozygous missense variants in 12 genes (*SFRP49, FBN3, CYP1A1, ARID2, OTOL1, DOCK6, PDGFRB, SLC20A1, ITGB4, NCAPG, PDGFA, ZNF184*)	Targeted exome sequencing of 196 candidate genes for HR	Short stature, 17/17 Genu varum, 12/17 Teeth falling out, 4/17 Hard to walk, 1/17 Bone pain, 1/17 Growth retardation, 2/17	P ↓, 15/17 ALP ↑, 10/17 Ca, N, 16/17 FGF23 (no significant difference between controls & patients)
[6]	2 y–6.5 y	Country: China (n = 3)	3/3	1	NA	*PHEX* mutation: Missense, nonsense	1.NGS (3 patients) 2.Sanger of *PHEX* (other family members)	Rickets, 3/3 Unstable gait, 3/3 Dentia tarda and tooth loss, 3/3 Costal margin valgus, 2/3 Cephalus quadratus, 2/3 Bracelet-like hands and feet, 1/3 Short stature, 3/3	P ↓, 3/3 ALP ↑, 2/3 FGF23 ↑, 3/3 PTH, N, 3/3 Ca, N, 3/3
[15]	3 m and 6 m	Country: USA (n = 2)	2/2	NA	NA	*PHEX* mutation: Missense	NA	Craniosynostosis, 2/2 Scaphocephaly, 2/2 Mild lower extremity bowing, 1/2	P ↓, 2/2 ALP ↑, 2/2 FGF23 ↑, 1/2 Ca, N, 2/2 PTH, N, 2/2 25(OH)D, N, 2/2

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n[2]	Biochemical features, n_2
			n[1]	Novel	*De novo*	Type			
[122]	8.7 y ± 3.9 y	Country: France (n = 44)	36/44	NA	11	*PHEX* mutation in 36 patients	NA	Protrusion of the cerebellar tonsils, 25% Craniosynostosis, 26/44 Chiari type I malformations, 10/44 Neurological symptoms, 2/44 Cranial index < 75% (n = 16) Mesocephaly, 18/44 Dental abscesses, 20/44 Leg bowing, 31/44	P ↓, 38/44 ALP ↑, 35/44
[123]	16 y	Country: Morocco (n = 1)	1/1	NA	NA	*PHEX* mutation: Frameshift (premature stop codon)	NA	Bilateral genu varum Metaphyseal bulges Osteoporosis Dental abscesses	P ↓ ALP ↑ $1,25(OH)_2D$ ↓ hypocalciuria
[124]	1.3 y–49 y	Country: Turkey Turkish (n = 23) (15 families)	21/23	7	6	12 *PHEX* mutation in 20 patients: Nonsense, missense, frameshift *SLC34A3* mutation in 1 patient: Compound Heterozygous-Frameshift	1. Sanger of *PHEX, FGF23, DMP1, ENPP1, CLCN5, SLC34A3*, and *SLC34A1* 2.CytoScan HD Array to identify large deletions	Short stature, 15/23 Genu varum, 18/23 Inability to walk, 6/23 Fractures, 1/23 Widening of wrist, 1/23 Nephrolithiasis, 1/23	P ↓, 23/23 ALP ↑, 18/23 25(OH)D ↓, 7/23 PTH ↑, 12/23
[125]	43 y	Country: UK Middle Eastern (n = 1) (sporadic-adult-onset)	1/1	1	NA	*PHEX* mutation: Missense	1. Sanger of *PHEX* 2. MLPA for *PHEX* gene dosage 3. Targeted NGS of *DMP1, ENPP1, FGF23, PHEX*, and *SLC34A3* 4. Western blot analysis of WT and mutant *PHEX* proteins	Psoriasis (psoriatic arthritis) Osteomalacia Pain and stiffness of lumbar back, hips and feet Swelling of metacarpophalangeal joints Dental abscesses Mild enthesopathic changes	P ↓ FGF23 ↑ Ca, N Cr, N ALP ↑ 25(OH)D, N PTH ↑ TmP/GFR ↓ $1,25(OH)_2D$, N

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[126]	26 y	Country: Korea Korean (n = 1)	1/1	1	1	*PHEX* mutation: Nonsense (mosaic pattern)	Targeted gene panel sequencing for Mendelian genes	Bilateral genu valgum Short stature Fractures Osteoarthritis in both hip joints	P ↓ TmP/GFR ↓ Ca, N PTH, N 25(OH)D3, N ALP, N Cr, N Urinary Ca/Cr, N
[127]	18 y	Country: China (n = 1)	1/1	1	1	*PHEX* mutation: Frameshift (premature stop codon)	Sanger of *PHEX, FGF23, DMP1*, and *ENPP1*	Bowing of legs Growth delay Genu valgus Gait instability Dental abscesses	P ↓ ALP ↑ 25(OH)D ↓ Ca, N PTH, N
[128]	40 y	Country: Japan Japanese (n = 1)	1/1	1	1	*PHEX* mutation: Frameshift (premature stop codon)	Sanger (not specified which genes)	Short stature Bow legs Gait disturbance Looser's zones in the tibias Calcification of the posterior Longitudinal ligament of the spine	P ↓ FGF23 ↑
[40]	5 m–58 y	Country: China Chinese (n = 261) (126 familial and 135 sporadic)	261/261	111	NA	166 *PHEX* mutations: Missense, nonsense, splice site, insertion, deletion, large insertions/ deletions	1. Sanger sequencing for point mutations 2. MLPA for large deletions/ /duplications	Bowed lower extremities, 47% Difficulty in ambulation, 31% Short stature, 6% Dental problems, 3.9% Central skeletal and dermatologic complaints, 5.7% Bone or joint pain, 4.2%	P ↓, 96.4% ALP ↑, 78.2% Ca, N, 100% i-PTH ↑ $1,25(OH)_2D3$, N 25(OH)D ↓ or N iFGF23 ↑, 91.9%

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Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n[2]	Biochemical features, n_2
			n[1]	Novel	*De novo*	Type			
[129]	11 m	Country: Korea Korean (n = 1) (Mother had HR without genetic test confirmation)	1/1	NA	NA	*PHEX* mutation: Large deletion	Sanger of *PHEX*	Scaphocephaly Craniosynostosis Macrocephaly with a long head shape Mild metaphyseal fraying (Not any other skeletal deformities)	P↓ TRP↓ Ca, N
[130]	2 y–50 y	Country: China Chinese (n = 9) (one family)	9/9	0	0	*PHEX* mutation: Nonsense	1. Sanger of *PHEX* 2. RT-PCR (*PHEX* & *FGF23* mRNA expression levels) 3. Cloning and Western blot analysis of wild type and mutant PHEX protein and wild type FGF23 protein (To identify molecular mechanism of *PHEX* mutation causing HR)	Short stature, 9/9 Joint deformities of hands, Genu valgum, 4/9 Genu varus, 5/9 Bone pain, 4/9 Fracture, 2/9 Premature tooth loss, 5/9	P↓, 6/9 ALP↑, 8/9 Ca, N, 9/9
[131]	< 18 y	Country: Turkey (n=166)	65/75	NA	NA	*PHEX* mutation in 60 patients *DMP1* mutation in 3 patients *SLC34A3* mutation in 2 patients	NA	Genu varum, 133/166 Genu valgum, 13/166 Bone pain, 28/166 Widening of wrist, 51/166 Rachitic rosary/thoracal abnormalities, 14/166 Frontal bossing, 12/166	P↓ ALP↑ Ca, N PTH↑ TRP↓ 25(OH)D↓, 27/166
[132]	5 y–15 y	Country: Malaysia Malay (n = 4)	4/4	0	1	2 *PHEX* variants: Missense 1 *FGF23* variant: Missense 3 *DMP1* variants: Missense and silent	Sanger sequencing of *PHEX*, *FGF23*, and *DMP1*	Short stature, 4/4 Bilateral leg bowing, 4/4 Frontal bossing, 2/4 Abnormal gait, 1/4 Scoliosis, 1/4 Bilateral wrist and ankles swelling, 2/4	P↓, 4/4 ALP↑, 4/4 Ca, N, 4/4 25(OH)D, N, 4/4

Table 1. *Clinical, biochemical, and genetic data in reported cases with X-linked dominant hypophosphataemic rickets (XLHR)*

References	Age group	Origin	Mutations				Methods	Clinical features, n^2	Biochemical features, n_2
			n^1	Novel	*De novo*	Type			
[133]	1 y–13 y	Country: China Chinese (Han ethnicity) (n = 80) (25 familial and 55 sporadic)	65/80	28	41	51 *PHEX* mutations in 65 patients: Nonsense, frameshift, missense, insertion, splicing, Small/large deletion de novo mosaic variants	1. Sanger of *PHEX* 2. Copy number analysis of the *PHEX* (qPCR at gDNA level) to detect large deletions	Growth retardation, 47/65 Genu varum or genu valgum, 62/65 Rib eversion, 39/65 Pectus carinatum, 31/65 Bracelet visualized, 42/65 Rachitic rosary, 15/65	P ↓, 65/65 ALP ↑, 60/65 Ca, N,58/65 25(OH)D3, N, 48/59 PTH ↑, 23/62 TRP ↓, 7/43
[21]	6 m–13 y	Country: China Chinese (n = 53) (24 familial and 29 sporadic)	53/53	27	26	47 *PHEX* mutations: Frameshift, nonsense, splicing, missense, inframe deletion, exonic deletions	1. Sanger of *PHEX* 2. MLPA of *PHEX* and *FGF23* to detect large deletions/ duplications 3. Minigene splicing assay 4. Cloning, immunofluorescence microscopy, immunoblot analysis and endopeptidase activity assay for PHEX protein	Genu varum, 39/53 Genu valgum, 4/53 Dental involvement, 13/53 Nephrocalcinosis, 6/53 Bone pain, 5/53 Muscle weakness, 2/53	P ↓, 53/53 ALP ↑, 52/53 TRP ↓, 46/53 iPTH ↑, 16/38 25(OH)D, N, 39/41
[134]	40 y–63 y	Country: China Chinese (n = 3) (one family)	3/3	0	0	One *PHEX* mutation in 3 patients: nonsense One *NPR2* mutation in 1 patient: missense	Whole exome sequencing	Short stature, 3/3 Osteodynia, 1/3 Bilateral leg bowing, 2/3 Progressive limp, 1/3 Bending deformity of the tibial shaft, 3/3 Absent teeth, 3/3	P ↓, 3/3 ALP ↑, 1/3 PTH ↑, 2/3 $1,25(OH)_2D$ ↓, 3/3 Ca, N, 3/3 TRP ↓, 3/3

y — year; m — month; d — day; n — number of study subjects; n1 — number of subjects with mutation/total number of study subjects; n2 — number of subjects with respective features/total number of study subjects; NA — not available; N — normal; P — serum phosphate; Ca — serum calcium; ALP — serum alkaline phosphatase; PTH — parathyroid hormone; FGF23 — serum fibroblast growth factor 23; TmP/GFR — ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate; 1,25(OH)2D-1,25 — dihydroxyvitamin D; TRP — tubular reabsorption of phosphate; SSCP — Single-stranded conformational polymorphism; dHPLC — denaturing high-performance liquid chromatography; MLPA — Multiplex ligation-dependent probe amplification; WES — whole exome sequencing; NGS — next generation sequencing

different genetic techniques, but Sanger sequencing has been the most widely used method for mutation screening. In addition to Sanger sequencing, single-stranded conformational polymorphism (SSCP) and denaturing high-performance liquid chromatography (DHPLC) were frequently performed in the 2000s for mutation detection. Multiplex ligation-dependent probe amplification (MLPA) has also been used to screen genes for copy number variation (CNV), usually when the result of Sanger sequencing for the target genes is negative. CNV analysis is helpful because some HR patients have been reported to have CNV in the *PHEX* gene [12]. With the evolution of DNA sequencing methods and to overcome the limitations of the Sanger method, next-generation sequencing (NGS) has become the choice sequencing technology; however, Sanger sequencing remains the gold standard and is used to validate the NGS results. In recent times, HR studies have included whole-exome sequencing, as well as targeted panel gene sequencing.

There are 407 different *PHEX* mutations listed in the Human Gene Mutation Database (HGMD) (public database, accessed January 12, 2021). The majority of *PHEX* mutations are missense and nonsense, followed by small deletions and splicing mutations (see Tab. 1). The HGMD and other published variants have reported mutations in all exons of *PHEX* but predominantly in the 3'end of the gene [13]. The C-terminal segment of the PHEX protein contains the catalytic site and the consensus sequences of the endopeptidases family, to which PHEX belongs [14]. As can be seen in Table 1, novel and *de novo PHEX* mutations are frequent in HR patients.

A variety of phenotypes are observed among patients with XLHR [3, 15–17], ranging from mild hypophosphataemia to severe bone deformities, which require surgery for correction [17]. Within the same family, members may manifest different features of the disease [3, 13, 15, 18]. Observations in XLHR patients showed that there were no significant correlations between genotype and phenotype [17, 19–21], and the phenotype was not gender dependent [22]. Nevertheless, Song et al. [23] reported that patients with mutations in the C-terminal of *PHEX* showed more severe skeletal disease. Table 1 shows the mutation type and associated phenotype in studies reporting cases with *PHEX* mutations.

Physical manifestations of XLHR

Clinical features appear mostly in childhood, with varying severity [1, 16]. In infancy, the first common feature, which may occur at six months of age, is frontal bossing [3, 8]. Other clinical features in infancy include rachitic rosary and craniotabes [24]. Primary craniosynostosis, previously not known to be a feature of HR, was recently reported in two unrelated XLHR infants confirmed to have mutations in the *PHEX* gene [15].

At the end of the first year of life, lower limb deformities appear due to the weight load on the undermineralised bone [7, 8, 25]. As the child starts ambulating, tibial torsion and progressive bowing of the legs become evident [3, 16, 24]. Other physical features are short stature due to decreased height growth [1, 24], features of rickets, namely Harrison's sulci, rachitic rosary, swelling of wrists and ankles, and dental abnormalities [1, 6, 16, 26, 27]. In children, the deformity of lower limbs includes genu varum, genu valgum, and coxa vara. Dental problems consist of noncarious teeth abscess, enamel defects, enlarged pulp chambers, taurodontism [3], and delayed tooth eruption [1]. Dental abscesses result from impaired mineralization of dentin and early decay of lacteal and permanent teeth [1, 18].

In adults, a common finding is osteomalacia, which can lead to bone pain and physical dysfunction [1, 3, 18, 28, 29]. Enthesopathy caused by calcification of tendons, ligaments, and joint capsules also occurs [15, 18, 24, 30, 31]. Furthermore, adults can manifest dental abnormalities such as periodontitis [25, 32, 33], dentin dysplasia [15, 23], and dentinal clefts [23]. Hearing loss has also been described in patients with XLHR, particularly in adulthood. Earlier reports of hearing impairment in XLHR in the 1980s were not genetically confirmed cases. The type of hearing loss reported in adults with XLHR is sensorineural hearing loss [34]. More recently, hearing impairment was described in a Chinese family in which an adult and a child with a novel *PHEX* mutation had the defect, but two other patients with the same mutation did not show any hearing problems [35].

Due to the variety of clinical signs and the rarity of XLHR, it is often diagnosed late and is therefore difficult to treat. XLHR conventional treatment includes oral phosphate and calcitriol supplementation in children, which cause improvement of rickets, reduced formation of dental abscesses, and prevention of growth failure. However, this treatment is unsuccessful for a significant number of patients [36, 37] and in some cases is associated with problems such as nephrocalcinosis and hyperparathyroidism [38]. For prepubertal children whose height does not improve with conventional treatment, recombinant human growth hormone (rhGH) treatment has been beneficial and has led to an increase in height [39].

Recent HR treatments have been developed based on the pathogenesis of HR. In 2018, burosumab was approved by the US Food and Drug Administration and European Medicines Agency for the treatment of

XLHR. Burosumab is a human monoclonal antibody that targets FGF23 and corrects the metabolism of vitamin D and levels of serum phosphate [40]. Children with XLHR who received burosumab as a treatment experienced a significant improvement in rickets, growth, and biochemical symptoms compared with patients receiving conventional therapies [38]. In addition to burosumab, other drugs such as the FGF23 receptor antagonist NVP-BGJ398 are being developed and are potential new therapies for XLHR [41].

Biochemical Findings of XLHR

Typical biochemical findings include hypophosphataemia, reduced tubular resorption of phosphate, and low-normal circulating 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels. Children present with elevated serum ALP levels. Other laboratory findings show normal serum calcium and circulating 25-hydroxyvitamin D, and elevated levels of circulating FGF23 [1, 42]. Nevertheless, phosphate intake can normalize FGF23 levels in XLHR patients [43]. In untreated patients with low phosphate levels, a FGF23 cut-off level of above 30 pg/mL is considered for XLHR diagnosis [44]. PTH levels in XLHR are normal or slightly increased [3, 6, 15, 27, 42, 45]. For example, approximately half of the newborns with XLHR show slightly elevated levels of PTH [8].

Autosomal dominant hypophosphataemic rickets

Autosomal dominant hypophosphataemic rickets (ADHR; MIM# 193100) is due to activating mutations in the *FGF23* (MIM#605380) gene [46]. Identification of the genetic cause of ADHR was the result of positional cloning research that determined a genetic locus on chromosome 12p13.3 [47], and eventually missense mutations, including R176Q, R179Q, and R179W were identified in the *FGF23* gene [46]. These *FGF23* mutations substitute the arginine residues in the site of protease cleavage. Consequently, intact serum FGF23 levels increase due to FGF23 resistance to cleavage [1, 4, 8, 18, 48–50].

Sixteen *FGF23* mutations have been reported in HGMD (public database, accessed January 12, 2021); however, only four missense mutations are associated with ADHR (R176Q, R179Q, R176W, and R179W) that localize within the cleavage site of FGF23. According to Table 2, the studies have reported these mutations to be heterozygous and mostly familial, and the incidence of *de novo* mutations in *FGF23* is much lower compared to *PHEX*.

Recent studies of a HR family with autosomal dominant inheritance identified mutations in the serum/glucocorticoid regulated kinase 3 (*SGK3;* MIM#607591) gene, a novel regulator of renal phosphate transport [51]. In Table 2, the genetic mutations and clinical presentations in reported cases of ADHR, as well as other rare types of HR, are presented.

Physical manifestations of ADHR

ADHR is characterized by variable age of onset and incomplete penetrance [1, 18, 52–55]. Investigations in three kindreds with ADHR showed that the severity of disease probably depends on FGF23 levels [56]. Different age of onset of clinical manifestations in ADHR patients were first described by Econs and McEnery [55]. Early-onset ADHR presents during childhood, resembling XLHR [3, 57–59], while late-onset ADHR presents during adolescence or adulthood, with different clinical manifestations. Although phosphate levels and growth are normal in childhood, patients manifest after puberty with weakness, bone pain, osteomalacia, osteoporosis, fractures, and rarely lithiasis, but no lower extremity deformities [3, 18, 53, 55, 59]. Dental problems such as tooth abscesses [60, 61] and dental hypoplasia [59] have also been reported in ADHR patients. A recent study by Liu et al. on patients with ADHR has indicated a genotype-phenotype correlation. This study showed that patients with R179 mutations (R179Q or R179W) had early-onset ADHR and mostly with a history of rickets, while patients with R176 mutations (R176Q or R176W) had late-onset ADHR [60].

Biochemical findings of ADHR

Laboratory findings in ADHR and XLHR patients are similar due to high serum concentrations of FGF23 [3]. In ADHR, the gain-of-function mutations in *FGF23* increase intact FGF23 levels, which inhibit renal reabsorption of phosphate, thus causing hypophosphataemia [62, 63]. Decreased 1,25-dihydroxyvitamin D production in the renal proximal tubules is another consequence of high FGF23 levels, similarly to all types of HR associated with high FGF23 levels [59].

In ADHR, the severity of the disease appears to depend on the concentration of FGF23 [56]. For instance, in some cases of early-onset ADHR, the serum phosphate concentrations and phosphate excretion were observed to return to normal levels in adulthood [54–56, 59, 64], which was associated with normal concentrations of FGF23 in adulthood [56]. Patients with late-onset ADHR are mostly women who manifest severe phosphate wasting and osteomalacia after pregnancy [53, 54]. It is noteworthy that the late onset in women may indicate the importance of iron status affecting FGF23 levels and phosphate regulation. Women are more prone to develop iron deficiency due to menstruation resulting in monthly blood loss. Some studies have suggested that iron plays a role in regulating *FGF23* expression

Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n_1	Novel	*De novo*	Type			
[59]	23 y–58 y	Country: Tunisia Tunisian (n = 4) (one family)	FGF23	4/4	1	0	Missense/ heterozygous	Sanger of *FGF23*	Short stature, 3/4 Lower limb weakness, 1/4 Difficulty in walking1/4 Muscle wasting, 1/4 Pigeon chest deformity, 3/4 Dental hypoplasia, 2/4 Frontal bossing, 2/4 Anterior bowing of legs, 3/4 Retroversion of the pelvis, 1/4 Bone pain, 1/4 Asthenia, 1/4 Fracture, 2/4	P ↓, 4/4 ALP ↑, 2/3 Ca, N, 4/4 TmP/GFR, 2/2
[61]	26 y and 30 y	Country: China Chinese (Han ethnic) (n = 2) (one family)	FGF23	2/2	0	0	Missense/ heterozygous (Mother had same mutation but phenotypically normal)	Sanger of *PHEX* and *FGF23*	Fatigue, 2/2 Tooth abscesses, 1/2 Painful swelling of the left ankle, 1/2 Back pain, 1/2 Difficulty in walking, 1/2	P ↓, 1/2 TmP/GFR ↓ ALP ↑, 1/2 FGF23 ↑, 2/2 Ca, N, 2/2 Cr, N, 2/2
[53]	38 y	Country: Greece Caucasian (n = 1)	FGF23	1/1	0	NA	Missense/Heterozygous	Sanger of *FGF23*	Bone pain Proximal muscle weakness Fracture Varus deformity Deformity of lumbar spine Osteopenia	P ↓ TmP/GFR ↓ ALP ↑ Ca, N iPTH, N 25(OH)D, N

Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n[1]	Novel	*De novo*	Type			
[54]	85 y and 57 y	Country: USA (n = 2) (one family)	FGF23	2/2	0	0	Missense/Heterozygous (Expression of this germline mutation was strikingly different in both individuals. Son was normal with no evidence of disease)	Sanger of *FGF23*	Bowed limbs, 1/2 Weight-bearing, 1/2 Physical impairment, 1/2 Weakness in arms and legs, 1/2 Rib pain, 1/2 Difficulty walking, 1/2 Pseudofractures, 1/2 Deformity of pelvis and femur, 1/2 Pigeon chest, 1/2 Knock-knee, 1/2	P ↓, 1/2 FGF23 ↑, 1/2 ALP ↑, 1/2 1,25 Vitamin D ↓, 1/2 PTH, N, 2/2 TRP ↓, 1/2
[135]	22 y	Country: USA (n = 1)	FGF23	1/1	0	NA	Missense/ Heterozygous	Genetic screens for *PHEX, DMP1*, and *FGF23*	Proximal muscle pain and weakness Neck and pubic bone fractures Tenderness in the thighs Waddling gait	P ↓ FGF23 ↑ 1,25(OH)$_2$D3 ↓ 25(OH)D ↓ Ca, N TmP/GFR ↓
[60]	2 y–62 y	Country: China Chinese (n = 20) (6 families)	FGF23	15 (R176) + 5 (R179)/20	0	NA	Missense/Heterozygous Genotype-phenotype correlation in two mutation groups: R176: adulthood onset (75%) R179: childhood onset (100%)	Sanger of *FGF23*	Patients with overt symptoms (11/20): Rickets, 3/20 Lower extremity deformity, 3/20 Growth retardation, 3/20 Bone pain, 10/20 Weakness, 3/20 Tooth abscesses, 10/20 Osteomalacia, 7/20 Fatigue, 7/20 Fractures, 7/20	P ↓, 11/20 Ca, N, 20/20 ALP ↑, 13/20 iPTH ↑, 8/16 TmP/GFR ↓, 5/7 FGF23 ↑, 3/19

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Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n[1]	Novel	*De novo*	Type			
[51]	3 y–56 y	Country: NA Turkish (n = 5) (one kindred)	*SGK3* (novel gene, Autosomal dominant)	5/5	1	0	Splice site: exon 13 skipping (Strictly segregated with patients in a heterozygous pattern — not present in the normal family members)	1. PCR-sequencing and copy number analysis (CytoScan HD Array) of *PHEX* and *FGF23* 2.Exome sequencing 3. Minigene assay for pre-mRNA splicing	Short stature, 5/5 Genu varum, 3/5 Discal hernia, 2/5 Femoroacetabular impingement, 1/5 Scoliosis, 1/5 Rotoscoliosis, 1/5	P ↓, 5/5 ALP ↑, 3/5 PTH ↑, 2/5 Ca, N, 5/5 $1,25(OH)_2D$ ↓, 1/5 25(OH)D, N, 5/5 iFGF23 ↑, 1/3 TmP/GFR ↓, 5/5 Urine Ca/Cr, N, 5/5
[68]	2 y–35 y	Country: USA (n = 8) (3 families)	DMP1	8/8	3	0	3 Homozygous mutations of *DMP1* in affected family members: 1 bp deletion (premature stop codon), splice acceptor site, missense (Unaffected parents were heterozygous)	1. Genome-wide linkage analysis using SNP array genotyping 2. Direct sequencing for mutations in *DSPP, DMP1, IBSP, MEPE*, and *SSP1* (SIBLING family) 3. Protein blot analysis	Short stature	P ↓, 8/8 ALP ↑, 8/8 iFGF23 ↑, 3/4 PTH ↑, 4/8 Ca, N, 8/8 25OHD ↓, 4/8 $1,25(OH)_2D$, N, 8/8 TmP/GFR ↓, 5/5 Urine Ca/Cr, N, 8/8
[71]	50 y and 53 y	Country: Japan Japanese (n = 2) (one family)	DMP1	2/2	1	0	Nonsense	Sanger of *DMP1*	Short stature, 2/2 Genu varum, 2/2 Growth retardation in childhood, 2/2 Cervical myelopathy, 2/2 Kyphosis, 1/2 Lost teeth, 1/2	P ↓, 2/2 1,25(OH)2D ↓, 1/2 $25(OH)_2D$ ↓, 1/2 TmP/GFR ↓, 2/2 iFGF23 ↑, 1/2 Ca, N, 2/2 iPTH, N, 2/2 Urine Ca, N, 2/2 Urine Ca/Cr, N, 1/2

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Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n[1]	Novel	*De novo*	Type			
[70]	38 y–78 y	Country: Finland Finnish (n = 2) (one family)	DMP1	2/2	1	0	One homozygous splice acceptor site	1. Nucleotide sequence analysis of *DMP1* 2. Expression analysis of *DMP1* and *FGF23* proteins	Knee varus deformities, 2/2 Bone pain, 2/2 Dental abscess Spinal ankylosis Enthesopathies, 2/2 Cranial hyperostosis, 2/2 (Two heterozygous carriers of the mutation also showed mild hypophosphatemia)	P ↓, 2/2 ALP ↑ FGF23 ↑, 2/2 PTH ↑, 2/2
[136]	1.3 y– –12.5 y	Country: Turkey and USA Turkish (n = 3)	DMP1	3/3	1	0	One homozygous mutation of *DMP1* in three patients: Frameshift (Premature stop codon)	Nucleotide sequence analysis of *DMP1*	Genu varum, 3/3 Short stature, 3/3 Rachitic rosary, 3/3 Enlarged pulp chambers of permanent and deciduous teeth, 3/3 Metaphyseal cupping and fraying, 3/3 Bowing of the femurs, 3/3	P ↓, 3/3 TmP/GFR ↓, 3/3 Ca, N, 3/3 ALP ↑, 3/3 PTH, N, 3/3 FGF23 ↑, 2/3
[72]	25 y and 44 y	Country: India Indian (n = 2) (one family)	DMP1, SPP1, CYP27B1, ABCC6	2/2	4	0	One homozygous mutation of *DMP1* in both patients: Nonsense One homozygous mutation of *SPP1* in both patients: Missense 2 heterozygous missense variants of *CYP27B1* and *ABCC6* in one patient	1. Sanger sequencing of *TNFRSF11B* and exon 1 of *TNFRSF11A* 2. Targeted NGS of 35 genes (related to bone) 3. Targeted NGS of 15 genes (related to phosphate and rickets) 4. Validation of variants by Sanger sequencing	Leg bowing, 2/2 Short stature, 2/2 Enthesopathy, 2/2 Tooth loss, 2/2 Osteosclerotic spine, 1/2 Difficulty walking, 1/2 Severe back pain, Kyphosis, 1/2 Frontal bossing, 2/2 Severe kyphoscoliosis, 1/2	P ↓, 2/2 ALP ↑, 2/2 FGF23 ↑, 2/2 Ca, N, 2/2 25(OH)D, N, 1/1 TmP/GFR ↓, 2/2

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Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n[1]	Novel	*De novo*	Type			
[137]	16 y–30 y	Country: Israel Bedouin (n = 3) (one family)	ENPP1	3/3	NA	0	One heterozygous Missense	1. Positional cloning 2. Functional analysis of *ENPP1* variant by cloning	Short stature, 2/3 Genu valgum, 2/3 Slight widening of the wrist, 2/3 Dental caries, 1/3	P ↓, 3/3 ALP ↑, 1/3 FGF23 ↑, 1/3 Ca, N, 3/3 PTH, N, 3/3 25OHD, N, 3/3 1,25(OH)$_2$D, 3/3 U Ca/Cr, N, 3/3 Tp/GFR ↓, 3/3
[73]	Birth –8 y	Country: NA Turkish and Israeli Arabic (n = 60) (4 families)	ENPP1	6/60	7	NA	3 homozygous mutations of *ENPP1* in 6 patients: Large deletion, 1 bp insertion (premature stop codon), missense 4 heterozygous *ENPP1* variants in 2 patients (not found in control group): 3 intronic, 1 synonymous	1. Genome-wide linkage analysis by using SNP array genotyping 2. Direct sequencing of *ENPP1*	Genu vara, 2/6 Genu valga, 1/6 Coxa valga, 1/6 Rickets, 5/6	P ↓, 6/6 ALP ↑, 4/6 FGF23 ↑, 3/6 Ca, N, 6/6 PTH, N, 6/6 25OHD ↑, 2/6 1,25(OH)$_2$D, N, 6/6 U Ca/Cr, N, 4/4 TmP/GFR, 6/6
[138]	62 y	Country: Japan Japanese (n = 1)	ENPP1	1/1	1	NA	Splice site mutation (skipping of exon 21)	1. Direct sequencing of *PHEX, FGF23, DMP1*, and *ENPP1* 2. mRNA analysis of *ENPP1* mutation	Short stature Bowing of legs Difficulty in walking Ossification of posterior longitudinal ligament Osteomalacia	P ↓ ALP ↑ FGF23 ↑ iPTH ↑
[74]	25 y–78 y	Country: USA Caucasian (n = 9)	ENPP1	7/9	1	0	2 *ENPP1* mutations in 7 patients: Missense	1. WES for the proband and parents 2. *ENPP1* Targeted Genotyping: cloning and Sanger sequencing for proband's siblings and children 3. *ENPP1* protein modelling	Joint pain, 1/9 Fibromyalgia and tophaceous gout, 1/9 Deaf/hearing loss, 2/9 Osteopaenia, 2/9 Intermittent periarticular inflammation of wrists, knees, elbows, ankles, and spine, 1/9 Back pain and stooped gait, 1/9 Enthesopathy, 1/9 Bowing of bilateral femurs, 2/9 Congenital heart defect, 1/9	P ↓, 2/9 iFGF23 ↑, 3/9 PTH ↑, 5/9 1,25(OH)$_2$D ↑, 6/9 25(OH)D, N, 8/8 Bone ALP ↑, 1/9 Ca, N, 9/9

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Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n[2]	Biochemical features, n[2]
				n[1]	Novel	*De novo*	Type			
[88]	2 y–35 y	Country: NA Gambian (n = 6) (one family)	SLC34A3	6/6	1	0	Homozygous mutation in 3 affected: Missense (Heterozygous in 3 unaffected)	DNA sequencing of *SLC34A3*	Short stature, 3/3 Knocked knee, 1/3 Bowed legs, 2/3 Bone pain, 2/2	P ↓, 3/3 Ca, N, 3/3 ALP ↑, 3/3 25(OH)D, N, 3/3 $1,25(OH)_2D$ ↑, 3/3 PTH ↓, 1/1 TMP/GFR ↓, 3/3 Urine Ca ↑, 3/3 cFGF23 ↑, 2/3
[92]	6.9 y	Country: USA (n = 1)	SLC34A3	1/1	1	NA	2 mutations of *SLC34A3* in one patient (compound heterozygote): Frameshift (premature stop codon) and 30 bp deletion	1. DNA sequencing of *SLC34A3* 2. PCR-RFLP analysis of deletions	Normal stature No rachitic or bony deformities Right flank pain Nephrolithiasis	P ↓ Ca ↑ Urine Ca ↑ iPTH ↓ $1,25(OH)_2D$ ↑ TmP/GFR ↓
[139]	29 y	Country: China Chinese (n = 1)	SLC34A3	1/1	1	0	2 mutations of *SLC34A3* in one patient (compound heterozygote): Missense (Parents were both asymptomatic heterozygous carriers of one of these two mutations)	DNA sequencing of *SLC34A3*	Nephrolithiasis Deformities in chest, upper and lower extremities Mild rachitic rosary Prominent genu valgum Enlargement of the wrists	P ↓ Urine Ca ↑ iPTH ↓ $1,25(OH)_2D$ ↑
[86]	19 y–54 y	Country: NA Vietnamese (n = 4) (one family)	SLC34A3	2/4	1	0	One mutation + one polymorphism in *SLC34A3* in one patient (compound heterozygote)	1. Sanger sequencing of *SLC34A3* 2. Array-based assay to detect potential copy number variants	Significant bone pain, 1/4 Rib and sacral fractures, 1/4	P ↓, 1/4 $1,25(OH)_2D$ ↑, 2/4 Urine Ca ↑, 1/4 PTH, N, 4/4 TmP/GFR ↓, 1/4 ALP, N, 4/4

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Table 2. *Clinical, biochemical and genetic data in reported cases with autosomal dominant hypophosphataemic rickets (ADHR), autosomal recessive hypophosphataemic rickets (ARHR), and hereditary hypophosphataemic rickets with hypercalciuria (HHRH)*

References	Age group	Origin	Gene	Mutations				Methods	Clinical features, n²	Biochemical features, n²
				n₁	Novel	*De novo*	Type			
[93]	3 y–60 y	Country: Iran Iranian (n = 12) (one kindred)	SLC34A3	10/12	0	0	One mutation in *SLC34A3*: 101bp deletion	Direct sequencing of *SLC34A3*	Kidney stone, 7/12 Bone deformity, 4/12	P ↓, 1/12 Ca, N, 12/12 ALP ↑, 6/12 PTH, N, 9/12 25(OH)D ↓, 5/12 TMP/GFR ↓, 3/12 Cr, N, 12/12
[140]	21 y	Country: Canada (n = 1)	SLC34A3	1/1	1	NA	Missense/ Homozygous	Sequencing of *SLC34A3*	Low bone mass Short stature Nephrocalcinosis Nephrolithiasis No bone deformities	P ↓ Urine Ca ↑ Phosphaturia PTH ↓ $1,25(OH)_2D3$ ↑
[141]	6 y–22 y	Country: USA (n = 3)	SLC34A3	3/3	5	0	5 heterozygous mutations	1. WES for index cases 2. Sanger sequencing of found genes for family members	Genu varum, 1/3 Nephrocalcinosis, 2/3 Bone pain, 1/3 Muscle weakness, 1/3 Genu valgum, 2/3 Kidney stones, 1/3	P ↓, 3/3 Ca, N, 3/3 ALP ↑, 1/3 25(OH)D ↑, 3/3 $1,25(OH)_2D$ ↑, 3/3 PTH ↓, 3/3 TRP ↓, 1/3 Urine Ca ↑, 1/2 Cr ↓, 2/3 Hypercalciuria, 3/3
[94]	14 y–68 y	Country: USA (n = 7) (4 affected+3 unaffected) (one kindred)	SLC34A3, SLC34A1	6/6	0	0	One heterozygous mutation in *SLC34A3*: missense One heterozygous mutation in *SLC34A1*: frameshift (3 patients with both mutations)	1. WES 2. NGS gene panel (Connective Tissue Gene Tests, Abnormal Mineralization Disorders Panel-15 genes) 3. Sanger sequencing for family members	Short stature, 7/7 Renal stones, 4/7 Rickets, 4/7	P ↓, 3/6 Ca, N, 6/6 ALP ↑, 1/6 25(OH)D ↓, 5/6 $1,25(OH)_2D$ ↑, 4/6 PTH ↓, 3/6 TmP/GFR ↓, 2/6 FGF23, N, 6/6

y — year; m — month; d — day; n — number of study subjects; n1 — number of subjects with mutation/total number of study subjects; n2 — number of subjects with respective features/total number of study subjects; N — normal; NA — not available; P — serum phosphate; Ca — serum calcium; ALP — serum alkaline phosphatase; PTH — parathyroid hormone; FGF23 — serum fibroblast growth factor 23; TmP/GFR — ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate; 1,25(OH)2D-1,25 — dihydroxyvitamin D; TRP — tubular reabsorption of phosphate

[65, 66]. In ADHR patients, low serum levels of iron correlate with elevated FGF23 levels, leading to more severe clinical features [67].

Autosomal recessive hypophosphataemic rickets

Autosomal recessive hypophosphataemic rickets (ARHR) occurs because of inactivating mutations in three genes, namely: *DMP1*, *ENPP1*, and *FAM20C*, resulting in ARHR types 1, 2, and 3, respectively. The physical, biochemical, and radiological features of ARHR in children are similar to those in XLHR and ADHR [3,8]. However, the severity of skeletal disorders in ARHR patients may be more significant than in other types of HR.

ARHR1 (MIM#241520) is the result of inactivating mutations in the dentin matrix acidic phosphoprotein 1 (*DMP1*; MIM#600980) gene [49,68]. DMP1 belongs to small integrin-binding ligand N-linked glycoprotein (SIBLING) and plays an important role in the mineralization of bone and dentin [69]. Nine mutations in *DMP1* have been listed in HGMD (public database, accessed January 12, 2021), which are mostly small deletions. There have been no *de novo* mutations reported thus far. In patients with *DMP1* homozygous mutations, dental problems include dental abscesses and tooth loss. The patients also present with skeletal malformations such as rickets, short stature, pathologic fractures, enthesopathies, kyphosis, and spinal ankylosis [70–72]. Osteosclerosis and bone overgrowth may also be observed in some ARHR1 patients [1, 72]. In contrast, heterozygous carriers of a novel splice site mutation in *DMP1* (IVS5-1G >A) have been reported to have focal osteomalacia, but show no features of rickets [70]. Biochemical investigations in healthy heterozygous carriers of this mutation revealed mild hypophosphataemia, elevated bone expression of *FGF23*, and increased phosphate levels in urine [70].

ARHR2 (MIM#613312) is due to loss-of-function mutations in the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*; MIM#173335) gene, which regulates mineralization of the bone through the matrix vesicle and pyrophosphate pathway [73]. Out of 70 *ENPP1* mutations reported in HGMD (public database, accessed January 12, 2021), nine mutations are associated with ARHR2, and the majority are missense mutations. In addition to HR, *ENPP1* mutations are also associated with generalized arterial calcification of infancy (GACI), ossification of the posterior longitudinal ligament of the spine, hearing loss during childhood, and insulin resistance [1, 8, 18, 74].

ARHR3 has been linked to loss-of-function mutations in the family with sequence similarity 20, member C (*FAM20C*; MIM#611061) gene [75]. Mutations in *FAM20C* were initially found to be the cause of the lethal Raine syndrome, which was characterized by generalized osteosclerosis [76]. Twenty-one *FAM20C* mutations are listed in HGMD (public database, accessed 12 January 2021) and are mostly associated with osteosclerotic bone dysplasia (Raine syndrome). In human case studies of the non-lethal, milder form of Raine syndrome, individuals with loss-of-function mutations in *FAM20C* showed osteosclerosis, no features of rickets, but hypophosphataemic osteomalacia [75]. In contrast, a study on *Fam20c* knock-out mice showed the development of HR, but no osteosclerosis was noted [77]. This phenotypic variation among species may be due to differences in gene expression [78]. Biochemical features in patients with *FAM20C* mutations are typical of HR and include hypophosphataemia, high levels of urinary phosphate, and increased levels of FGF23. Interestingly, patients with a mild phenotype had normalization of serum phosphate levels after puberty [75]. Severe dental demineralization disease was also reported [75]. A recent study in children with non-lethal Raine syndrome reported clinical and biochemical features of HR such as hypophosphataemia, short stature, and rickets due to mutations in *FAM20C* [79].

Hypophosphataemic rickets with hyperparathyroidism

Hypophosphataemic rickets with hyperparathyroidism is very rare, with only one case report so far. It is due to a *de novo* chromosomal abnormality near the Klotho (*KL*; MIM#604824) gene such that a structural variation mutation involving a translocation occurs between chromosomes 13 and 9, and the breakpoint on chromosome 13 is located adjacent to the *KL* gene. The increase in plasma αKlotho, a subfamily of the Klotho protein family, is the result of this translocation, which eventually leads to elevated levels of FGF23, PTH, and hypercalcaemia, as well as a decrease in serum phosphate and vitamin D3 (cholecalciferol) [8, 80–82].

Hypophosphataemic rickets with normal or low FGF23 levels

Hereditary hypophosphataemic rickets with hypercalciuria

The first case of hereditary hypophosphataemic rickets with hypercalciuria (HHRH; MIM#241530) was reported in a Bedouin kindred who showed an autosomal recessive pattern of inheritance [83]. HHRH is due to homozygous or compound heterozygous inactivating mutations of the solute carrier family 34 (sodium/phosphate co-transporter), member

3 (*SLC34A3;* MIM#609826) gene [84, 85]. There are 36 mutations reported in HGMD (public database, accessed 12 January 2021), of which 17 are missense and nonsense mutations. Most of the *SLC34A3* mutations are found to be familial (see Tab. 2). The *SLC34A3* gene encodes a type 2 co-transporter of sodium/phosphate (NaPi2c), which is expressed predominantly in the kidney and contributes to controlling inorganic phosphate reabsorption in the renal proximal tubule [1]. The mutations in this gene cause reduced renal reabsorption of phosphate and hypophosphataemia (see Fig. 1). The unique features of HHRH are high levels of serum 1,25$(OH)_2$D and hypercalciuria, distinguishing it from other types of HR [3, 8, 85]. The levels of serum PTH are normal or slightly low in patients with HHRH (Tab. 2).

Manifestations of early-onset HHRH include hypophosphataemia, rickets, nephrolithiasis [86–88], and early dental caries [89]. Rarely, carriers with heterozygous mutations of *SLC34A3* may have delayed-onset phenotypes [86] manifesting as hypercalciuria and nephrocalcinosis with normal phosphate levels [84, 85, 90, 91]. In HHRH, varying clinical features have been reported among patients from the same family [92–94]. A recent study of a kindred with autosomal dominant inheritance pattern revealed digenic heterozygous mutations in the *SLC34A3* and *SLC34A1* genes (see Tab. 2). This study was the first report of dominant HHRH. The severity of the disease was higher in patients with both mutations than in those who had only one mutation [94].

X-linked recessive hypophosphataemic rickets

The cause of X-linked recessive hypophosphataemic rickets (MIM#300554) is loss-of-function mutations in the chloride voltage-gated channel 5 (*CLCN5;* MIM#300008) gene [95]. The protein encoded by this gene is a member of the chloride channel (CLC) family [96], which is expressed in renal proximal tubule cells [97]. X-linked recessive HR is referred to as a type of Dent disease complex [98, 99]. There are 254 mutations reported in HGMD (public database, accessed 12 January 2021) for *CLCN5*; however, only a few of these mutations are associated with X-linked recessive hypophosphataemic rickets.

There are a few reported kindreds with X-linked recessive hypophosphataemic rickets. The clinical features of X-linked recessive hypophosphataemic rickets reported in an Italian family included low serum phosphate levels, rickets or osteomalacia, proteinuria and hypercalciuria followed by the development of nephrocalcinosis in adulthood [100]. A genetic study later confirmed the presence of *CLCN5* mutation in this family [95]. The second reported kindred did not demonstrate nephrocalcinosis [101]. More recently, a *CLCN5* mutation has been reported in a male teenager with short stature, bowed legs, hypophosphataemia, and medullary nephrocalcinosis [12].

Diagnosis of hypophosphataemic rickets

Several criteria are considered for the accurate diagnosis of rickets. A strategy that can be useful in diagnosing hypophosphataemic rickets by using clinical features and widely available biochemical tests is summarized in the flowchart in Figure 2. The initial diagnosis of rickets is usually based on physical, radiological, and biochemical features. The data collected in Table 1 and Table 2 show that the hallmarks of HR, including lower limb deformity, hypophosphataemia and elevated ALP, are present in most of the patients studied. The family history is helpful when it is positive. Nonetheless, absence of family history does not preclude the diagnosis of HR because many are due to *de novo* mutations. Consanguinity increases the risk of genetic diseases. Genetic HR is considered when other conditions that may have HR-like features are ruled out. As can be deduced from Table 1 and 2, blood and urine calcium levels will help in differentiating the type of genetic HR. Furthermore, identifying specific clinical features such as osteosclerosis, early-onset hearing loss, arterial calcification, nephrolithiasis, and nephrocalcinosis will also help to point to a specific type of HR to guide genetic analysis.

Conclusions

Hypophosphataemic rickets (HR) is a genetic disorder caused by mutations in genes involved with phosphate regulation. These genes include *PHEX*, *FGF23*, *DMP1*, *ENPP1*, *FAM20C*, *KL*, *SLC34A3*, and *CLCN5*, which, if mutated, lead to XLHR, ADHR, ARHR1, ARHR2, ARHR3, HR with hyperparathyroidism, HHRH, and X-linked recessive HR, respectively. The absence of renal loss of other metabolites, including calcium and proteins, suggests FGF23-dependent HR, while the presence of increased amounts of these metabolites in the urine suggests FGF23-independent HR in which the origin of the pathology is in the renal tubule ion transport genes for phosphate. FGF23 measurement could also be used to differentiate FGF23-dependent HR from FGF23-independent HR. However, genetic testing is more reliable for accurate diagnosis of HR. HR typically occurs in childhood with hypophosphataemia and leg deformities. Although several genes and various mutations of these genes contribute to the different types of HR, the phenotype is similar but with variable severity. The presence of clinical features other than

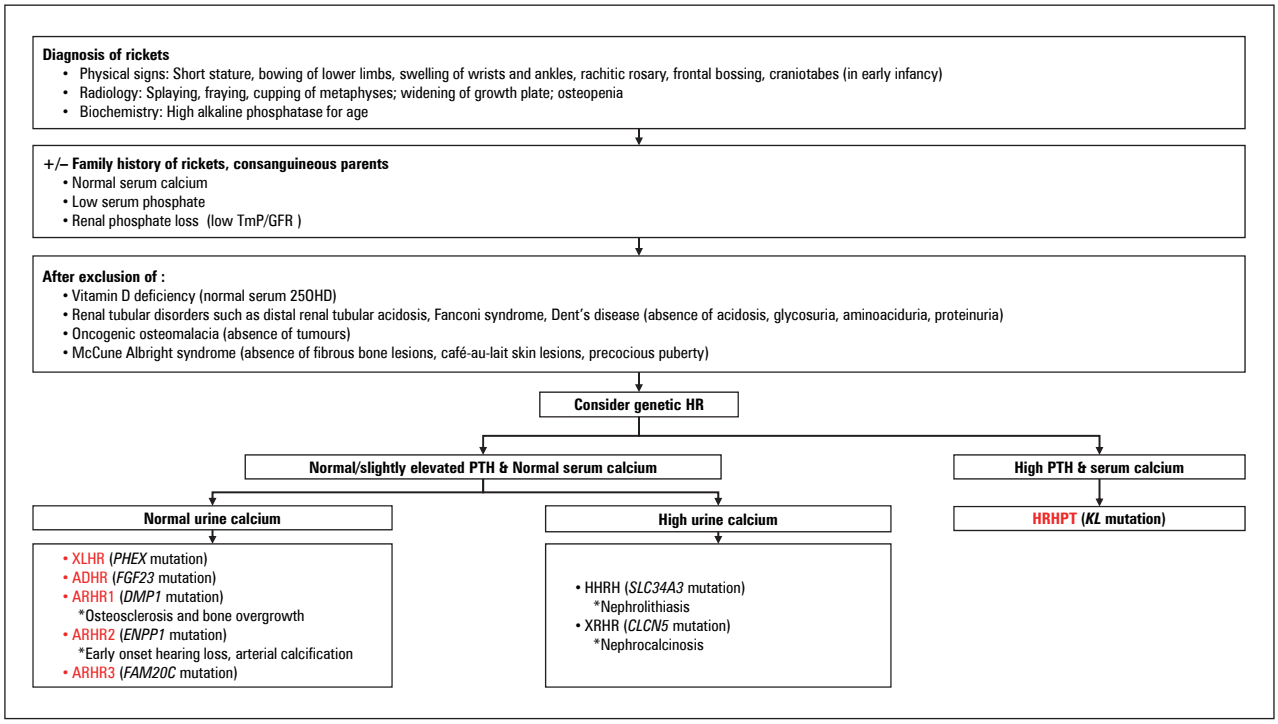

Figure 2. *Flow diagram for diagnosing hypophosphataemic rickets. Highlighted in red indicates HR with high serum FGF23 and low or inappropriately normal 1,25-dihyroxyvitamin D levels in the presence of hypophosphataemia. *specific suggestive clinical features to direct genetic testing; TmP/GFR — maximum renal tubular phosphate reabsorption per unit of glomerular filtration rate; 25OHD — 25-hydroxyvitamin D; HR — hypophosphataemic rickets; HHRH — hereditary hypophosphataemic rickets with hypercalciuria; HRHPT — hypophosphataemic rickets and hyperparathyroidism; XLHR — X-linked hypophosphataemic rickets; ADHR — autosomal dominant hypophosphataemic rickets; XRHR — X-linked recessive hypophosphataemic rickets; ARHR — autosomal recessive hypophosphataemic rickets*

REVIEW

rickets can help in determining the rarer types of HR and direct genetic analysis to look for the specific gene mutation. If the phenotype and genotype of patients with HR are carefully determined, the underlying mechanisms of the disease can be investigated, and this allows the opportunity for rational therapies to be developed.

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Conflict of interests

The authors state that they have no conflict of interests.

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