Hypophosphatemic Rickets

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INTRODUCTION

The endocrinologist Fuller Albright has been credited with the first description of hypophosphatemic rickets (HR) that failed to respond to high doses of vitamin D. The diagnostic label vitamin D–resistant rickets was later changed into X-linked HR (XLHR). The currently preferred term is X-linked hypophosphatemia (XLH).1,2 In up to 85% of familial and sporadic cases of HR, specific disease-causing genetic variants can be identified.2,3 The molecular defect underlying XLHR, a mutation in phosphate

Disclosure Statement: No disclosures.

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KEY POINTS

- Hypophosphatemia disorders can be divided conceptionally into those with increased fibroblast growth factor 23 (FGF23) levels (caused by mutations of extrarenal factors or by tumors) and those with normal or suppressed FGF23 (due to mutations tubular phosphate transporters). Rickets are the consequence of dysregulated phosphate transport and/or FGF23 excess.
- X-linked hypophosphatemia is due to a hemizygous dominant mutation of the phosphate-regulating endopeptidase homolog, X-linked gene leading to unregulated FGF23 production.
- Disease manifestations (rickets, leg bowing, growth delay; osteomalacia, enthesopathies, tooth decay; tertiary hyperparathyroidism), differential diagnoses (inherited forms, tumor-induced osteomalacia), and therapeutic goals change with age.
- Conventional treatment with phosphate supplements and pharmacologic doses of active vitamin D may require the addition of growth hormone and calcimimetics. New biological therapeutics, including FGF23 targeting monoclonal antibodies or recombinant receptor blockers, are being developed and becoming available.
- Lastly, identification of genetic mutations associated with hypophosphatemia syndromes has contributed to our understanding of the pathogenesis and potential treatment of hypercalciuria, nephrocalcinosis, and renal stones disease.

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The endocrinologist Fuller Albright has been credited with the first description of hypophosphatemic rickets (HR) that failed to respond to high doses of vitamin D. The diagnostic label vitamin D–resistant rickets was later changed into X-linked HR (XLHR). The currently preferred term is X-linked hypophosphatemia (XLH).1,2 In up to 85% of familial and sporadic cases of HR, specific disease-causing genetic variants can be identified.2,3 The molecular defect underlying XLHR, a mutation in phosphate
(PO₄)-regulating endopeptidase homolog, X-linked (PHEX), was reported in 1995. How the product of the mutated PHEX gene leads to hypophosphatemia is not yet entirely solved. An autosomal dominant form of HR was subsequently traced to an activating mutation in the gene encoding fibroblast growth factor 23 (FGF23).

XLHR is the most common of genetically defined hypophosphatemic disorders and serves as the prototype of hereditary PO₄-wasting conditions. This review focuses on the physiologic aspects of PO₄ regulation and the genetic and clinical therapeutic aspects of XLHR. Other hypophosphatemia syndromes are briefly presented.

PHOSPHATE HOMEOSTASIS

Phosphorus, the most abundant anion in the body, is an essential element for numerous cellular molecules, including nucleic acids, proteins, and lipids. It is critical for bone formation, and it is involved in acid-base regulation and cellular physiology. Rickets is a disease of the growth plate due to insufficient availability of PO₄ (inorganic phosphorus [Pi]). It only affects growing children. PO₄ deficiency may be due to poor absorption from the gut or renal wasting.

The average adult body contains about 700 g of phosphorus: 85% is found in skeletal bones and teeth, 14% in soft tissues, and only 1% is present in the extracellular fluid, which is in equilibrium with the major phosphorus stores. Plasma PO₄ is bound to proteins and lipids (16%), whereas the remainder is present as orthophosphate or free Pi, which exists as monovalent H₂PO₄⁻ and divalent HPO₄²⁻ in a 1:4 M ratio at physiologic pH and is filtered into the Bowman space of the glomerulus.

The primary organ involved in the maintenance of the serum PO₄ concentration is the kidney. The overall phosphorus balance is accomplished by intestinal absorption and renal excretion, which is regulated by the serum PO₄ level, vitamin D, parathyroid hormone (PTH), and phosphatoninins (Fig. 1). The ability of a cell to sense changes in extracellular PO₄ levels is critical for Pi homeostasis and skeletal mineralization. Recent work has provided evidence for the molecular basis of the long-postulated Pi sensing mechanism and for intracellular signaling by extracellular PO₄.

**Phosphorus Absorption**

Intestinal absorption of phosphorus is nutrition dependent. Only 30% of PO₄ absorption is controlled by active 1,25-dihydroxycholecalciferol (1,25(OH)₂D or calcitriol), which contrasts with the tight regulation of PO₄ reabsorption in the kidney. Requirements of Pi are highest during the third trimester of gestation and in infants to support adequate skeletal bone mineralization. Nutritional uptake of phosphorus in the gut is approximately 16 mg per kilogram of body weight in children or 800 to 1500 mg per day in adults. Pi transport across the epithelial brush border membrane is mediated almost entirely by the sodium-dependent PO₄ cotransporter II (NaPi-IIb) transporter (encoded by SLC34A2; solute carrier family 34 (sodium phosphate), member 2). Because PO₄ is bound to polyvalent cations in the gut, including Ca²⁺ and Mg²⁺, only about two-thirds of the ingested PO₄ is absorbed. The daily turnover of PO₄ in skeletal bone, due to physiologic remodeling, amounts to 3 mg/kg (200 mg in adults).

**Phosphorus Excretion**

The major site of Pi excretion is the kidney (900 mg daily in adults consuming an average diet). Pi passes freely through the glomerular filtration barrier. Its concentration in the Bowman space (the glomerular filtrate) equates the concentration of total free PO₄ in plasma. Between 80% and 97% of the filtered PO₄ load is reabsorbed from the tubular lumen (fractional tubular reabsorption of PO₄ [TRP]), mainly in the proximal convoluted
segments; the remainder (3%–20%) is excreted in the final urine (fractional excretion of PO₄ [FEPO₄]). Both can be calculated from simultaneously measured creatinine and PO₄ concentrations in plasma and in urine (see later discussion). There is no reabsorption in the loop of Henle. The extent and mechanisms of reabsorption in the distal tubule, if any, is controversial and may be limited to conditions of PO₄ deprivation.¹³ Tubular PO₄ reabsorption is a saturable process. When the PO₄ concentration in the glomerular filtrate exceeds the physiologic threshold, PO₄ excretion increases linearly with an increase in glomerular filtration rate (GFR) (and the filtered load).¹³,¹⁴

PO₄ reabsorption is regulated by PTH and phosphatonin, mainly endocrine FGF23.¹¹ PO₄ leaves the proximal tubular epithelial cells via a postulated electrogentic PO₄-anion exchanger (Fig. 2).¹³,¹⁵

**Phosphate Transporters**

Reabsorption of PO₄ from the tubular lumen is a unidirectional, transcellular process.¹⁶ Apical entry into the proximal tubular epithelial cells against the intracellular/tubular concentration gradient is facilitated by sodium/PO₄ cotransporters. The tubular capacity of PO₄ reabsorption depends on the abundance of Na/Pi cotransporters in the proximal tubular epithelial cell apical brush border membrane. Physiologically important Pi transporters in the kidney belong to 2 isoforms of the SLC34 family of solute carriers, the type II cotransporters NaPi-IIa (SLC34A1; solute carrier family 34 (sodium phosphate), member 1) and NaPi-IIc (SLC34A3; solute carrier family 34 (sodium phosphate), member 3) and the type III sodium-dependent PO₄ symporter PIT-2 (SLC20A2; solute carrier family 20 member 2)⁶,⁷,¹¹,¹⁷–¹⁹ (Table 1).

Physiologically, expression of NaPi-IIa and NaPi-IIc is highest in early convoluted proximal tubules (S1 segment) and in juxtamedullary nephrons but spreads to the
late proximal tubule (S2/S3 segments) and to superficial nephrons during PO4 depletion.\textsuperscript{6,20} The 3 Pi transporters have differential sensitivities to pH and regulation by dietary Pi intake and phosphaturic hormones. Type II transporters are selective for divalent PO4 (HPO$_4^{2-}$), while type III transporters favour monovalent PO4 (H$_2$PO$_4^-$).\textsuperscript{19} (see \textbf{Fig. 2}). A third member of the SLC34 family, NaPi-IIb, is expressed in the luminal brush border of the small intestine but also in the lungs and testis.\textsuperscript{13} The type III PO4 transporter PiT-1 (\textit{SLC20A1}) is expressed ubiquitously.\textsuperscript{21–23} PiT-1 and PiT-2 facilitate Pi sensing and intracellular signaling.\textsuperscript{8} Studies in PiT-2 knockout mice suggest that PiT-2 is involved in normal bone development and growth and that it plays a role in cortical and trabecular bone metabolism, likely by regulating PO4 transport and mineralization processes in the bone.\textsuperscript{23} In humans, mutations in \textit{SLC20A2} have been linked to familial idiopathic basal ganglia calcification and fetal growth restriction, among others (see \textbf{Table 1}).\textsuperscript{24}

\textbf{Fig. 2.} Schematic drawing of proximal tubular phosphate transport. Three apical (luminal) cotransporters mediate phosphate reabsorption. They differ with respect to valence of PO4, stoichiometry of Na$^+$ and PO4, electrogenicity, and pH gating. The affinities of NaPi-IIa, NaPi-IIc and PiT-2 are approximately 300 to 2000-fold higher for PO4 than for Na$^+$. PO4 leaves the proximal tubular epithelial cell via a postulated electrogenic PO4 anion exchanger. Acidosis leads to the addition of a hydrogen ion to divalent PO4 and inhibition (direct pH gating) of Na$^+$-coupled PO4 transport by type II cotransporters (Na-IIa and Na-IIc). (\textit{Adapted from} Curthoys NP, Moe OW. Proximal tubule function and response to acidosis. \textit{Clin J Am Soc Nephrol} 2014;9(9):1627–38.)
<table>
<thead>
<tr>
<th>Transporter/Channel&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Gene</th>
<th>Chromosomal Location MIM</th>
<th>Protein Expression</th>
<th>Function, Mechanism</th>
<th>Comments, Disease Associations</th>
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<td><strong>Type II</strong></td>
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<tr>
<td>NaPi-Ila (NPT2a)</td>
<td>SLC34A1</td>
<td>5q35.3</td>
<td>(Apical) brush border of proximal tubular epithelial cell (predominantly S1 segment)</td>
<td>Accounts for 70%-80% of renal tubular PO$_4$ reabsorption (in mice)</td>
<td>Overlapping syndrome of hypophosphatemia, hypercalcemia, and nephrocalcinosis (NPHLOP1# 182309 FRTS2# 613388 HCINF2# 616963)</td>
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<td>Na$^+$ coupled PO$_4$ transporter (Na/Pi cotransporter)</td>
<td>SLC34A3</td>
<td>9q34.3</td>
<td>Physiologically exclusively along proximal tubular epithelium of deep nephrons (also expressed in bone, with unclear function)</td>
<td>Accounts for 10% of PO$_4$ reabsorption</td>
<td>Hereditary hypophosphatemic rickets with hypercalciuria (HHRH # 24530) Isolated hypercalciuria and nephrolithiasis&lt;sup&gt;131,133&lt;/sup&gt;</td>
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<tr>
<td>NaPi-IIb (NPT2b)</td>
<td>SLC34A2</td>
<td>4p15.2</td>
<td>Broad expression: Intestine Lung (alveolar type II epithelial cells)</td>
<td>Intestinal Pi absorption Alveolar surfactant production Transport stoichiometry 3:1 Na$^+$: divalent HPO$_4^{2-}$ per transport cycle (electrogenic)</td>
<td>Pulmonary alveolar microlithiasis (autosomal recessive)</td>
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<td><strong>Type III</strong></td>
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<td>PiT-1 (Na-dependent Pi transporter [symporter]-1)</td>
<td>SLC20A1</td>
<td>2q14.1</td>
<td>Ubiquitous</td>
<td>Small contribution to tubular PO$_4$ transport Pi sensing</td>
<td>Major Pi transporter in brain&lt;sup&gt;22&lt;/sup&gt;</td>
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<td>Glvr-1</td>
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<td>PiT-2</td>
<td>SLC20A2</td>
<td>8p11.21</td>
<td>Colocalize to brush border of proximal tubule (with NaPi-IIa and NaPi-Ilc)</td>
<td>Transports mainly monovalent PO$_4$ (H$_2$PO$_4^-$) Pi-dependent secretion of FGF23 Pi sensing</td>
<td>Basal ganglial calcification&lt;sup&gt;134&lt;/sup&gt; No known defect of renal PO$_4$ handling&lt;sup&gt;19&lt;/sup&gt;</td>
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Abbreviation: Glvr-1, Gibbon ape leukemia virus receptor-1.

<sup>a</sup> Mutations in 2 other genes may directly affect renal PO$_4$ transport, NHERF1 (Na/H exchanger factor-1 or SLC9A3R1 [MIM * 604990]; see also Fig. 5), associated with nephrolithiasis, osteoporosis, and hypophosphatemia (NPHLOP2),<sup>135,136</sup> and XPR1 (xenotropic and polytrophic retrovirus receptor [MIM *605237]), associated with basal ganglia calcifications.<sup>134</sup>
Regulation of Phosphate Transport and Serum Concentration

Multiple mechanisms regulate Pi transport. PTH, calcitomin, glucocorticoids, and other drugs, such as calcineurin inhibitors, as well as acidosis inhibit tubular reabsorption. In contrast, growth hormone, IGF-1 and insulin, thyroid hormone, and hypocalcemia and PO₄ depletion lead to increased Pi reabsorption.

Important regulators of the serum PO₄ level are PTH and phosphatonin. The latter are humoral factors with phosphaturic activity. They inhibit PO₄ reabsorption and decrease the level of 1,25(OH)₂D. PTH and phosphatonsins (foremost FGF23) diminish PO₄ reabsorption by decreasing the abundance of apically expression Na/Pi cotransporters, which augments phosphaturia. The drivers of PTH and phosphatonin secretion are serum calcium, PO₄, and 1,25(OH)₂D concentrations (Fig. 3).

Fibroblast growth factor 23

FGF23 is a glycoprotein of 32 kD, produced and secreted by osteoblasts and osteocytes.28,29 The description of its hormonal, phosphaturic function in 2000 established the importance of bones as an endocrine tissue.31 Synthesis and secretion of FGF23 is stimulated by elevated serum Pi concentrations and 1,25(OH)₂D (see Fig. 3). The full-length protein, encoded by 3 exons, includes an N-terminal hydrophobic, FGF homology domain, and a C-terminal domain that interacts with Klotho to form the FGF/Klotho-FGFR receptor complex (see later discussion). Intact FGF23 is cleaved at the amino acid residues Arg (176)-X-X-Arg (179)/Ser (180) recognition sequence, which generates 2 inactive (N- and C-terminal) fragments.28 (Fig. 4).

The precise mechanism underlying FGF23 dysregulation, for example, in XLH and tumor-induced osteomalacia is still being worked out.37 Recent studies suggest that iron deficiency stimulates FGF23 gene transcription, with the involvement of hypoxia-inducible factor 1 (HIF1α).37–39 FGF23 signaling diminishes sodium-dependent Pi reabsorption; it also inhibits 1α-hydroxylase (CYP27B1) and increases 24-hydroxylase activity, both of which reduce the availability of 1,25(OH)₂D (see Fig. 3). Reduced availability of active D₃ limits calcium absorption in the gut and calcium reabsorption in renal tubules.

Fig. 3. Regulation of FGF23, αKlotho, PTH, calcitriol, phosphate and calcium. Stimulatory and inhibitory effects are indicated.
Klotho

Klotho has been originally described in 1997 as the product of a gene named KL or KLOTHO; its mutation resulted in premature aging of transgenic mice who also presented growth retardation, vascular calcification, and osteomalacia, among others. The name is derived from the goddess of fate in Greek mythology who spins the thread of life.

In humans, \( \alpha \)-Klotho exists as a full-length, single-pass (trans)membrane form and a pleiotropic, soluble (shed) extracellular form (sKlotho). \( \alpha \)-Klotho is highly expressed in kidneys, parathyroid gland, choroid plexus, and sinoatrial node and minimally in bone and cartilage. Both the transmembrane form and soluble Klotho interact with the FGF receptor in proximal tubular cells converting it to a high-affinity receptor for FGF23. Signaling of the FGF23-FGFR-Klotho complex leads to the internalization and degradation of NaPi-IIa and NaPi-IIc in the proximal tubule, inhibition of 1,25(OH)\(_2\)D synthesis, and increased 24-hydroxylase activity. sKlotho influences Na\(^+\)-K\(^+\)-ATPase activity in the basolateral membrane, which leads to an increased Na\(^+\) ion gradient and enhanced transepithelial calcium transport in the kidney and the choroid plexus in the brain. sKlotho also plays a direct role in calcium homeostasis by regulating the transient receptor potential vanilloid type 5 (TRPV5) calcium channel at the apical membrane of the distal convoluted and connecting tubular cells responsible for calcium reabsorption in the distal nephron.

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Phosphate regulating endopeptidase homolog, X-linked

PHEX comprises 18 exons and codes for an 86.5 kD, type II membrane protein with an N-terminal cytoplasmic tail, a transmembrane domain, and a long extracellular C-terminus. The PHEX protein is a member of the neutral endopeptidase family of zinc metalloproteinases that mediate the activation or degradation of peptide

**Fig. 4.** The FGF23 molecule with the cleavage \( R_{176}^{X}XR_{179} \) recognition motif. The N-terminal signal peptide is removed before secretion from osteocytes/osteoblasts. Proteolytic cleavage of FGF23 between Arg179 and Ser180 generates 2 inactive (N- and C-terminal) fragments. (Adapted from Kinoshita Y, Fukumoto S. X-linked hypophosphatemia and FGF23-related hypophosphatemic diseases: prospect for new treatment. Endocr Rev 2018;39(3):274–91; and Gonciulea AR, De Beur JSM. Fibroblast growth factor 23-mediated bone disease. Endocrinol Metab Clin North Am 2017;46(1):19–39.)
Fig. 5. FGF23 signaling in proximal tubular epithelial cells. Osteocyte/osteoblast-derived, endocrine FGF23 binds to the FGF receptor, FGFR1c and its coreceptor, αKlotho. The FGF23-FGFR-Klotho complex is stabilized by the receptor-binding arm (RBA) of Klotho. This ternary complex dimerizes via heparan sulfate (stick lines) to form a quaternary complex, which enables intracellular signal transduction. The kidney is the main source of
hormones. It is expressed in osteoblasts and osteoclasts of skeletal bones and in teeth (odontoblasts) and parathyroid glands as well as lung, brain, ovary, testicle, and muscle but not in kidneys. It binds to matrix extracellular phosphoglycoprotein (MEPE) and relieves the inhibitory effect of these proteins on bone mineralization. The interaction between PHEX, dentin matrix protein-1 (DMP1), and \( \alpha_5\beta_3 \)-integrin, which form a trimeric complex on the osteocyte plasma membrane, regulates and restricts FGF23 expression, whereas acidic serine- and aspartate-rich motif (ASARM) peptides, derived from MEPE and other bone and dental matrix proteins, competitively inhibit the trimeric complex and increase FGF23 expression. Inactivating mutations in PHEX lead to an accumulation of ASARM peptide, a substrate for PHEX and a strong inhibitor of mineralization, and increased circulating levels of FGF23 that result in phosphaturia, hypophosphatemia, and suppression of 25-hydroxyvitamin D to 1,25 dihydroxy-vitamin D conversion (1,25(OH)\(_2\)D).

Parathyroid hormone

PTH is an important hormonal effector of PO\(_4\) and calcium homeostasis. It regulates renal PO\(_4\) handling and bone turnover and amplifies the effects of vitamin D. Low serum Ca\(^{++}\) concentrations trigger rapid release of PTH from secretory granules in parathyroid gland chief cells via the calcium-sensing receptor. PTH mobilizes PO\(_4\) from skeletal bones into the blood stream, possibly by enhancing osteoclastic bone resorption. It induces the expression of 1\(\alpha\)-hydroxylase in the proximal tubule of the kidney and the generation of 1,25(OH)\(_2\)D in a variety of tissues, including osteoblasts.

PTH binding to its receptors on proximal tubular epithelial cells leads to diminished abundance of apical proximal tubular NaPi-II cotransporters and diminished reabsorption of filtered Pi along the proximal tubule. It also interferes with PO\(_4\) reabsorption through the inhibition of basolateral Na\(^{+}\)-K\(^{+}\)-ATPase, which removes intracellular sodium in exchange for potassium. The basolateral exclusion of Na\(^{+}\) is required to allow active transport of PO\(_4\) across the apical membrane, which generates the necessary Na\(^{+}\) gradient (see Fig. 2). PTH causes phosphaturia within minutes by impeding the apical Pi transport.

HYPOPHOSPHATEMIA, RICKETS, AND OSTEOMALACIA

Clinical Findings

The clinical presentation of hypophosphatemia syndromes depends on the duration of hypophosphatemia and the age of patients (infancy and childhood vs adulthood).
Different forms of hypophosphatemia cause similar, albeit not identical, clinical features and radiographical changes. Bone pain and deformities, fractures, disproportionate short stature, and dental abscesses are predominantly seen in chronically hypophosphatemic children. Adults may present with osteomalacia, bone pain, stiffness, and enthesopathy.\textsuperscript{59,66,67}

**Bone**

Osteoblasts regulate the synthesis of bone matrix and bone mineralization, including the deposition of hydroxyapatite (\(\text{Ca}_3(\text{PO}_4)_2\text{Ca(OH)}_2\)). Multinucleated osteoclasts are responsible for bone resorption.\textsuperscript{68} Healthy bone and bone development depend on the coordinated activities of osteoblasts and osteoclasts who receive input from PTH, calcitriol and FGF23, among others, and the transport of calcium and PO\(_4\) in and out of zones of bone remodeling.\textsuperscript{68,69} The epiphyseal growth plate influences longitudinal bone growth.\textsuperscript{62} Growth velocity is the result of chondrocyte proliferation, matrix production, and chondrocyte function.\textsuperscript{62,70}

**HYP** is the murine homolog of human *PHEX*. The HYP mouse, a model for (human) XLH, demonstrates substantial abnormalities in the growth plate.\textsuperscript{4} The primary defect in these mice is impaired osteoblast-dependent mineralization.\textsuperscript{62,71} Circulating FGF23-like fibroblast growth factors directly inhibit the proliferation and differentiation of chondrocytes at the growth plate, suggesting that growth plate maturation and bone formation are regulated by PO\(_4\) and FGF23.\textsuperscript{62,72}

**HYPOPHOSPHATEMIA SYNDROMES**

From a mechanistic and conceptual viewpoint, hypophosphatemia syndromes can be divided into those with increased FGF23 levels and those with normal or suppressed FGF23. Hypophosphatemia with increased FGF23 levels is caused by extrarenal factors, whereas hypophosphatemia with normal or suppressed FGF23 is due to mutations in genes encoding tubular PO\(_4\) transporters. Rickets are the consequence of dysregulated PO\(_4\) transport. Inherited disorders of renal PO\(_4\) handling contrast with acquired hypophosphatemia syndromes due to insufficient dietary intake or absorption or due to tubulotoxic drugs or hormonally active tumors.\textsuperscript{73}

The most common inherited form of hypophosphatemia and rickets is X-linked dominant hypophosphatemic rickets (XLH or XLHR; OMIM 307800) with a prevalence of 1 per 20,000 general population.\textsuperscript{74} It accounts for approximately 80% of familial cases of hypophosphatemia\textsuperscript{7} and serves as the prototype of defective tubular PO\(_4\) transport due to extrarenal defects resulting in unregulated FGF23 activity.

**Hypophosphatemia Disorders with Increased Fibroblast Growth Factor 23 Activity (Extrarenal Inherited Defects That Impact on Renal Phosphate Reabsorption)**

**X-linked hypophosphatemia**

XLH is caused by loss-of-function mutations in *PHEX* (Xp22.1). Loss of PHEX is thought to cause phosphaturia by suppressing expression of NaPi transporters in the proximal tubule. Sustained tubular loss of PO\(_4\) leads to profound hypophosphatemia, low mineral density.\textsuperscript{75,76} Leg deformity and short stature (disproportional dwarfism with predominant shortening of lower limbs) are the consequences of decreased incorporation of PO\(_4\) into growing bone and subtle dysregulation of renal 1,25(OH)\(_2\)D synthesis.\textsuperscript{2,62}

**Presentation** X-linked hypophosphatemia is a dominant genetic disease. Hemizygous females who inherit a dysfunctional (mutated) *PHEX* allele have renal PO\(_4\) wasting and severe bone deformities indistinguishable from affected (heterozygous) males.\textsuperscript{77} The incidence is 4 to 5 per 100,000 live births.\textsuperscript{78} During fetal life, bone is
protected by maternal blood PO4 levels (presuming the mother is unaffected) and the newborn skeleton is radiologically normal.\textsuperscript{79} FGF23-driven phosphaturia is evident within the first few weeks of life, confirmed by TRP,\textsuperscript{80} and serum PO4 decreases to less than the normal range within the first month (Goodyer P, unpublished data, 2018). Serum PO4 reaches a nadir less than 1 mM by about 6 months of age and the secondary increase in alkaline PO4 increases to about 3 to 6 times the upper limit of normal. Interestingly, the TRP improves as serum PO4 (and the filtered load of PO4) declines and the calculation of the tubular maximum reabsorption of PO4 (TmP)/GFR is needed to identify the mutant renal phenotype. The TmP/GFR ratio corresponds to the theoretic lower limit of serum PO4 less than which all filtered PO4 would be reabsorbed, assuming that the PO4 concentration in serum is equal to its concentration in the glomerular filtrate. It can be calculated as \( \text{TmP/GFR} = \frac{\text{SPO4}}{(\text{UPO4} \times \text{SCr/UCr})} \) where UPO4 denotes urine PO4, and SCr and UCr serum and urine creatinine concentrations, respectively.\textsuperscript{47,81} Although serum calcium and 1,25 (OH)\textsubscript{2}D levels are normal, nearly half of affected newborns with XLH have slightly elevated PTH levels, reflecting subtle dysregulation of 1,25(OH)\textsubscript{2}D. Skeletal deformities emerge in the second half of the first year of life because of the weight load on the undermineralized bone. Long bone metaphyses show fuzziness of the growth zone with cupping. Long bones exhibit decreased mineralization amid coarse, sclerotic trabeculae. Radiographs show frontal bossing of the skull, widening of the wrist, and bowing of the legs, which compromise body length. The angle between the femur and hip becomes progressively more oblique, and leg bowing may produce either valgus or varus deformities. The cancellous compartment of long bones (trabecular bone), particularly the tibia, is undermineralized (Fig. 6).\textsuperscript{2,82} Without therapy, linear growth decelerates until 4 to 5 years of age.\textsuperscript{79}

**Early oral phosphate/calcitriol therapy** Early intervention with balanced oral PO4/calcitriol supplementation ameliorates hypophosphatemia, gradually reduces serum alkaline phosphatase, accelerates linear growth,\textsuperscript{79} and minimizes the severity of skeletal deformity. However, excessive oral PO4 load without additional calcitriol decreases serum ionized calcium and causes secondary hyperparathyroidism that adds to the FGF23-induced phosphaturia. One approach to balanced oral PO4/calcitriol therapy is to introduce therapy as soon as the diagnosis is confirmed and monitor the following parameters every 1 to 3 months:

![Fig. 6.](image)

- Child with radiographic changes due to XLH demonstrating (A) Cupping of metaphyses of the wrist, (B) typical bowing of legs (varus deformity) and undermineralization of the trabecular (cancellous) bones, and (C) ragged (frayed) metaphysis of the femur.
Oral PO₄ supplements should be introduced gradually over 1 to 2 months to allow for upregulation of intestinal PO₄ absorption and avoid PO₄-induced diarrhea. The dose of oral PO₄ should be divided 4 times a day and gradually increased from 15 to 50 to 100 mg of PO₄ per kilogram per day. The authors monitor peak serum PO₄ about 1 hour after the oral dose and adjust the PO₄ dose to bring the peak serum PO₄ concentration into the low normal range.

Oral PO₄ must be accompanied by calcitriol 25 to 50 ng/kg/d divided twice a day (about 40–80 ng/kg/d of 1-hydroxycholecaldiferol [alfacalcidol]), sufficient to keep intact PTH levels within the normal range. With successful therapy, normal rates of linear growth can be expected. If urine calcium/creatinine levels are consistently elevated, this may reflect excessive PO₄/calcitriol therapy and predispose to medullary nephrocalcinosis. Although medullary nephrocalcinosis does not seem to compromise renal function in childhood, it may be prudent to reduce the doses of PO₄ and calcitriol (in parallel) when this occurs.

Interestingly, secondary hyperparathyroidism can also be offset by oral cinacalcet (a calcimimetic) in XLH. This permits lowering doses of calcitriol to maintain normal intactPTH levels and decreasing the oral PO₄ dose needed by reducing PTH-induced phosphaturia. When oral therapy is started late or adherence is poor, skeletal deformities may become severe enough to require orthopedic intervention. In this case, surgery should be performed after a 3- to 6-month period of intense therapy to achieve good metabolic control and lower alkaline phosphatase levels. Close postoperative monitoring is equally important to maintain axial leg alignment. Whether the addition of D-mimetics (eg, paricalcitol) improves outcomes, especially in patients with XLH and secondary hyperparathyroidism, requires further studies. Recombinant human growth hormone has been used to stimulate growth in children with XLH, but the effect on final adult height seems to be modest. Although elevated levels of FGF23 are associated with left ventricular hypertrophy in chronic kidney disease, the heart is generally not affected in XLH.

X-linked hypophosphatemia in adolescence During early to midadolescence, adherence to prescribed dosing may be suboptimal. The growth spurt at this time may further alter calcium/PO₄ homeostasis. This period is a period of risk for the development of tertiary hyperparathyroidism. The pathogenesis of this phenomenon is unknown, but several observations are pertinent:

- Mild secondary hyperparathyroidism is evident in some affected patients before any oral PO₄ therapy.
- The PHEX gene is not expressed in the kidney but is strongly expressed in parathyroid tissue, implying a role in normal PTH gland biology.
- Excessive oral PO₄, if not accompanied by sufficient calcitriol, transiently increases intact PTH levels in serum. It is conceivable that repeated stimulation also drives chief cell proliferation with its attendant risk of mutation in the genes that regulate cell cycle and risk of a benign adenoma.
- Tertiary hyperparathyroidism occurs in the second decade of life in a minority (20%-30%) of patients with XLH and with higher frequency in some families more than in others. It is recognized by the onset of gradually increasing total serum calcium levels with inappropriate serum iPTH. Often, a single benign parathyroid adenoma may be identified by a combination of technetium-99 m sestamibi.
methoxyisobutylisonitrile) single-photon emission computed tomography imaging, and neck ultrasound. Hypercalcemia induces a shift from mild medullary nephrocalcinosis (associated with therapy) to a broader pattern of cortical nephrocalcinosis. When hypercalcemia is severe, there may be progressive loss of GFR, leading to end-stage renal failure. Predictably, the characteristic FGF23-driven phosphaturia recurs in renal allografts. To avert the consequences of sustained hypercalcemia, cinacalcet may be used temporarily to suppress serum calcium for months at a time. However, this strategy does not seem to cause involution of the offending benign adenoma, so subtotal parathyroidectomy with or without subcutaneous autotransplantation of any normal-appearing resected tissue is eventually required in most cases. Intraoperative measurement of serum iPTH is important to ascertain whether the offending tissue has been removed. Postoperative bone hunger may require calcium supplementation.

- Adolescents are at risk for dental abscesses due to defective dentin formation. Careful dental care to prevent caries is important. As linear growth comes to an end during adolescence, the primary rationale for oral PO₄/calcitriol therapy changes and some physicians reduce the intensity of therapy. Many patients are asymptomatic despite marked hypophosphatemia when therapy is stopped. However, others report mild bone pain and weakness without minimal calcitriol and PO₄ supplementation. Furthermore, there are observations in adult patients (discussed later) suggesting ongoing benefit in regard to dental and joint symptoms. In view of the well-known problems of medication adherence in adolescents, it seems reasonable to decrease the dose and dosing frequency in this period. It is prudent to restart full therapy, should patients sustain a traumatic injury and bone fracture or if a woman becomes pregnant (whether or not the fetus is affected). Because breast milk PO₄ is low in untreated female patients with XLH, unaffected offspring should have oral PO₄ supplementation with evaporated milk by bottle during the breastfeeding period.

**Adulthood** Although early calcitriol/PO₄ therapy minimizes joint deformities and improves final height, adult height remains about 2 SD less than the normal range. Treated patients show better bone mineralization, but adult bone contains fewer trabeculae and considerable trabecular inhomogeneity. Dual-energy x-ray absorptiometry studies must be analyzed with caution, because perarticular calcifications may falsely elevate bone mineral density estimates. Adults with XLH exhibit fibrochondrocyte hyperplasia in tendons and ligaments, causing them to thicken and calcify. Most patients have multiple calcified entheses and report discomfort and limitation of movements in facet joints, particularly in the shoulders, lower back, and neck. Occasionally, this can lead to foraminal stenosis that compresses nerve roots. Calcification of vertebral entheses is less common in patients who were treated with calcitriol and PO₄ during childhood. The extent of enthesopathies correlates with decreased quality of life scores in adults with XLH. Adults with XLH exhibit defects in both dentin and acellular cementum layers, increasing the risk of dental abscesses and tooth detachment. Continued calcitriol/PO₄ therapy in adulthood reduces the risk of severe dental complications.

**Alternative treatment approaches** Based on the improved understanding of the central role of FGF23 in XLH and other hypophosphatemias, treatment with specifically designed inhibitors is a rationale and promising approach. A recent publication describes the results of an open-label treatment trial with burosumab, a
subcutaneously injected monoclonal antibody in 5- to 12-year-old children with XLH. The antibody led to improved TRP, serum PO₄ concentrations, linear growth, and clinical parameters. A 24-week analysis of a double-blind, placebo-controlled randomized controlled trial in adult patients testing the same anti-FGF23 monoclonal antibody revealed better healing of fractures and improved biochemical markers of bone formation and resorption. Other ongoing pediatric trials are listed on the Clinical Trials Web site (https://clinicaltrials.gov).

**Autosomal dominant hypophosphatemia**

Autosomal dominant hypophosphatemia (ADH) is caused by activating missense mutations of arginine residues at (R) 176 or 179 in FGF23 that render the protein resistant to cleavage by FGF23-targeting converting enzymes and leads to high serum concentrations of intact FGF23 (see Fig. 4). The penetrance of this comparably rare form of hypophosphatemia is variable. Clinical and laboratory findings can be similar to those in XLH, especially in patients with severe renal PO₄ wasting early in childhood. A low serum iron concentration is associated with increased FGF23 expression and more severe disease manifestations.

Treatment of ADH includes PO₄ supplements and calcitriol, similar to the treatment of XLH. Patients should be screened for iron deficiency. If present, appropriate iron therapy may normalize tubular PO₄ reabsorption and allow discontinuation of calcitriol and PO₄ supplement.

**Autosomal recessive hypophosphatemia**

Autosomal recessive forms of hypophosphatemia have been linked to inactivating mutations in several genes (Table 2). Patients present during childhood with clinical, laboratory, and radiological findings resembling those seen in patients with XLH and ADHR. The first variety, ARHR1, is caused by mutations in Dentin Matrix Protein-1 (DMP1). DMP1 mutation leads to increased FGF23 production and impaired osteocyte maturation and skeletal mineralization (see Fig. 1).

ARHR2 results from an inactivating mutation of the gene encoding ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1), which regulates matrix vesicle pathway and pyrophosphate-mediated bone mineralization. Mutations of this gene have been linked to idiopathic infantile arterial calcification, ossification of the posterior longitudinal ligament of the spine, and insulin resistance.

**Hypophosphatemic rickets with hyperparathyroidism**

This form of hypophosphatemia is caused by a de novo translocation with a breakpoint on chromosome 13q13.1, close to the Klotho gene, which leads to high plasma levels of αKlotho, the FGFR coreceptor for FGF23. Patients with this chromosomal abnormality also have increased FGF23 levels, in keeping with the importance of αKlotho in the regulation of serum PO₄, FGF23 expression, and PTH secretion.

**Fibrous dysplasia/McCune-Albright syndrome**

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is due to somatic (non-inherited, mosaic) activating mutations in the GNAS gene in bone, endocrine glands, and skin. The gene encodes the α-subunit of the guanine nucleotide-binding, stimulatory G-protein (Gsα). Its mutation causes osteoblastic differentiation, increased bone absorption, and fibrosis, which replaces bone marrow and bone by fibrous tissue.

The phenotype is highly variable. Patients with FD/MAS develop fibro-osseous masses, café-au-lait spots, precocious puberty, and other endocrine disorders due to hypersecretion of various hormonal molecules. Additional features are
<table>
<thead>
<tr>
<th>Disease MIM Phenotype</th>
<th>Genetic Variants (Gene Products)</th>
<th>MIM Gene* Chromosomal Location</th>
<th>Tissue Expression</th>
<th>Effects and Biological Consequences</th>
<th>Clinical Importance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLH(R) X-linked hypophosphatemia/ hypophosphatemic rickets #307800</td>
<td>PHEX Loss-of-function mutation X-linked (dominant)</td>
<td>*300550 Xp22.2-p.22.1</td>
<td>Mainly bone/teeth (ectoenzyme); also skin, muscle, brain</td>
<td>Biological action incompletely understood (FGF23 is not a PHEX substrate) ↑ FGF23 mRNA in osteocytes and ↑ iFGF23 protein levels</td>
<td>Hyperphosphaturia Hypophosphatemia Normocalcemia Inappropriately low or normal calcitriol Rickets/osteomalacia</td>
<td>Most common form of inherited rickets ~1 per 20,000 Full penetrance, onset from birth</td>
</tr>
<tr>
<td>ADHR Autosomal dominant hypophosphatemic rickets #193100</td>
<td>FGF23 Gain of function mutation AD</td>
<td>*605380 12p13.32</td>
<td>Bone (mouse brain)</td>
<td>Resistance to cleavage (mutation in RXXR motif [Arg residues at positions 176 of 179]); stabilization (and elevation) of intact circulating (active) FGF23 levels</td>
<td>Hyperphosphaturia, hypophosphatemia Normocalcemia Inappropriately low or normal 1,25(OH)2D3 Rickets/osteomalacia</td>
<td>Incomplete penetrance, with variable onset Iron deficiency increases iFGF23 in patients with ADHR</td>
</tr>
<tr>
<td>ARHR1 Autosomal recessive hypophosphatemia (hypophosphatemic rickets) type 1 #241520</td>
<td>DMP1 Loss-of-function mutation AR</td>
<td>*600980 4q22.1</td>
<td>Mineralized tissue (osteoblast, osteocyte), also heart, kidney</td>
<td>Hydroxyapatite nucleation (?) Defective osteocyte maturation ↑ iFGF23 production in osteocytes</td>
<td>Hyperphosphaturia, hypophosphatemia Inappropriately normal 1,25(OH)2D3 Rickets, osteomalacia</td>
<td>—</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Disease</th>
<th>MIM</th>
<th>Genetic Variants</th>
<th>Chromosomal Location</th>
<th>Tissue Expression</th>
<th>Effects and Biological Consequences</th>
<th>Clinical Importance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARHR2</td>
<td>#613312</td>
<td>ENPP1</td>
<td>Loss-of-function mutation</td>
<td>AR</td>
<td>6q23.2</td>
<td>Chondrocytes, renal tubules, parathyroid, placenta, others</td>
<td>Ectonucleotide pyrophosphatase/phosphodiesterase-1 converts Pi into PPi inhibiting skeletal mineralization; it may be involved in control of FGF23 production</td>
</tr>
<tr>
<td>ARHR3</td>
<td>#611061</td>
<td>FAM20C</td>
<td>Loss-of-function mutation</td>
<td>AR</td>
<td>7p22.3</td>
<td>Mineralized tissue, Casein kinase (recognizes X-E motif)</td>
<td>Casein kinase (recognizes S-X-Emotif) Loss of FAM20c may reduce functional DMP1 and lead to partial stabilization of FGF23 (resistance to physiologic furin-mediated cleavage); clinical importance: hyperphosphaturia, hyperparathyroidism, renal osteodystrophy, renal osteosclerosis, osteomalacia, hyperostosis, idiopathic infantile arterial calcification</td>
</tr>
</tbody>
</table>

*ARHR2: Autosomal recessive hypophosphatemia (hypophosphatemic rickets) type 2
*ARHR3: Autosomal recessive hypophosphatemia (hypophosphatemic rickets) type 3

**Table 2 (continued)**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Chromosome</th>
<th>Kidney</th>
<th>Renal Effects</th>
<th>Medical Effects</th>
<th>Genetic Details</th>
<th>Disease Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemic Rickets and Hyperparathyroidism (HRHPT) #612089</td>
<td>$\alpha KL$ (Klotho) de novo balanced chromosome 9:13 translocation; fusion of APRIN and $\alpha KL$ genes</td>
<td>Ch 13q13.1</td>
<td>Renal PTEC, renal artery, aorta, parathyroid, brain, others</td>
<td>$\uparrow$ circulating Klotho in plasma $\uparrow$ FGF23</td>
<td>Hyperphosphaturia, Hypophosphatemia, Hypercalcemia, Heterotopic calcifications</td>
<td>Extremely rare</td>
<td></td>
</tr>
<tr>
<td>Fibrous dysplasia and McCune-Albright syndrome (FD/MAS) #174800</td>
<td>GNAS1 Gain-of-function (alpha-subunit, stimulating G-protein, $G_s$) Mosaic (postzygotic)</td>
<td>*139320 20q13.32</td>
<td>Mutated GNAS1 in fibrous skeletal lesions</td>
<td>Excess expression of FGF23 in focal FD tissues</td>
<td>Fibrous skeletal lesions and solitary or multiple localized mineralization defects</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Tumor-induced osteomalacia (TIO)</td>
<td>9:13 translocation/ fusions (in some cases)</td>
<td>N/A</td>
<td>Tumorous tissue</td>
<td>Paraneoplastic PMT (phosphaturic mesenchymal tumor) with $\uparrow$ FGF23 production, Fibronectin/FGFR1 fusion protein, FGFR1 over expression</td>
<td>Hypophosphatemia, Renal Pi wasting Osteomalacia</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; FD, Fibrous dysplasia MAS, McCune-Albright syndrome; N/A, not applicable.
hyperthyroidism, pituitary gigantism (growth hormone), and Cushing syndrome (cortisol) due to adrenal hyperplasia, among others. The skeletal abnormalities are described as monostotic (Monostotic fibrous dysplasia, usually asymptomatic) or diffuse polyostotic changes polyostotic fibrous dysplasia that cause substantial morbidity or even death.\textsuperscript{28,116}

Fibrous bony lesions are rich in FGF23-producing cells. Excess FGF23 causes PO\textsubscript{4} wasting in about one-half of patients.\textsuperscript{18,117} Clinically important hypophosphatemia and rickets are more common in patients with MAS than in (P)FD.\textsuperscript{18,118} The degree of (excess) FGF23 production has been attributed to alterations in FGF23 processing in FD lesions\textsuperscript{119} and seems to correlate with the extent of FD.\textsuperscript{117}

Therapeutic interventions for patients with FD are mainly surgical, that is, correction/stabilization of fractures and deformities. Medical treatment with (antiresorptive) bisphosphonates has been successfully tried.\textsuperscript{118}

**Hypophosphatemia Disorders with Normal or Suppressed Fibroblast Growth Factor 23 Activity (Inherited Intrarenal Phosphate Transport Defects)**

**Hypophosphatemia, hypercalcemia, and nephrocalcinosis**

A homozygous mutation in \textit{SLC34A1} (NaPi-IIa), identified in a kindred in Israel (see \textbf{Table 1}; \textbf{Table 3}), was associated with hypophosphatemia, rickets, frequent fractures, and stunted growth.\textsuperscript{120,121} The patients had hypercalciuria associated with increased 1,25(OH)\textsubscript{2}D levels and features of (partial) renal Fanconi syndrome and mild-moderate chronic kidney disease in adulthood (Fanconi renotubular syndrome-2 [FRTS2]).\textsuperscript{121} Subsequently, 4 more cases were reported from Argentina and Turkey (without Fanconi features) and an additional infant from the original kindred in Israel.\textsuperscript{122,123}

Schlingmann and colleagues\textsuperscript{47} recently described homozygous mutations in \textit{SLC34A1} in 4 infants from 3 Turkish families with parental consanguinity. In an extension study, 12 of 126 children with sporadic idiopathic infantile hypercalcemia were found to have biallelic (autosomal recessive) mutations of the renal PO\textsubscript{4} transporter (all negative for \textit{CYP24A1} [24-hydroxylase] variants). In addition to PO\textsubscript{4} wasting, the patients showed inappropriately high 1,25 (OH)\textsubscript{2}D serum concentrations with corresponding hypercalcemia and hypercalciuria and suppressed intact PTH and FGF23 levels (see \textbf{Table 3}; \textbf{Table 4}).

Larger deletions, including \textit{SLC34A1}, can occur as part of Sotos syndrome (associated with hypophosphatemia)\textsuperscript{19,124}

Heterozygous variants in \textit{SLC34A1} were found among 2 of 20 patients with hypophosphatemia, demineralized bone, and nephrolithiasis, associated with a decreased threshold for PO\textsubscript{4} reabsorption.\textsuperscript{18,125} However, the initial interpretation of the described condition (NPHLOP1) as autosomal dominant remains controversial\textsuperscript{6,126} (see \textbf{Table 3}).

**Hereditary hypophosphatemic rickets with hypercalciuria**

Initially described in a Bedouin kindred,\textsuperscript{127} hereditary hypophosphatemic rickets with hypercalciuria is characterized by hypophosphatemia and rickets due to tubular PO\textsubscript{4} wasting. It is caused by homozygous or compound heterozygous loss-of-function mutations in \textit{SLC34A3} (NaPi-Iic)\textsuperscript{18,128,129} (see \textbf{Table 3}). Consequently, serum 1,25(OH)\textsubscript{2}D is high and PTH and FGF23 are reduced, resulting in increased calcium absorption in the gut and secondary hypercalciuria, medullary nephrocalcinosis, and urolithiasis (see \textbf{Table 4}).\textsuperscript{18,127–130}

Persons carrying one mutated allele are generally healthy and have a normal PO\textsubscript{4} balance but may have hypercalciuria and an increased risk of nephrocalcinosis and kidney stones.\textsuperscript{18,128,131}
### Table 3
Hypophosphatemia and hypophosphatemic rickets: hypophosphatemia disorders with normal or suppressed fibroblast growth factor 23 activity

<table>
<thead>
<tr>
<th>Disease MIM Phenotype #</th>
<th>Genetic Variant</th>
<th>MIM Gene*</th>
<th>Tissue Expression</th>
<th>Effects and Biological Consequences</th>
<th>Comments/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlapping syndrome of hypophosphatemia, hypercalcemia, and nephrocalcinosis (HHN) NPHLOP1# 612286(^b)</td>
<td>SLC34A1 (solute carrier family 34, member 1) NaPi-IIa (sodium/PO(_4) cotransporter) AR(^{b,d})</td>
<td>*182309 5q35.3</td>
<td>Kidney (PTEC)</td>
<td>Renal Pi wasting, hypophosphatemia †FGF23, †1,25(OH)(_2)D Hypercalcemia, hypercalciuria Nephrocalcinosis/stones Rickets, skeletal fractures</td>
<td>Clinical phenotype may improve in adulthood(^{19})</td>
</tr>
<tr>
<td>Nephrolithiasis and osteoporosis associated with hypophosphatemia(^{125}) FRTS2# 613388(^c)</td>
<td>SLC34A3 (solute carrier family 34, member 3) NaPi-IIc (sodium/PO(_4) cotransporter)</td>
<td>*609826 9q34.3</td>
<td>Kidney (PTEC)</td>
<td>Renal Pi wasting Hypophosphatemia †1,25(OH)(_2)D hypercalciuria suppressed PTH †intestinal Ca(^{++}) absorption Nephrocalcinosis, stones</td>
<td>Rickets are common; clinical symptoms seem to persist into adulthood(^{19})</td>
</tr>
<tr>
<td>Fanconi renotubular syndrome-2(^{120-123}) HCINF2 or IH# 616963 Infantile hypercalciemia-2(^{47})</td>
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</tr>
</tbody>
</table>

Abbreviation: PTEC, proximal tubular epithelial cells.

\(^a\) See footnote to Table 1.
\(^b\) Initially described as autosomal dominant,\(^{125}\) but the role of the reported SLC34A1 variant is controversial.\(^6\)
\(^c\) Few patients with mild to moderate chronic kidney disease in adulthood and modified biochemical profile.\(^{121}\)
\(^d\) Larger deletions, including the SLC34A1 gene, can occur as part of Sotos syndrome.\(^{19,124}\)
### Table 4
Biochemical abnormalities in patients with hypophosphatemic rickets

<table>
<thead>
<tr>
<th>Disease MIM Phenotype</th>
<th>Genetic Variants</th>
<th>FGF23</th>
<th>Serum PO4</th>
<th>Serum Calcium</th>
<th>25(OH)D3</th>
<th>1,25(OH)2D3</th>
<th>PTH</th>
<th>Urine Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLH</td>
<td>PHEX</td>
<td>↑ or inappropriately N</td>
<td>↓</td>
<td>N or ↓</td>
<td>N</td>
<td>↓ or inappropriately N</td>
<td>N or ↑</td>
<td>N</td>
</tr>
<tr>
<td>X-linked dominant hypophosphatemia/rickets# 307800</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHR</td>
<td>FGF23 Activating mutation</td>
<td>↑ or inappropriately N</td>
<td>↓</td>
<td>N or ↓</td>
<td>N</td>
<td>↓ or inappropriately N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>AD hypophosphatemic rickets# 193100</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ARHR</td>
<td>DMP1 ENPP1</td>
<td>↑ or inappropriately N</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>↓ or inappropriately N</td>
<td>N</td>
<td>N or ↓</td>
</tr>
<tr>
<td>AR hypophosphatemic rickets Type 1# 241520 Type 2# 613312</td>
<td></td>
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<td></td>
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<tr>
<td>HRHPT</td>
<td>Balanced Chr 9:13 FN1- FGFR1 translocation/fusion</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>FD/MAS</td>
<td>GNAS1</td>
<td>↑(^a)</td>
<td>N or ↓</td>
<td>N</td>
<td>—</td>
<td>N or ↓</td>
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<td>N</td>
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</tr>
<tr>
<td>HHN</td>
<td>SLC3A1 (NPT2a) NaPi-IIa</td>
<td>↓ or N</td>
<td>↓</td>
<td>↑ or N</td>
<td>N or ↓</td>
<td>↓ (in children)</td>
<td>↑ (HCINF2)</td>
<td>↓ or N</td>
</tr>
<tr>
<td>Hypophosphatemia, hypercalcemia, and nephrocalcinosis NPHLOP1# 612286 FRTS2# 613388 HCINF2# 616963</td>
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<tr>
<td>Hereditary hypophosphatemic rickets with hypercalcuria #241530</td>
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<td></td>
</tr>
<tr>
<td>SLC34A3 (NPT2c) NaPi-llc</td>
<td>↓ or N</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓ or N</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>TIO</td>
<td>Chr 9:13 FN1-FGFR1 translocation/fusion (in some)</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N or ↓</td>
<td>N or ↑</td>
<td>—</td>
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<tr>
<td>Tumor-induced osteomalacia</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nutritional (vitamin D deficient) rickets —</td>
<td>↓ or N</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** see Footnote to Table 1.

\(^a\) High FGF23 levels due to high number of FGF23-producing cells in fibrous bone lesions.

*Data from Ref. 2,11,18,19,121,123,137,138*
Hypophosphatemia due to Acquired Defects in Phosphate Handling

Tumor-induced osteomalacia

Tumor-induced osteomalacia is a paraneoplastic disorder caused by the secretion of phosphatonin (phosphaturic hormones), including FGF23 (see Table 2), which leads to tubular P wasting and hypophosphatemia, osteomalacia, and vitamin D abnormalities. Plasma PTH, PTH-related protein, and calcium concentrations are normal (see Table 4).

SUMMARY

Hypophosphatemic rickets, most due to the X-linked dominant form caused by pathogenic variants of the PHEX gene, continues to pose therapeutic challenges with important consequences for growth and bone development, high risk of fractures and poor bone healing, dental problems, and nephrolithiasis or nephrocalcinosis. Conventional treatment consists of PO₄ supplement and pharmacologically dosed calcitriol carefully monitoring for clinical efficacy and treatment-emergent adverse effects. Genetic testing is encouraged, especially in sporadic cases. FGF23 measurement, although currently not routinely offered, has implications for the differential diagnosis of hypophosphatemia syndromes and, potentially, treatment monitoring. Newer therapeutic modalities focus on calcium sensing receptor modulation (cinacalcet) and biological molecules targeting FGF23 or its receptors (in clinical studies). The first trial results with biological agents are now becoming available and must be compared with the known, long-term effects of conventional treatments.

ACKNOWLEDGMENTS

We thank Giuseppe Pascale for help in the design of the figures.

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