Published in final edited form as:

Semin Nephrol. 2013 March ; 33(2): 143–157. doi:10.1016/j.semnephrol.2012.12.015.

Insights from Genetic Disorders of Phosphate Homeostasis

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Abstract

The molecular identification and characterization of genetic defects leading to a number of rare inherited or acquired disorders affecting phosphate homeostasis has added tremendous detail to our understanding of the regulation of phosphate balance. The identification of the key phosphate-regulating hormone, fibroblast growth factor 23 (FGF23), as well as other molecules that control its production, such as the glycosyltransferase GALNT3, the endopeptidase PHEX and the matrix protein DMP1, and molecules that function as downstream effectors of FGF23, such as the longevity factor Klotho and the phosphate transporters NPT2a and NPT2c, has permitted us to understand the elegant and complex interplay that exists between the kidneys, bone, parathyroid, and gut. Such insights from genetic disorders have allowed not only the design of potent targeted therapies for some of these rare genetic disorders, such as using anti-FGF23 antibodies for treatment of X-linked hypophosphatemic rickets, but also have led to clinically relevant observations related to the dysregulation of mineral ion homeostasis in chronic kidney disease. Thus, we are able to leverage our knowledge of rare human disorders affecting only few individuals, to understand and potentially treat disease processes that affect millions of patients.

INTRODUCTION

The regulation of phosphate homeostasis involves several different hormones that act on kidney, intestine, and bone. Fibroblast growth factor 23 (FGF23) is likely the primary regulator of extracellular phosphate concentration, although the mechanism by which FGF23-producing cells “sense” phosphate remains to be elucidated. Synthesized in bone, FGF23 is released into the circulation and acts on the proximal tubule to enhance, within hours, urinary phosphate excretion by reducing the expression levels of two sodium-dependent phosphate co-transporters, NPT2a and NPT2c. Furthermore, FGF23 decreases renal production of 1,25-dihydroxyvitamin D (1,25(OH)₂D) and thus reduces intestinal phosphate absorption. Two other hormones, parathyroid hormone (PTH), whose chief role is regulation of extracellular calcium ion concentration, and 1,25(OH)₂D, contribute to maintaining phosphate balance. PTH also acts on the proximal tubule, where it rapidly decreases NPT2a and NPT2c expression and thereby leads to phosphaturia. However, in

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contrast to FGF23, PTH increases production of 1,25(OH)₂D, which then acts on the intestine to enhance the absorption of calcium (and phosphate). Together with PTH, 1,25(OH)₂D furthermore acts on bone to increase the release of calcium (and phosphate) into the extracellular fluid. PTH and 1,25(OH)₂D thus help maintain extracellular calcium concentration within normal limits, but both hormones also increase the extracellular phosphate concentration. Phosphate regulation therefore can be either independent of, or intimately tied to calcium regulation.

Disorders with abnormal regulation of phosphate homeostasis are broadly divided based on whether they lead to hyperphosphatemia or hypophosphatemia; they can be further classified according to whether they are FGF23-dependent or -independent (Table 1). Since the mid-1990s, the molecular definition of a number of rare inherited and acquired disorders has resulted in the identification and characterization of several proteins that contribute to the normal regulation of phosphate homeostasis; these include FGF23, PHosphate-regulating protein with homologies to Endo-peptidases on the X chromosome (PHEX), dentin matrix protein 1 (DMP1), FGF receptor 1 (FGFR1), the longevity factor Klotho, the glycosyltransferase GALNT3 (which is responsible for initiating mucin-type O-linked glycosylation of FGF23), and the two sodium-dependent phosphate co-transporters, NPT2a and NPT2c. With few exceptions that will be discussed in the text, it remains largely unknown, however, whether and how the different phosphate-regulating proteins interact with each other. Furthermore, it is almost certain that additional molecules contribute to these regulatory events, and that genetic studies will continue to be of pivotal importance for the identification of genes encoding novel regulators of phosphate homeostasis. For example, in a cohort of 46 patients with familial hypophosphatemia (see below), sequence analysis identified PHEX mutations in 27 patients, mutations in FGF23 in only 1, mutations in DMP1 in none, and mutations in neither gene in 18 patients. These findings indicate that additional as-of-yet unknown genetic defects can cause hereditary hypophosphatemia disorders and that the definition of the underlying genetic defect will result in the definition of novel phosphate-regulating molecules¹.

The circulating levels and activity of the major phosphate regulators, including FGF23, PTH and 1,25(OH)₂D are altered in chronic kidney disease (CKD) and likely contribute to the significant morbidity and mortality in this patient population. Understanding the molecular mechanisms of phosphate regulation highlighted by genetic studies in mice and humans is likely to contribute to the development of novel therapies for CKD patients.

In this paper, we will first review the major regulators of phosphate homeostasis introduced above. We will then review disorders of phosphate homeostasis, separated into hyperphosphatemic versus hypophosphatemic disorders, to further expand on the contribution of genetic and clinical syndromes to phosphate homeostasis. Finally, we will highlight how insights from genetics can help us think about mineral metabolism disturbances in CKD and hypothesize about some potential therapeutic options.

REGULATORS OF PHOSPHATE HOMEOSTASIS

Fibroblast growth factor 23 (FGF23)

FGF23 is a member of the endocrine group of fibroblast growth factors (which includes FGF19 and FGF21). It was initially identified as the genetic cause of autosomal dominant hypophosphatemic rickets (ADHR)² and was, independently, isolated from tumors that cause oncogenic osteomalacia, an acquired phosphate-wasting disorder, where FGF23 mRNA and protein were found to be markedly overexpressed³. *In vivo* findings indicated that this hormone promotes, either directly or indirectly, renal phosphate excretion^{3, 4}. The chief site of FGF23 expression is bone, where it is produced mainly by osteocytes, the most

abundant cells in bone^{5–7}. FGF23 mRNA is not detectable by Northern blot analysis in other tissues, although it has been identified by reverse transcriptase (RT)-PCR in heart, liver, thymus, small intestine, and brain^{2, 3, 8}. The FGF23 gene comprises of 3 exons encoding a 251 amino acid protein, including a signal peptide of 24 residues (Figure 1). The mature protein is modified by O-glycosylation between residues 162–228 by GALNT3 and is presumed to be cleaved by a subtilisin-like proprotein convertase between Arg179 and Ser 180^{9, 10}; glycosylation is thought to prevent cleavage. SPC2, in conjunction with 7B2, may be the enzyme responsible for FGF23 cleavage¹¹. Intact FGF23 is thought to be the active hormone capable of inducing hypophosphatemia⁹, while the smaller N- and C-terminal fragments are devoid of activity, or act as an inhibitor of FGF23, at least at high concentrations¹².

Control of FGF23 production

FGF23 production is increased by dietary phosphate loading and 1,25(OH)₂D or PTH administration in both animals and humans^{13–16} (Figure 2). The mechanism by which phosphate regulates FGF23 production is not clear, but several lines of evidence support a direct effect of 1,25(OH)₂D on FGF23 expression through vitamin D binding elements in the FGF23 promoter¹⁷. PTH may have either a direct or indirect effect on FGF23 production. For example, mice expressing a constitutively active PTH/PTHrP receptor in osteocytes have both increased FGF23 mRNA levels in bone and elevated FGF23 levels in the circulation¹⁸ and both mice and humans who have received PTH infusions show increased circulating FGF23 levels after 6–8 hours^{14, 18, 19}. One study, however, suggests that early on, PTH might have suppressive effects on FGF23, as PTH infusion led to a modest reduction in FGF23 levels within one hour after PTH infusion, coinciding with a decrease in phosphate levels²⁰.

Additional pathways affecting FGF23 production have been identified by studies in humans and mice that are null for dentin matrix protein 1 (DMP1). DMP1 is a bone matrix protein and mutations in DMP1 lead to increased expression of FGF23^{21, 22}, suggesting that DMP1 normally represses FGF23 (Figure 3). Genetic studies of mice carrying both the *Dmp1* and *Fgf23* mutations suggest that *Fgf23* is epistatic to *Dmp1*, as the double mutants have a phenotype very similar to the *Fgf23* single mutant animals²³. Moreover, only the 57 kDa C-terminal fragment of DMP1 appears to be responsible for this regulatory role²⁴. Furthermore, animals and humans carrying mutations in the PHEX gene also exhibit FGF23-dependent hypophosphatemia^{7, 25}. Thus, both DMP1 and PHEX are thought to be negative regulators of FGF23 (Figure 3) and they may affect FGF23 production via an FGFR-dependent pathways^{26, 27}.

Further insight into the regulation of FGF23 production and processing comes from studies of ADHR patients, whose disease severity (degree of hypophosphatemia) appears to correlate with their iron status²⁸. Through elegant experiments in animals engineered to carry the ADHR mutation, which makes FGF23 resistant to cleavage, Farrow *et al.* showed that a low iron status leads to up-regulation of FGF23 message in bone, potentially through a hypoxia-inducible factor (HIF)-dependent mechanism, and also to increased degradation of FGF23 protein in bone²⁹ (Figure 4). Finally, recent work analyzing the phenotype of patients with fibrous dysplasia, who have elevated circulating FGF23 levels, but frequently no hypophosphatemia, have suggested that a significant portion of FGF23 in the circulation of these patients is not intact and thus not biologically active, at least with regards to phosphate regulation^{5, 30}. The genetic defect in fibrous dysplasia, an activating mutation in the alpha-subunit of the stimulatory G protein (G_sα), increases intracellular cAMP levels. Bhattacharyya *et al.* showed that increased cAMP levels decrease the activity of GALNT3, the enzyme required for O-glycosylation of FGF23, and thus allowing increased degradation of the non- or underglycosylated, intact FGF23³⁰ (Figure 4).

FGF23 effects on phosphate homeostasis

While FGF23 can bind to multiple FGF receptors, the presence of Klotho, a transmembrane protein associated with longevity, allows for tissue-specific binding of FGF23 to the FGF receptor 1 splice variant FGFR1c^{31, 32}. Further support for the role of Klotho in control of phosphate homeostasis comes from the observation that when Klotho is absent (as in Klotho-null mice), animals develop severe hyperphosphatemia— a phenotype indistinguishable from that of Fgf23-null mice^{6, 33, 34}; however, distinct from the latter animals, Klotho-null mice have dramatically elevated FGF23 levels³². Recent identification of Klotho-independent actions of FGF23 on myocardial cells has expanded the repertoire of FGF23 beyond phosphate regulation³⁵.

Animals receiving recombinant FGF23 intraperitoneally and nude mice transplanted with cell lines stably expressing FGF23 develop hypophosphatemia due to increased urinary phosphate excretion^{3, 9}. FGF23 reduces the expression of the sodium-dependent phosphate co-transporters NPT2a and NPT2c at the apical membrane of renal proximal tubules through FGFR1/Klotho signaling and mitogen activated protein kinase (MAPK) activation^{36, 37} (Figure 2). Furthermore, there is an FGF23-dependent reduction in the activity of the 1 alpha (1 α)-hydroxylase and increase in the 24-hydroxylase in proximal tubules leading to a reduction in serum 1,25(OH)₂D levels^{38, 39}.

Parathyroid hormone (PTH)

PTH gene transcription (as well as PTH peptide secretion) is regulated by the extracellular concentration of calcium and phosphate, and through a vitamin D response element upstream of the transcription start site^{40–42}. In its mature form the PTH peptide comprises 84 amino acids, which is derived from a longer pre-pro peptide (reviewed in ⁴³). After secretion, PTH is cleared from the circulation with a short half-life of about 2 minutes, via non-saturable hepatic and renal uptake.

PTH and PTHrP (PTH-related peptide, an autocrine/paracrine hormone related to PTH with no known effects on phosphate regulation, unless secreted by different tumors) both mediate their actions through a common G-protein coupled receptor^{43, 44}. The receptor is abundantly, though not exclusively, expressed in kidney and bone, where it mediates the endocrine actions of PTH, by signaling through G(s) alpha (G_s α)/PKA and G(q)/PLC/PKC. Specifically, in the proximal renal tubule PTH acts via basolateral (and apical) PTH/PTHrP receptors (PTHR1) whose activation leads to internalization of the NPT2a and NPT2c phosphate transporters and thus phosphaturia⁴⁵ (Figure 2). In the proximal renal tubule PTH also stimulates 1,25(OH)₂D production. In the distal tubule, PTH increases calcium reabsorption⁴⁶. In bone, PTH acts on osteoblasts, and, indirectly, on osteoclasts to modulate bone formation.

PTH effects on phosphate homeostasis

Genetic disorders affecting PTH production or signaling can have significant effects on phosphate metabolism (Table 1). Given the direct and/or indirect effects of PTH on FGF23 production, some of the effects are FGF23-dependent. For example, one case report of a patient with Jansen's disease (due to a constitutive activation of the PTH/PTHrP receptor), characterized by hypophosphatemia and hypercalcemia despite low PTH and PTHrP, found FGF23 levels to be elevated⁴⁷. In addition, in patients with McCune-Albright syndrome/fibrous dysplasia of bone, due to activating mutations in G_s α , FGF23 levels were elevated in those patients who had renal phosphate-wasting and hypophosphatemia^{5, 48}. Conversely, patients with maternally inherited inactivating mutations in G_s α , i.e. individuals with pseudohypoparathyroidism type Ia (PHP-Ia), show PTH-resistant hypocalcemia and hyperphosphatemia⁴⁹. Through as-of-yet unknown mechanisms, G_s α expression from the

paternal allele is silenced in the proximal renal tubules, thus leading to a complete lack or severe reduction of G_{α} in this portion of the kidney and thus to PTH-resistant hyperphosphatemia. FGF23 levels seem to be mildly elevated in the few patients where this hormone has been measured, but not sufficiently to normalize serum phosphorus levels.

Mice with deletion of the PTH gene develop mild hyperphosphatemia and hypocalcemia, analogous to patients with hypoparathyroidism⁵⁰. Interestingly, FGF23 levels are also reduced, suggesting that the hyperphosphatemia in these animals does not increase FGF23 secretion, which may be related to the absence of PTH or $1,25(\text{OH})_2\text{D}$. In humans with familial isolated hypoparathyroidism, a clinical syndrome that can result from mutations in the PTH gene, in the genes encoding the calcium-sensing receptor (CaSR), or a transcription factor necessary for parathyroid gland development called glial cells missing B (GCMB), hyperphosphatemia is also common⁵¹. FGF23 levels have only been measured in few patients with idiopathic hypoparathyroidism and were found to be elevated⁵². Moreover, in patients who developed transient hypoparathyroidism after thyroid surgery, hyperphosphatemia developed and preceded FGF23 elevation⁵³. Finally, in Fgf23-null mice, injection of PTH had phosphaturic and anabolic effects even in the absence of FGF23 protein⁵⁴. Thus, PTH deficiency or excess has independent effects on renal phosphate handling that may or may not be modulated by its effects on FGF23.

$1,25(\text{OH})_2\text{D}$ or calcitriol

Vitamin D₃ can be synthesized in the skin by ultraviolet light from 7-dehydrocholesterol or obtained from the diet⁵⁵. It requires hydroxylation in the liver to form the prohormone 25-hydroxyvitamin D ($25(\text{OH})\text{D}$). In the proximal tubule, $25(\text{OH})\text{D}$ is further hydroxylated by the enzyme 1α hydroxylase to yield the biologically active hormone calcitriol ($1,25(\text{OH})_2\text{D}$). The activity of the 1α -hydroxylase is regulated by extracellular concentrations of ionized calcium, inorganic phosphate, PTH, and FGF23⁵¹. $1,25(\text{OH})_2\text{D}$ binds in target organs (e.g. intestine, bones, kidneys and parathyroids) to the intracellular vitamin D receptor (VDR), and thereby activates the transcription of genes in bone, kidney and enterocytes that help increase gut absorption of calcium and phosphate, reduce urinary calcium losses, and increase bone resorption, thereby ensuring adequate extracellular concentration of calcium and phosphate⁵⁶. Mutations in the genes encoding the 1α -hydroxylase and the VDR are associated with rickets⁵⁷.

Calcitriol effects on phosphate homeostasis

$1,25(\text{OH})_2\text{D}$ is part of a feedback loop with FGF23, whereby $1,25(\text{OH})_2\text{D}$ increases FGF23 production in bone while FGF23 reduces $1,25(\text{OH})_2\text{D}$ production in kidney by inhibiting the $1,25(\text{OH})_2\text{D}$ anabolic enzyme 1α -hydroxylase and stimulating the catabolic enzyme 24 -hydroxylase (Figure 2). $1,25(\text{OH})_2\text{D}$ also inhibits PTH synthesis and secretion. Both in animals that are null for the VDR or the 1α -hydroxylase and in the human counterparts with vitamin D-deficient rickets (VDDR1 and 2, Table 1), there is significant hypocalcemia (due to impaired intestinal calcium absorption) and hypophosphatemia (due to elevated PTH). Thus, vitamin D indirectly affects phosphate homeostasis via FGF23 and PTH.

$1,25(\text{OH})_2\text{D}$ also directly increases phosphate absorption in certain parts of animal intestine by regulating the amount of NPT2b, a sodium-phosphate co-transporter highly homologous to NPT2a and NPT2c^{58, 59}. VDR-null mice have low FGF23 levels, consistent with the lack of $1,25(\text{OH})_2\text{D}$ required for the stimulation of FGF23 synthesis and hypophosphatemia. When the hypocalcemia and hypophosphatemia in these animals are corrected by increased dietary intake of calcium and phosphate, FGF23 levels also increase. However, injection of FGF23 protein in VDR-null mice is able to trigger phosphaturia, suggesting that FGF23 works in the absence of the VDR⁶⁰.

Other proteins with phosphaturic properties

Besides FGF23, MEPE (matrix extracellular phosphoglycoprotein), sFRP4 (secreted frizzled-related protein 4), and FGF7 were also shown to be overexpressed by tumors that cause oncogenic osteomalacia^{61–63}. While *in vivo* or *in vitro* experiments suggested that these putative phosphate regulators could be involved in the renal regulation of phosphate handling, genetic ablation of MEPE and sFRP4 in mice did not lead to a hyperphosphatemic phenotype the way genetic ablation of FGF23 does^{64, 65}. Moreover, sFRP4 levels did not change with development of renal insufficiency, a state of elevated phosphate, and sFRP4 circulating levels were not elevated in patients with oncogenic osteomalacia⁶⁶. Furthermore, MEPE expression in bone in patients with CKD was not different from expression in individuals with normal renal function⁶⁷. The physiological importance of these proteins in phosphate homeostasis thus remains unclear.

HYPERPHOSPHATEMIC DISORDERS

Due to reduced secretion of biologically active FGF23

Several variants of the rare syndrome hyperphosphatemic familial tumoral calcinosis (HFTC, Table 1) have been described; an autosomal dominant (AD) form⁶⁸ and two autosomal recessive (AR) forms that are caused by mutations in two different genes⁶⁹. Individuals with the AD form usually have elevated serum 1,25(OH)₂D levels, and a specific dental lesion, but classic findings of tumoral calcinosis, such as subcutaneous calcifications, may not always be present. The molecular defect of this form of the disorder remains unknown.

The autosomal recessive forms of HFTC can be severe, and are typically characterized by hyperphosphatemia and often massive calcium deposits in the skin and subcutaneous tissues; in some patients, however, only few minor abnormalities are noted⁷⁰. HFTC can be caused by either homozygous or compound heterozygous mutations in *GALNT3*, which encodes a glycosyltransferase responsible for initiating mucin-type O-glycosylation (HFTC Type 1, Table 1), or homozygous mutations in *FGF23* (HFTC type 2, Table 1)^{69, 71, 72}. Interestingly, the concentrations of carboxyl-terminal (inactive) FGF23 were significantly elevated in affected individuals with either mutation. These findings suggested defective post-translational modifications of FGF23, which were indeed observed in cells transiently expressing FGF23 mutants that cause AR tumoral calcinosis⁷³. The FGF23 mutations causing HFTC2 interfere with glycosylation of the protein and thus lead to increased degradation of the intact, biologically active hormone (Figure 4).

Patients with hyperostosis with hyperphosphatemia have features of tumoral calcinosis and elevated phosphate levels, but also recurrent painful swelling of long bones⁷⁴. While the majority of cases appear to be sporadic, consanguineous parents were described for some patients, implying that the disease can be recessive. Recently, *GALNT3* mutations were also identified in the recessive form of this disease, indicating that one of the two forms of tumoral calcinosis and hyperostosis with hyperphosphatemia are allelic variants⁷⁵. As in patients with the recessive forms of HFTC, C-terminal FGF23 concentrations are significantly elevated.

Due to FGF23 resistance

An exciting addition to the molecular characterization of the tumoral calcinosis phenotype was published in 2007, when a homozygous point mutation in the *Klotho* gene was identified in a 13-year old patient with severe vascular and soft tissue calcification, hyperphosphatemia, hypercalcemia and elevated 1,25(OH)₂D as well as FGF23 levels (HFTC Type 3, Table 1)⁷⁶. The biochemical and clinical phenotype was reminiscent of that

of the Klotho-null mouse and was shown *in vitro* to lead to reduced ability of FGF23 to signal through its receptor³³, resulting in FGF23 resistance.

FGF23-independent hyperphosphatemic disorders

Several disorders that lead to PTH resistance or deficiency are characterized by hyperphosphatemia, including pseudohypoparathyroidism and isolated hypoparathyroidism (Table 1). We will focus on pseudohypoparathyroidism; for discussion on isolated hypoparathyroidism see Thakker *et al.*⁷⁷.

Patients with pseudohypoparathyroidism (PHP) have hypocalcemia and hyperphosphatemia due to PTH-resistance rather than PTH-deficiency. Affected individuals show partial or complete resistance to biologically active, exogenous PTH as demonstrated by a lack of a PTH-induced increase in urinary cyclic AMP and urinary phosphate excretion; this condition is now referred to as PHP type I (review⁷⁸). If associated with other endocrine deficiencies and characteristic physical stigmata, now collectively referred to as Albright's Hereditary Osteodystrophy (AHO), the condition is called PHP type 1A (PHP1A). PHP1A is caused by heterozygous inactivating mutations within exons 1–13 of *GNAS*, which encode the stimulatory G protein ($G_s\alpha$) (review⁷⁸). These mutations were shown to lead to an approximately 50% reduction in $G_s\alpha$ activity/protein in most tissues. However, in few tissues like the proximal renal tubules, the thyroid, or the pituitary, $G_s\alpha$ is derived mainly from the maternal allele; maternally inherited $G_s\alpha$ mutations thus lead to a more pronounced or complete loss of $G_s\alpha$ thus explaining the resistance towards PTH and other hormones that mediate their actions through G protein-coupled receptors⁷⁸.

Mutations at the *GNAS* locus yield complex phenotypes. For example, the same heterozygous mutation can lead to a different phenotype if inherited from the mother (resistance towards several hormones, including PTH, PHP1A) or the father (no hormone resistance, pseudopseudohypoparathyroidism (PPHP)). Observations consistent with these findings in humans were made in mice that are heterozygous for the ablation of exon 2 of the *Gnas* gene. Animals that had inherited the mutant allele from a female showed undetectable $G_s\alpha$ protein in the renal cortex and decreased blood calcium concentration due to resistance toward PTH. In contrast, offspring that had obtained the mutant allele lacking exon 2 from a male showed no evidence for endocrine abnormalities⁷⁹.

Mutations in the *GNAS* gene encoding $G_s\alpha$ have not been detected in patients with PHP type 1B (PHP1B), a disorder in which affected individuals show PTH-resistant hypocalcemia and hyperphosphatemia, but usually lack developmental defects. A genome-wide search to identify the location of the “PHP1B gene” mapped the PHP1B locus to chromosome 20q13.3, which contains the *GNAS* locus, and it was furthermore shown that the genetic defect is paternally imprinted, i.e. it is inherited in the same mode as the PTH-resistant hypocalcemia in kindreds with PHP1A and/or PPHP⁸⁰. The identification of deletions within an unrelated gene, syntaxin 16, located 220 kb upstream of *GNAS* were linked to methylation changes at the *GNAS* locus. It is presumed that the loss of methylation at *GNAS* exon A/B, which allows biallelic expression from its promoter, reduces or abolishes $G_s\alpha$ expression in the proximal renal tubules and thus leads to PTH-resistance in this tissue, but not in bone or most other tissues, where the PTH/PTHrP receptor mediates the actions of PTHrP.

Finally, several recently identified mutations in the *CYP24A1* gene, which encodes the 24-hydroxylase enzyme responsible for metabolizing both 1,25(OH)₂D and its prohormone 25(OH) vitamin D were reported to cause the syndrome idiopathic infantile hypercalcemia^{81, 82}. The clinical manifestations are due to inability to metabolize 1,25(OH)₂D leading to hypercalcemia, and hypercalciuria, with suppressed PTH. Phosphate

levels in one case were either at the upper limit of normal or elevated, though FGF23 levels were not reported⁸¹.

HYPOPHOSPHATEMIC DISORDERS

Due to excess of biologically active FGF23 – genetic causes

Autosomal dominant hypophosphatemic rickets (ADHR) is characterized by low serum phosphate concentrations, bone pain, rickets that can result in deformities of the legs in children, while adults present with osteomalacia (clinical and laboratory findings can be variable). Positional cloning efforts led in one large ADHR kindred to the identification of FGF23 as a phosphate-regulating hormone (Table 1); mutational analyses of several unrelated ADHR families identified missense mutations affecting codons 176 (arginine) and 179 (arginine) of FGF23. The clustering of these ADHR missense mutations that alter the conserved arginine residues lead to the speculation that they may cause “gain-of-function”, since mutations at this R¹⁷⁶XXR¹⁷⁹ cleavage site for furin-like (or subtilisin-like) proprotein convertases prevent inactivation of the biological active, intact FGF23 (Figure 4). This hypothesis was confirmed by injecting versions of recombinant FGF23 protein carrying these mutations into animals and demonstrating hypophosphatemia⁹.

X-linked hypophosphatemia (XLH) is the most frequent inherited phosphate-wasting disorder. Just like ADHR, it is characterized by hypophosphatemia due to urinary phosphate-wasting, low circulating 1,25(OH)₂D concentration and rickets/osteomalacia. This disorder is caused by inactivating mutations in PHEX (previously called PEX), a gene located on the X-chromosome^{83, 84} (Table 1). PHEX, which is expressed in bone, and other tissues such as kidney and parathyroid, shows significant peptide sequence homology to the M13 family of zinc metalloproteinases. All members of the M13 family are integral membrane glycoproteins that have endopeptidase activity and consist of a short N-terminal cytoplasmic domain, a single transmembrane hydrophobic region and a large extracellular domain; their substrates range from atrial natriuretic peptide, enkephalin, substance P and bradykinin, to endothelin. The substrate(s) for PHEX remains to be established. Although circulating FGF23 concentrations are elevated in patients with XLH⁸⁵, FGF23 does not appear to be a substrate for PHEX^{10, 25, 86}. However, genetic ablation of Fgf23 in male Hyp mice, i.e. animals that are null for Fgf23 and Phex, leads to blood phosphate levels that are indistinguishable from those in mice lacking Fgf23 alone, indicating that FGF23 resides genetically down-stream of Phex^{6, 7}, and that Phex normally suppresses FGF23 (Figure 3). Furthermore, Hyp mice normalize their blood phosphate levels and heal their rachitic changes when injected with inactivating antibodies to FGF23, indicating that FGF23 is indeed the phosphaturic principle in XLH⁸⁷.

Several matrix proteins, including matrix extracellular phosphoglycoprotein (MEPE), DMP1 and osteopontin have acidic serine-and-aspartic acid-rich motif(s) (ASARM). Accumulation of ASARM in Hyp mice may account for the osteomalacia phenotype, as treatment of osteoblast cells with ASARM peptide inhibited mineralization^{88, 89}. PHEX is able to cleave ASARM and the ASARM containing MEPE inhibits PHEX activity⁹⁰. Thus PHEX, through modulation of matrix-derived peptide fragments may affect mineralization and/or FGF23 expression. The exact mechanism of this interaction is not known.

The clinical findings of affected individuals from kindreds with autosomal recessive forms of hypophosphatemia (ARHR) show significant similarities to those observed in patients affected by ADHR or XLH, including hypophosphatemia, rickets, skeletal deformities, and dental defects, and affected individuals develop osteosclerotic bone lesions and enthesopathies later in life⁹¹. Patients affected by ARHR have FGF23 levels that are either elevated or inappropriately normal for the level of serum phosphorous^{21, 22}. Homozygous

mutations in two genes so far have been identified as responsible for the ARHR phenotype: DMP1 and ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) (Table 1, Figure 3). DMP1 is a bone- and teeth-protein that is exported into the extracellular matrix where it regulates the nucleation of hydroxyapatite. It undergoes post-translational modifications that yield a 94 kDa mature protein, which is then rapidly cleaved into a 37 kDa and a 57 kDa fragment. Transgenic expression of the 57 kDa DMP1 fragment alone is sufficient to suppress FGF23 secretion and to reverse the phenotype of *Dmp1*-null animals^{24, 92}.

DMP1 mutations in humans appear to be inactivating, suggesting that loss of DMP1 function results in hypophosphatemia. Accordingly, *Dmp1*-null mice show severe defects in dentine, bone, and cartilage, as well as hypophosphatemia and osteomalacia⁹³. Furthermore, FGF23 levels in osteocytes and in serum are drastically elevated in these animals²². Based on these findings DMP1 appears to inhibit FGF23 expression, thereby regulating phosphate homeostasis (Figure 3).

ENPP1 mutations, originally linked to a disorder referred to as Generalized Arterial Calcification of Infancy (GACI) were also identified as one of the etiologies of ARHR^{94, 95}. ENPP1 generates pyrophosphate, a mineralization inhibitor, and animals with *Enpp1* mutations have defective bone mineralization and increased both vascular and soft-tissue calcifications⁹⁶. Importantly, FGF23 levels were elevated in the circulation of mice and humans with ENPP1 loss of function mutations^{94, 96}. The mechanism by which ENPP1 modulates FGF23 expression/production is not clear.

Intriguingly, mutations in the transporter ABCC6 (ATP-binding cassette subfamily C number 6), previously linked to the rare clinical disorder Pseudoxanthoma Elasticum (PXE), were also reported to lead to the GACI phenotype, as well as to hypophosphatemic rickets in one individual⁹⁷. ABCC6 is a transmembrane protein expressed mainly in the liver. How mutations in this transporter lead to arterial calcification or abnormal phosphate homeostasis is not clear. FGF23 levels have not been reported in either patients with PXE or mice with *Abcc6* deletion. Thus, while in humans there may be a phenotypic overlap between ENPP1 or ABCC6 mutations and GACI or PXE with respect to the clinical and laboratory findings, it is not clear if the hypophosphatemic rickets reported with both is due to the same mechanism.

Fibrous dysplasia (FD) is caused by heterozygous activating, post-zygotic mutations in exon 8 of *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein ($G_s\alpha$) that lead in the dysplastic regions to a cAMP-dependent increase in the production of FGF23 by osteoblasts/osteocytes and fibrous cells^{5, 98} (Table 1). Some patients with FD have hypophosphatemia, though others do not. Further work revealed a relatively more pronounced increase in C-terminal FGF23 fragments than intact FGF23 in FD patients as compared with normal controls. *In vitro* studies then showed a cAMP-dependent decreased GALNT3 activity (presumably leading to decreased O-linked glycosylation of FGF23 protein), and increased furin activity, thus allowing increased cleavage of FGF23 by furin-like proteases³⁰ (Figure 4).

Due to excess of biologically active FGF23 – acquired forms

Oncogenic osteomalacia (OOM; also referred to as tumor-induced osteomalacia, TIO) is a rare disorder characterized by hypophosphatemia, renal phosphate wasting, low circulating 1,25(OH)₂D levels and osteomalacia that develops in previously unaffected individuals⁹⁹. Clinically, there are considerable similarities between OOM, XLH and ADHR. OOM is caused by usually small, often difficult to locate tumors, most frequently hemangiopericytomas. The clinical and biochemical abnormalities resolve rapidly after the removal of the tumor. OOM tumors express PHEX and FGF23, as well as variably SFRP4,

MEPE, DMP1 and others^{100,4, 62}. However, only circulating FGF23 concentrations have been reliably identified as either elevated or inappropriately normal, and thus causative of the clinical phenotype^{86, 101}.

FGF23-independent Hypophosphatemic disorders

Hypophosphatemic disorders independent of FGF23 can be either due to defects in renal phosphate handling (due to mutations affecting the phosphate transporters directly, or mutations that impair tubular transport generally), or due to malfunction in the two other phosphate-regulating hormones, vitamin D and/or PTH.

Two main sodium-dependent phosphate transporters are responsible for the bulk of phosphate reabsorption by the proximal tubule: NPT2a (encoded by the *SLC34A1* gene) and NPT2c (encoded by the *SLC34A3* gene). Heterozygous mutations in NPT2a that appear to show impaired function *in vitro* were reported in patients with urolithiasis or osteoporosis and persistent idiopathic hypophosphatemia due to decreased tubular phosphate reabsorption; however controversy exists as to whether the identified mutations alone can explain the phenotype^{102, 103}. Recently, a homozygous mutation in NPT2a was identified in two members of a consanguineous family affected by autosomal recessive renal Fanconi syndrome¹⁰⁴. The mutations resulted in retention of the transporter inside cells, rather than on the cell membrane and thus complete loss of function. FGF23 levels in these individuals were expectedly low (due to hypophosphatemia)¹⁰⁴.

Patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH, Table 1), an autosomal recessive disorder, show hypophosphatemia and increased serum alkaline phosphatase activity, elevation in circulating 1,25(OH)₂D leading to serum calcium levels at the upper end of the normal range, hypercalciuria and decreased PTH levels¹⁰⁵. After excluding mutations in NPT2a, in several kindreds, homozygous or compound heterozygous mutations were identified in the related phosphate transporter NPT2c^{106–108}. In mice, ablation of NPT2a leads to renal phosphate-wasting and hypophosphatemia, while ablation of NPT2c does not significantly impair phosphate homeostasis¹⁰⁹. The mutations identified in HHRH patients suggest that in humans NPT2c has a more important role in phosphate homeostasis than initially thought.

A related sodium-phosphate co-transporter, NPT2b, is expressed in several tissues including lung, intestine, pancreas, testis, prostate and kidney¹¹⁰. In animals, NPT2b deletion is lethal, likely due to defects in placental transfer of phosphate to the developing fetus¹¹¹. NPT2b deletion targeted to the intestine revealed a significant role for this transporter in phosphate absorption from the diet, although it did not lead to hypophosphatemia due to compensatory increase in renal phosphate reabsorption⁵⁹. In humans, homozygous mutations in NPT2b also do not exhibit alterations in serum phosphate levels, but rather lead to pulmonary alveolar microlithiasis, a rare syndrome characterized by calcium-phosphate depositions in alveoli¹¹².

Hypophosphatemia is also a feature of vitamin D-deficient rickets due to lack of nutritional vitamin D or reduced sunlight exposure, and it, together with hypocalcemia and osteomalacia, is reversible with vitamin D supplementation. A rare subset of rickets is due to vitamin D-dependent or -resistant rickets (VDDR, autosomal recessive, Table 1). Patients with VDDR type 1 (VDDR1) show clinical and laboratory findings that are similar to those observed in patients with vitamin D-deficient rickets. However, unlike in vitamin D-deficiency, patients with VDDR1 do not respond to treatment with vitamin D and treatment with the active compound 1,25(OH)₂D is required instead. VDDR1 was therefore initially named *pseudovitamin D deficiency rickets*¹¹³. Clarification of the abnormal vitamin D metabolism led to the recognition that VDDR1 was due to a defect in the renal 1α-

hydroxylase enzyme (encoded by the CYP27B1 gene); consequently serum 1,25(OH)₂D concentration is low¹¹⁴. All patients so far with VDDR1 have been found to carry homozygous or compound heterozygous mutations in the 1 α -hydroxylase gene^{115,116, 117}. Mutations that confer partial enzyme activity *in vitro* were found in the two patients with mild laboratory abnormalities, suggesting that such mutations contribute to the phenotypic variation observed in patients with 1 α -hydroxylase deficiency¹¹⁸.

Subsequently another condition was recognized and called vitamin D-dependent rickets type 2 (VDDR2). In this condition, which is due to end organ resistance to 1,25(OH)₂D, the serum 1,25(OH)₂D concentration is markedly elevated. Most of the patients have early onset rickets but the first reported patient was a 22 year old woman who had skeletal pain for seven years¹¹⁹ and another patient presented at the age of 50 years following five years of symptoms¹²⁰. VDDR2 is due to defects in the vitamin D receptor. Similarly, VDR-null mutant mice have the features consistent with those observed in patients with VDDR2. VDR-null animals have growth retardation, skeletal deformities and an earlier mortality, and adult mice developed alopecia, as well as hypocalcemia and hypophosphatemia, with markedly elevated serum 1,25(OH)₂D concentrations.

OTHER HYPOPHOSPHATEMIC DISORDERS

There are several other genetic disorders associated with hypophosphatemia and often with other defects in proximal tubular function. These include: Dent's disease, an X-linked recessive disorder caused by mutations in *CLCN5* encoding the voltage-gated chloride channel CLC-5^{121, 122} and Lowe syndrome (oculo-cerebro-renal syndrome), another X-linked recessive disorder that is caused by mutations in *OCRL1*¹²³. Furthermore, Fanconi-Bickel syndrome, which is caused by homozygous or compound heterozygous mutations in *GLUT2*, can be associated with severe hypophosphatemia, but this feature is often not very prominent¹²⁴. Other rare hypophosphatemic diseases are osteoglophonic dysplasia, an autosomal dominant disorder, which was recently shown to be caused by different heterozygous missense mutations in the *FGFR1*¹²⁵, and linear nevus sebaceous syndrome (also known as epidermal nevus syndrome), in which elevated FGF23 were observed^{126, 127}.

IMPLICATIONS FOR CHRONIC KIDNEY DISEASE TREATMENT

CKD (specifically late stage CKD) is a special clinical scenario of acquired hyperphosphatemia despite elevated levels of the phosphaturic hormones FGF23 and PTH. Thus, it can be considered most similar to end-organ resistance syndromes (such as tumoral calcinosis/HFTC due to Klotho deficiency). Several potential therapeutic interventions based on the current understanding of phosphate homeostasis have either been proposed or have already been tried in animal or human studies (Table 2). These will be discussed below.

Modulation of FGF23 levels or activity

Elevated FGF23 levels contribute to the increased morbidity, faster disease progression and increased mortality in both patients with CKD and those on dialysis (reviewed elsewhere in this issue) raising the possibility that appropriate interventions with phosphate binders, inhibitors of FGF23 actions, or antibodies to FGF23 may be clinically beneficial. FGF23 neutralizing antibodies were first tried in the mouse model for XLH, the Hyp mouse, where treatment was able to normalize serum phosphate levels, decrease PTH and improve, but not cure, the bone mineralization phenotype¹²⁸. Such antibodies are currently in a phase I/II clinical trial for treatment of adult XLH patients, a disorder where elevated FGF23 levels lead to phosphate wasting (drug name: KRN23, made by Kirin pharma, clinical trial ID NCT01340482). No information is yet available about the outcome of this trial. If safe and

effective in humans with XLH, such antibodies might be useful in patients with end-stage kidney disease on dialysis to reduce or prevent the “off-target” effects of FGF23 such as those on the heart; the development of hyperphosphatemia due to interfering with FGF23 action on the kidney will not be a significant concern in this patient population.

Besides this proof of concept study in XLH patients, the anti-FGF23 antibodies were tried in a rat model of GBM nephritis, where they slowed CKD progression¹²⁹. As might be expected based on genetic diseases with low or ineffective FGF23 levels, these CKD animals developed hyperphosphatemia as a side-effect of therapy. Thus, in a CKD population, where elevated FGF23 levels serve to increase renal phosphate excretion and thus prevent overt hyperphosphatemia until late in disease, interfering with FGF23 action may not be beneficial, as the resulting hyperphosphatemia will have detrimental consequences of its own. In a dialysis population, where elevated FGF23 levels no longer affect phosphate excretion, interfering with FGF23 action may thus be safe and would have the benefit of disrupting the “off-target” effects of FGF23.

One report in animals used an anti-Klotho antibody to block interaction of FGF23 with the Klotho/FGF receptor complex and thus prevent FGF23 action³². This antibody was able to prevent in wild-type mice Klotho/FGFR activation by FGF23, but also led to increase in serum phosphate and FGF23 levels, similar to the human condition of HFTC due to Klotho deficiency. Recent reports of “off-target” effects of FGF23 in a Klotho-independent manner suggest FGF23 can have direct effects on the heart and lead to LVH³⁵. Thus, it may be undesirable to further increase circulating FGF23 levels in a CKD population.

Recent reports have highlighted FGF23 cleavage (presumably within the osteocyte/osteoblast) as an important locus of control of circulating intact and active FGF23 levels^{29, 30} (Figure 4). For example, in normal individuals, iron deficiency appears to correlate with increased levels of FGF23 as determined by the C-terminal FGF23 assay^{28, 130}. Furthermore, mice on a low iron diet show increased FGF23 production by osteocytes and elevated levels of C-terminal, but not intact FGF23; bone homogenates furthermore revealed smaller FGF23 fragments²⁹. However, in patients on peritoneal dialysis, only full length FGF23 was observed in the circulation and several different studies showed an excellent correlation between FGF23 levels measured by intact and C-terminal FGF23 assays^{131, 132}. Thus, an important question in the field remains: is FGF23 processing impaired or inhibited in CKD/ESRD despite the higher frequency of iron deficiency in this population? CKD may thus be a state of impaired FGF23 processing (similar to ADHR) as well as end-organ resistance.

Currently, no known treatments can increase FGF23 processing. It is plausible, however, that in the coming years, once the FGF23 processing pathway is better delineated, small molecules or compounds will be identified that can increase FGF23 processing. Such therapy might be also most helpful in the advanced CKD/dialysis patient population, as reducing levels of biologically active FGF23 by cleaving it earlier in CKD may lead to hyperphosphatemia and unintended morbidity.

Modulation of phosphate transport

The renal proximal tubule cell is the convergent site of action of both FGF23 and PTH, which decrease the amount and surface localization of the two principal phosphate transporters, NPT2a and NPT2c, thereby leading to phosphaturia. Thus, inhibition of NPT2a and/or NPT2c expression or function may lead to phosphaturia, at least in patients with sufficiently preserved renal function, which should lead to a decrease of FGF23 levels as well as increase in 1,25(OH)₂D levels (as observed in patients with NPT2a and NPT2c mutations)^{104, 108}. However, NPT2a/NPT2c inhibition might also lead to a more generalized

proximal tubule dysfunction, given the findings of Fanconi syndrome in patients with NPT2a mutations¹⁰⁴. Interestingly, soluble Klotho was shown to be able to lead to phosphaturia in animals *in vivo* after infusion, even in the absence of Fgf23, and acutely decrease surface expression of NPT2a *in vitro*¹³³. Thus, soluble Klotho may be an alternative phosphaturic therapeutic option. However, a case report describing a *de novo* translocation resulting in overexpression of Klotho, with elevated circulating Klotho levels, showed in addition to hypophosphatemia, parathyroid gland hyperplasia and elevated FGF23 levels¹³⁴. As the exact mechanisms of the observed changes are not well understood, it is possible that soluble Klotho infusions may also lead to undesirable side-effects, such as parathyroid gland hyperplasia, for example.

PTH is also able to acutely and chronically lead to phosphaturia and decreased serum phosphate levels. In CKD, patients develop secondary hyperparathyroidism, but despite PTH resistance, fractional excretion of phosphate correlates with PTH in this population¹³⁵. However, it is not clear if acute administration of PTH in the setting of pre-existing hyperparathyroidism will still have a phosphaturic effect, especially in late CKD. In a rat model of CKD, intermittent administration of PTH (amino acids 1–34, the active part of the molecule) led to an apparent increase in phosphate levels¹³⁶. In this particular animal study, intermittent PTH administration protected against bone loss in this CKD model, and there have been calls for use of PTH therapy in dialysis patients with adynamic bone disease and fractures to try to prevent recurrent fractures¹³⁷. It remains to be seen if hypercalcemia will be a limiting side effect in either CKD or dialysis patients.

Finally, inhibition of the 24-hydroxylase enzyme (encoded by CYP24) is expected to lead to persistently elevated 1,25(OH)₂D levels. One compound with CYP24 inhibitory activity, called lunacalcipol and manufactured by Cytochroma, a Canadian-based company, is in a phase II clinical trial¹³⁸ (clinical trial ID NCT01453634). Given the clinical and laboratory phenotype of the genetic defect in CYP24, hypercalcemia may be an important limiting side effect.

CONCLUDING REMARKS

Identification and molecular characterization of the genetic etiology for rare inherited and sporadic disorders of phosphate homeostasis has revolutionized the mineral metabolism field and significantly increased our understanding of mineral ion homeostasis and bone development. Despite significant advances in the field, however, much remains unknown about the hormonal system involved in the regulating phosphate and many questions remain unanswered; for example: how is phosphate “sensed” by cells? Is there one single organ or location that expresses the phosphate-sensor for the entire organism? How exactly is FGF23 processed or secreted? What drives the elevated FGF23 production in kidney failure? Continued work is required to characterize additional acquired or inherited disorders of phosphate metabolism (for example autosomal dominant forms of tumoral calcinosis or forms of hypophosphatemia that are not caused by mutations in known genes; non-PHEX, non-DMP1, non-ENPP1, non-FGF23), which will undoubtedly add new regulators and hormones to the phosphate field. Current efforts should furthermore focus on providing a mechanistic understanding of the interactions between already identified players, such as FGF23, PTH, DMP1, PHEX, and ENPP1.

Acknowledgments

HJ is supported by grants from the NIH, NIDDK (DK-46718 and DK-50708).

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Figure 1.

Schematic presentation of the FGF-23 precursor, which comprises a signal peptide for efficient secretion (amino acid residues 1–24; white area). The mature FGF-23 (25–251) is glycosylated between amino acid residues 166–228, and it undergoes cleavage at the RXXR (176–179) through proprotein (subtilisin or furin-type) convertases to generate fragments that appear to be devoid of phosphaturic activity. Glycosylation via GALNT3 prevents cleavage. The C-terminal fragment contains the epitopes for both capture and detection antibodies used in the Immutopics FGF23 ELISA currently used clinically on a limited basis.

Figure 2.

Schematic of total body phosphate regulation. FGF23 is produced in bone by osteocytes. Parathyroid hormone (PTH) is produced by the parathyroid glands. Both hormones activate their specific cognate receptors, FGFR1c with co-receptor Klotho and PTH/PTHrP receptor (PTHR1), respectively, on the proximal renal tubules to reduce the apical expression of the sodium-dependent phosphate co-transporters NPT2a and NPT2c; PTH furthermore increases expression of the renal 1- α hydroxylase, while FGF23 inhibits this mitochondrial enzyme (they have opposite effects on 1,25(OH)₂D production in the kidney). PTH and FGF23 affect each other's production through a potential negative feedback loop that is still being elucidated (thus the arrows between them are hashed). 1,25(OH)₂D increases phosphate absorption by the gut via increase of NaPi-IIb transporters (NPT2b). 1,25(OH)₂D also participates in negative feedback loops with FGF23 (it stimulates FGF23 production) and PTH (it inhibits PTH production). (modified from Bergwitz and Jüppner, 2010).

Figure 3.

Molecules and conditions affecting production of FGF23 by osteocytes. Inset with osteocytes from cortical bone shows acid-etched bone, 400x power (courtesy of Lynda Bonewald). A cartoon of an osteocyte is used to show that FGF23 production is increased in the absence of PHEX, DMP1 or ENPP1 (shown in red) suggesting they normally negatively regulate FGF23. FGF23 production is increased in states of PTH excess, or after endogenous supplementation with PTH or calcitriol, suggesting that they normally positively regulate FGF23. FGF23 stability is decreased when GALNT3 is absent, suggesting that glycosylation by GALNT3 modification stabilizes FGF23.

Figure 4.

Cartoon summarizing recent work on control of FGF23 degradation. In the left panel, FGF23 undergoes O-linked glycosylation to FGF23-GalNAc and is secreted intact; non-glycosylated, or under-glycosylated FGF23 is degraded. In the right panel, either inhibition of GALNT3-dependent glycosylation (in $G_s\alpha$ stimulated cells of patients with fibrous dysplasia), or stimulation of cleavage (in the case of iron deficiency) lead to increased amounts of FGF23 fragments in the circulation compared to intact protein. $G_s\alpha$ is a signaling molecule downstream of the PTH receptor as well as other G-protein coupled receptors (thus denoted as PTHR1/other R? (receptors)). It is not known if PTH has effects on FGF23 cleavage. Both patients with fibrous dysplasia and animals with iron deficiency also show increased FGF23 expression in bone. Arrows with an arrowhead at the end signify stimulatory effects, arrows with a line at the end signify inhibitory effects. GalNAc=glycosylated FGF23.

Table 1

Human genetic disorders of phosphate

Disorder	Abbreviation	Gene	Mechanism
Hyperphosphatemic			
Hyperphosphatemic familial tumoral calcinosis type 1, AR	HFTC	GALNT3	FGF23 deficiency
Hyperphosphatemic familial tumoral calcinosis type 2, AR	HFTC	FGF23	FGF23 deficiency
Hyperphosphatemic familial tumoral calcinosis type 3, AR	HFTC	Klotho	FGF23 resistance
Pseudohypoparathyroidism, AD imprinted	PHP1A PHP1B	GNAS	PTH resistance
Familial isolated hypoparathyroidism, AD or AR	FIH	CaSR GCMB PTH	PTH deficiency
Hypophosphatemic			
X-linked hypophosphatemia	XLH	Phex	FGF23 excess
Autosomal dominant hypophosphatemic rickets, AD	ADHR	FGF23	FGF23 excess
Autosomal recessive hypophosphatemic rickets, AR	ARHR1 ARHR2	DMP1 ENPP1	FGF23 excess
Hereditary hypophosphatemic rickets with hypercalciuria, AR	HHRH	SLC34A3 (NPT2c)	Tubular phosphate wasting
Vitamin D resistant rickets, AR	VDDR1 VDDR2	CYP27B1 VDR	1,25(OH) ₂ D deficiency or resistance
Jansen disease, AD		PTHR1	FGF23 excess
Fanconi renotubular syndrome 2, AR	RFS	SLC34A1 (NPT2a)	Tubular phosphate wasting
Fibrous Dysplasia, post-zygotic somatic	FD	GNAS	FGF23 excess

AR=autosomal recessive, AD=autosomal dominant (adapted from Bergwitz and Jüppner 2010)

Table 2

Potential therapeutic targets in CKD.

Intervention	Target	Potential effects	Potential
<i>Anti-FGF23 antibodies</i>	<i>FGF23 intact protein</i>	<i>Slow CKD disease progression</i>	<i>hyperphosphatemia</i>
FGF23 cleavage stimulation	FGF23 intact protein	Reduced full-length FGF23	hyperphosphatemia
<i>Soluble klotho</i>	<i>NPT2a</i>	<i>Renal phosphate wasting</i>	<i>Parathyroid hyperplasia</i>
NPT2 inhibitors	NPT2a NPT2c	Renal phosphate wasting	Fanconi-type syndrome
<u>CYP24 inhibitors</u>	<u>CYP24</u>	<u>Prolonged 1,25(OH)₂D half-life</u>	<u>Hypercalcemia, hyperphosphatemia</u>
<i>PTH analogs</i>	<i>PTHrP</i>	<i>Lower phosphate levels Improved ABD</i>	<i>hypercalcemia</i>

Italicized entries are based on animal studies. Underlined entries are based on human data. Other entries are speculative as discussed in the text based on recent *in vitro* and *in vivo* studies.