Physiology of the Developing Kidney: Disorders and Therapy of Calcium and Phosphorous Homeostasis

11

Amita Sharma, Rajesh V. Thakker, and Harald Jüppner

Contents

A. Sharma (✉)
Department of Pediatrics, Pediatric Nephrology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
e-mail: asharma5@mgh.harvard.edu

R.V. Thakker
Radcliffe Department of Medicine, Academic Endocrine Unit, University of Oxford, OCDEM (Oxford Centre for Diabetes, Endocrinology and Metabolism), The Churchill Hospital Headington, Oxford, UK
e-mail: rajesh.thakker@ndm.ox.ac.uk

H. Jüppner
Departments of Medicine and Pediatrics, Endocrine Unit and Pediatric Nephrology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
e-mail: jueppner@helix.mgh.harvard.edu

E.D. Avner et al. (eds.), *Pediatric Nephrology*,
DOI 10.1007/978-3-662-43596-0_10

Introduction

The regulation of calcium and phosphate homeostasis involves several different hormones that act on the kidney, intestine, and bone. The most important calcium-regulating peptide hormone is parathyroid hormone (PTH). Its production and secretion by the parathyroid glands increases in response to a decrease in the extracellular calcium concentration. PTH increases (1) the 1α-hydroxylase activity in the proximal renal tubules to promote production of the biologically active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) from its precursor 25-hydroxyvitamin D, thereby enhancing intestinal absorption of calcium (and phosphorus); (2) it stimulates bone resorption, thus releasing calcium and (phosphorus); (3) it enhances calcium reabsorption in the distal renal tubules; and (4) it promotes urinary phosphate excretion. These phosphaturic actions of PTH occur within minutes by reducing the expression of two sodium-dependent phosphate cotransporters, NPT2a and NPT2c, in the proximal convoluted tubules. The long-term regulation of phosphate homeostasis involves fibroblast growth factor 23 (FGF23), a more recently discovered hormone made by osteocytes and probably osteoblasts. Like PTH, FGF23 reduces the expression of NPT2a and NPT2c, but the time courses for the effects of both hormones are very different [1–3]. Furthermore, in contrast to the stimulatory actions of PTH on 1α-hydroxylase, FGF23 reduces the expression of this enzyme in the proximal renal tubules, and it enhances 24-hydroxylase, leading to two different mechanisms to a reduction in serum $1, 25(OH)_2D$ levels [4–8].

This chapter will review the physiological and biochemical mechanisms underlying calcium and phosphate homeostasis and the genetic basis of rare inherited disorders that provided important novel insights into the regulation of these minerals [9].

Regulators of Calcium and Phosphate Homeostasis

Parathyroid Hormone (PTH) and PTH-Related Peptide (PTHrP)

The mature secreted form of PTH peptide comprises 84 amino acids, which is derived from a longer prepropeptide (for review, see Ref. [10]). PTH gene transcription (as well as PTH peptide secretion) is regulated primarily by the extracellular concentration of calcium and through a vitamin D response element upstream of the transcription start site [11, 12]. Phosphate affects also parathyroid gland activity, independent of concomitant changes in ambient calcium concentration, parathyroid gland activity; however, these effects take several hours and may result from secondary changes in hormone biosynthesis rather than secretion [13–15].

PTH secretion by the parathyroid glands is regulated through the calcium-sensing receptor (CaSR), which recognizes remarkably small perturbations in calcium and responds quickly by altering PTH secretion. This G protein-coupled receptor is stimulated by extracellular calcium and requires coupling to two closely related G proteins, namely, Gαq and Gα11, to activate the Ca^{+2}/IP3/PKC signaling pathway. Besides being expressed in the chief cells of the parathyroid glands, the CaSR is expressed in the kidneys and in several other tissues, albeit at lower abundance, which are not directly involved in the regulation of calcium homeostasis. In addition to regulating PTH secretion, the CaSR plays an important role in regulating aquaporin trafficking in the kidneys [16].

The PTH-related peptide (PTHrP also known as PTHrH, PTH-related hormone), which was first isolated from tumors that cause the humoral hypercalcemia of malignancy, shares significant amino acid sequence homology with PTH [17–19]. PTH and PTHrP, although distinct

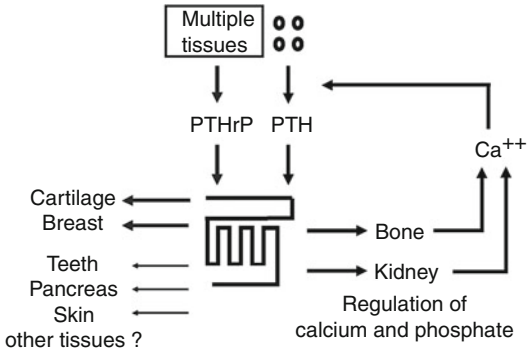

Fig. 1 Parathyroid hormone (PTH) mediates its endocrine actions through the PTH/PTHrP receptor expressed in the kidney and the bone to regulate mineral ion homeostasis and bone metabolism. In numerous other tissues, this G protein-coupled receptor mediates the paracrine actions of PTHrP; particularly important is its role in the growth plate

products of different genes, exhibit considerable functional and structural similarities, including equivalent positions of the boundaries between some of the coding exons and of the adjacent introns; both may have evolved from a shared ancestral gene [10, 20]. PTHrP is a larger, more complex protein than PTH that functions as an autocrine/paracrine rather than an endocrine factor with a little influence on calcium homeostasis except when secreted in large concentrations [21]. Its most prominent functions involve the regulation of chondrocyte proliferation and differentiation, and consequently bone elongation and growth [22]. It also affects mammary gland development and function [23, 24].

PTH and PTHrP both mediate their actions through a common G protein-coupled receptor, the PTH/PTHrP receptor [25, 26] (Fig. 1). In the kidney and bone, it mediates the endocrine actions of PTH. However, the most abundant expression of the PTH/PTHrP receptor occurs in chondrocytes of the metaphyseal growth plate where it mediates the autocrine/paracrine actions of PTHrP, i.e., it delays the hypertrophic differentiation of growth plate chondrocytes [22, 27]. A closely related receptor, the PTH2 receptor, shares more than 50 % homology with the PTH/PTHrP receptor [28]. Its primary ligand, TIP39 (tuberoinfundibular peptide of 39 residues), is involved in nociception and reproduction [29–31].

Vitamin D and Its Metabolites

Most of the vitamin D (D_2 and D_3) in healthy individuals is derived from the precursor 7-dehydrocholestrol through exposure to ultraviolet light. It is made in the skin and is stored in muscle or fat [32, 33]. Presumably through the enzyme CYP2R1 [34, 35], the prohormone undergoes hydroxylation in the liver to form the 25-hydroxyvitamin D metabolite (25(OH)D). In the proximal convoluted tubular cells of the kidney, 25(OH)D is further hydroxylated by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (1α-hydroxylase; CYP27B) to yield the biologically active metabolite 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) [32, 33]. The expression of CYP27B is regulated by extracellular concentrations of ionized calcium, inorganic phosphate, PTH, and FGF23 [36]. $1,25(OH)_2D$ binds in target organs (e.g., the intestine, bones, kidneys, and parathyroids) to the intracellular vitamin D receptor (VDR) [37] and thereby activates the transcription of genes in the bone, kidney, and enterocytes that help increase gut absorption of calcium, reduce urinary calcium losses, and increase bone resorption, thereby ensuring adequate extracellular concentration of calcium and phosphate [33, 37]. Homozygous or compound heterozygous mutations in CYP27B, CYP2R1, or VDR lead to hypocalcemia, which increases PTH secretion, thus enhancing urinary phosphate excretion, which leads to the development of rickets/osteomalacia [32–35].

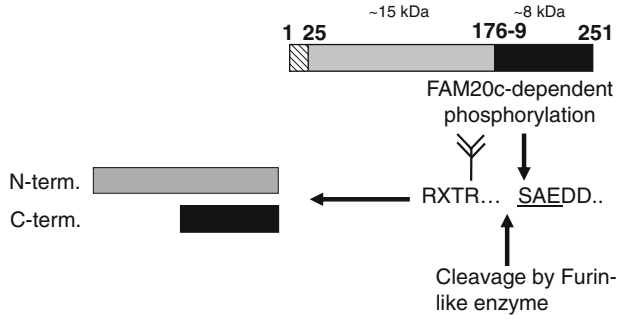

Fig. 2 The primary structure of FGF23. The C-terminal and the N-terminal portions of FGF23 are connected by an "RXXR" motif, which is the recognition site for a furin-like protease. Mutations at this site make FGF23 resistant to the cleavage by a furin-like protease, thereby stabilizing the intact bioactive FGF23 molecule

Fibroblast Growth Factor 23 (FGF23) and Other Proteins with Phosphaturic Properties

Fibroblast growth factor 23 (FGF23), which is probably the most important phosphate-regulating hormone, belongs to a large family of structurally related proteins. FGF23 was discovered through two independent approaches, namely, positional cloning to define the molecular cause of autosomal dominant hypophosphatemic rickets (ADHR) [38] and sequence analysis of cDNAs derived from rare mesenchymal tumors that cause tumor-induced osteomalacia (TIO) [6, 39]. The FGF23 gene consists of 3 exons that encode a 251-amino acid precursor protein comprising a hydrophobic leader sequence (residues 1–24), thus allowing its secretion into the blood circulation (Fig. 2). The Golgi casein kinase Fam20C phosphorylates Ser^{180} of FGF23, which reduces O-glycosylation of Thr^{178} by the polypeptide *N*-acetylgalactosaminyltransferase 3 (GALNT3), thus making the hormone prone to proteolytic cleavage between Arg^{179} and Ser^{180} by the subtilisin-like proprotein convertase SPC2 [40, 41]. Only full-length FGF23 has phosphaturic activity [7], yet C-terminal fragments appear to have some biological activity since they can antagonize the actions of the intact hormone [42] (Fig. 2).

FGF23 is most closely related to fibroblast growth factors 21 and 19, but shows limited homology also with other fibroblast growth factors [38, 43]. FGF23 mRNA could not be detected by Northern blot analysis in normal tissues, but it has been identified by reverse transcriptase (RT)-PCR in the heart, liver, thymus, small intestine, and brain [38, 43]. The most abundant expression of FGF23 occurs in the bone cells, particularly in osteocytes, which represent the largest population of bone cells [44–47]. Its regulation remains incompletely understood, but mice that are null for DMP1, ENPP1, or Fam20C show an increased expression of FGF23, suggesting that each of these proteins are negative regulators of FGF23 expression and/or activity [48–50]. Consistent with these findings, humans with inactivating mutations in any of these three genes show increased urinary phosphate excretion leading to hypophosphatemia [48, 51–57].

In the presence of αKlotho, a protein associated with longevity [58, 59], FGF23 binds with high affinity to FGFR1 [59, 60] (Fig. 3). Consistent with a role of Klotho in the regulation of phosphate homeostasis, mice that are "null" for Klotho develop severe hyperphosphatemia due to diminished urinary phosphate excretion. These animals furthermore show elevated 1, 25$(OH)_2$D levels, i.e., findings that are similar to those observed in the FGF23-null mice [4, 45, 46]. Klotho-null mice have dramatically elevated FGF23 levels [60, 61].

FGF23-null mice ($FGF23^{-/-}$) develop hyperphosphatemia and elevated serum 1,25 $(OH)_2$D concentration, and they die prematurely, secondary to renal failure because of glomerular capillary calcifications [45, 62, 63]. $FGF23^{-/-}$ animals furthermore show reduced bone turnover, an unexpected increase in osteoid, and diminished osteoblast and osteoclast number and activity.

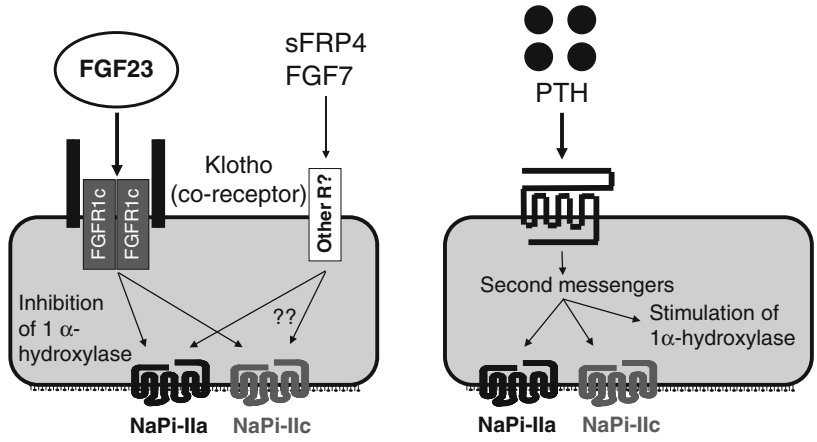

Fig. 3 Effect of FGF23 and PTH on the proximal tubular cells. (**a**) FGF23 binds to the FGFR1c and Klotho complex and inhibits 1α-hydroxylase. At the same time, this cascade inhibits the apical expression of NaPi-IIa and NaPi-IIc. (**b**) PTH binds to the PTHR(GPCR) and inhibits the expression of NaPi-IIa and NaPi-IIc, whereas it simulates 1α-hydroxylase activity. Thus, FGF23 only acts as stimulate phosphaturia, and PTH acts both P and Ca homeostasis simultaneously

Animals overexpressing FGF23 transgenically show increased unmineralized osteoid because of increased urinary phosphate excretion leading to hypophosphatemia as well as significant widening of growth plates leading to deformities of weight-bearing bones [45, 64].

In addition to FGF23, other cDNAs were overrepresented in libraries derived from tumors that cause oncogenic osteomalacia [6, 65, 66]. These included DMP1, MEPE, sFRP4, and FGF-7 and were implicated in phosphate handling in vivo and/or in vitro, suggesting that "phosphatonins" other than FGF23 may be involved in the renal regulation of phosphate homeostasis [66–68]. Their role needs to be elucidated more as the ablation of sFRP4 in mice at least does not affect phosphate homeostasis [69].

Hypercalcemia and Hypophosphatemia Due to Increased Parathyroid Hormone Secretion

Hypercalcemia can be observed in several different nonfamilial (sporadic) or familial disorders. Besides physical examination and a careful review of the family history, the evaluation of several additional laboratory parameters is required for diagnostic work-up (Fig. 4).

Parathyroid Tumors

Increased parathyroid gland activity can be seen in patients with multiple gland hyperplasia, adenomas, and, rarely, parathyroid carcinoma. Two principal defects can lead to the development of parathyroid tumors: (1) a heterozygous mutation that enhances the activity of a gene (gain-of-function mutation), which is therefore referred to as a proto-oncogene, or (2) homozygous loss-of-function mutation in a tumor-suppressor gene, which is therefore referred to as a recessive oncogene. Parathyroid tumors usually occur as an isolated and sporadic endocrinopathy or as part of inherited tumor syndromes [70] such as the multiple endocrine neoplasias (MEN) or hereditary hyperparathyroidism with jaw tumors [71, 72]. Sporadic parathyroid tumors can be caused by single somatic mutations that lead to the activation or overexpression of proto-oncogenes, such as PRAD1 (*par*athyroid *a*denoma *1*) or RET (mutated in MEN2), or by mutations in tumor-suppressor genes – predicted to be located on several different chromosomes, for example, chromosome 1p (RIZ1) and 11q3 (MEN1) – that allow

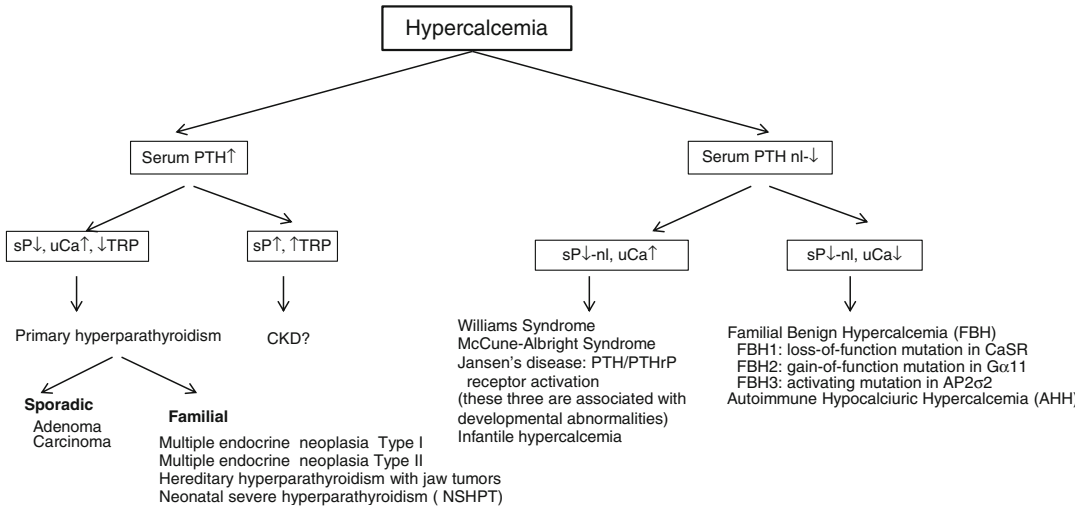

Fig. 4 Flow diagram for the work-up of patients with hypercalcemia

for the clonal expansion of a single parathyroid cell and its progeny (see Ref. [73] for a detailed review of this topic in adults). In children, parathyroid tumors are rare, with adenomas being the most common abnormality [74].

Hyperparathyroidism in Chronic Kidney Disease

Chronic overstimulation of the parathyroid glands frequently occurs in patients with chronic kidney disease (CKD), which may lead to the development of hyperplasia transitioning to adenoma (tertiary hyperparathyroidism) due to the clonal expansion of one or several parathyroid cells [75], through a process possibly involving the reduced expression of different cyclin-dependent kinase inhibitors [76] and an abnormal WNT β-catenin signaling pathway [77]. Increased levels of biologically active circulating FGF23 [78–81] and decreased levels of $1,25(OH)_2D$ [5, 82–84] contribute to the development of hyperparathyroidism.

Non-syndromic Isolated Hyperparathyroidism

PTH structural changes as the cause of hyperparathyroidism appear to be rare. One patient, who presented with hypercalcemia and hypophosphatemia, yet undetectable levels of PTH in the circulation, was reported. A single parathyroid adenoma was identified that secreted a mutant PTH molecule, which was truncated after amino acid residue 52, thus explaining why different two-site immunometric PTH assays had been unable to detect elevated circulating levels of this hormone [85]. After surgical removal of the adenoma, clinical symptoms and biochemical abnormalities resolved.

Hypercalcemic Disorders Without Elevated Parathyroid Hormone Secretion

Disorders of the Calcium-Sensing Receptor (CaSR) and the Downstream Signaling Molecules

CaSR is a G protein-coupled receptor (GPCR) located on chromosome 3q21.1 [86] that couples through Gαq and Gα11 to the Ca^{2+}/IP3/PKC signaling pathway. Three hypocalciuric hypercalcemic disorders are caused by abnormalities in calcium-sensing receptor (CaSR) function: (1) familial benign hypercalcemia (*FBH*), also referred to as familial hypocalciuric hypercalcemia (*FHH)*, (2) neonatal severe

hyperparathyroidism (*NSHPT*), and (3) autoimmune hypocalciuric hypercalcemia (*AHH*) caused by acquired autoantibodies against the *CaSR*.

Familial Hypocalciuric Hypercalcemia (FHH): FHH1 (CaSR), FHH2 (Gα11), FHH3 (AP2σ1)

FHH is a genetically heterogeneous disorder which may be inherited as an autosomal dominant trait, although patients often have no family history as they may have developed a de novo mutation. Affected patients are usually asymptomatic or have nonspecific symptoms such as fatigue, weakness, painful joints, and headache, and the diagnosis is often only suspected after routine biochemical screening shows elevated serum calcium levels.

Three variants of *FHH* have been defined at the molecular level; these are (1) loss-of-function mutations in CaSR *(FHH1)* [87–92]; (2) loss-of-function in Gα11, the signaling protein at the CaSR (*FHH2)* [93, 94]; and (3) loss-of-function mutations in AP2σ1 (adapter protein-2 sigma subunit), a central component of clathrin-coated vesicles (*FHH* 3) [95]. *FHH2* and FHH3 families were initially linked genetically to chromosome 19p (FHH_{19p}) and 19q13 [96] (FHH_{OK}), respectively [97, 98]. Heterozygous loss-of-function CaSR mutations were found in approximately two-thirds of the affected members of investigated *FHH* kindreds *(FHH1)* [87, 92, 99, 100]. CaSR mutations cluster around low-affinity calcium-binding sites (that are similar to calsequestrin) containing aspartate- and glutamate-rich regions (codons 39–300) within the extracellular domain of the receptor [101, 102] and show gene-dosage effect [87–92, 102]; for details of CaSR mutations, visit http://www.casrdb.mcgill.ca. Another heterozygous mutation in exon 4 of *CaSR* gene (F180C, TTC > TGC) leads to *FHH* phenotype only in vitamin D deficiency state. Vitamin D deficiency probably impaired *CaSR* expression, thus leading to increased PTH secretion; consistent with this conclusion, vitamin D supplementation resulted in the normalization of PTH levels [103]. Individuals in *FHH* families carrying the CaSR mutation L137P have shown increased susceptibility for chronic pancreatitis, when compounded with a mutation (N34S) in the pancreatic secretory trypsin inhibitor gene (*SPINK1*) [104].

Neonatal Severe Hyperparathyroidism (NSHPT)

Patients with severe neonatal hyperparathyroidism usually have homozygous or compound heterozygous CaSR mutations that are both inactivating [87, 88, 90, 105–107]. Infants with NSHPT usually exhibit severe bone disease driven by markedly increased PTH, leading to significant mortality, if left untreated [108, 109]. Some patients with sporadic neonatal hyperparathyroidism have been reported to carry de novo heterozygous CaSR mutations [89], thereby suggesting the involvement of factors other than the dosage of the mutant gene or dominant-negative actions on the wild-type CaSR [105]. A novel heterozygous de novo mutation (R551K) was shown recently to cause NSHPT, which gradually reverted to asymptomatic FBH without the need for surgical intervention [110].

Autoimmune Hypocalciuric Hypercalcemia (AHH)

AHH is an acquired disorder with circulating antibodies directed against the extracellular domain of the *CaSR*. Some of these antibodies stimulate the release of PTH when tested with dispersed human parathyroid cells in vitro, probably by reducing the activation of the CaSR by extracellular calcium [111]. *AHH* diagnosis should be considered for patients who have hyperparathyroidism in combination with other autoimmune disorders [111, 112] and lack mutations associated with *FHH*. *AHH* was initially described in four individuals from two unrelated kindreds. Among them, three patients had antithyroid antibodies, and one had celiac sprue with antigliadin and anti-endomyseal antibodies [111]. Another patient described had an IgG4 blocking autoantibody against CaSR. Regression of biochemical abnormalities and autoimmune dysregulation followed glucocorticoid treatment [112]. An autoantibody isolated from a patient with *AHH* caused distinct conformational changes in CaSR favoring coupling to Gα11 and uncoupling from Gi. These allosteric changes

Fig. 5 Patient with a severe form of Jansen's metaphyseal chondrodysplasia. (From [114], with permission)

occurred at a site in close proximity to the binding site for calcimimetics [113].

Jansen's Metaphyseal Chondrodysplasia (JMC)

JMC is a rare autosomal dominant disease that is characterized by short-limbed dwarfism caused by an abnormal regulation of chondrocyte proliferation and differentiation in the metaphyseal growth plate [114] (Figs. 5 and 6) that is usually associated with severe hypercalcemia and hypophosphatemia, despite normal or undetectable serum levels of PTH or PTHrP [115]. JMC is caused by heterozygous mutations in the PTH/PTHrP receptor that lead to constitutive PTH- and PTHrP-independent receptor activation [116–118]. Since the PTH/PTHrP receptor is most abundantly expressed in the kidney, bone, and growth plates, these findings provided a likely explanation for the abnormalities observed in mineral homeostasis and for the associated defects in chondrocyte growth and differentiation. Several different heterozygous mutations in the PTH/PTHrP receptor have been identified in the severe form of JMC; these involve codon 223 (His → Arg), codon 410 (Thr → Pro or Arg), and codon 458 (Ile → Arg or Lys). The expression of these mutant receptors in suitable cells resulted in constitutive agonist-independent accumulation of cAMP, while the basal accumulation of inositol phosphates was not measurably increased. The H223R mutation is the most frequent cause of JMC, while all other mutations were found in only single patients [116–122]. Transgenic mice, in which the expression of a PTH/PTHrP receptor carrying the H223R mutation was targeted to the growth plate by the rat α1 (II) collagen promoter, showed a significant delay in chondrocyte differentiation, supporting the conclusion that the defect in endochondral bone formation in JMC patients is caused by the constitutively active mutant receptor [123]. The slowed differentiation of growth plate chondrocytes was associated with an upregulation of cyclin- and E2F-dependent gene expression, indicating that the PTH/PTHrP receptor controls the timing of cell cycle exit and the onset of differentiation of chondrocytes [124]. The Thr410Arg mutation in PTH/PTHrP receptor leads to less pronounced skeletal and laboratory abnormalities, i.e., only mild skeletal dysplasia and relatively normal stature and high-normal plasma calcium concentration associated with normal or suppressed serum PTH levels and with hypercalciuria leading to nephrolithiasis in two individuals [125]. In comparison to PTH/PTHrP receptors with the Thr410Pro mutation, the Thr410Arg mutation showed less pronounced agonist-independent cAMP accumulation in vitro [117, 126].

Williams Syndrome

Williams syndrome (WS) is a hemizygous continuous deletion syndrome caused by the deletion of 25–30 genes on chromosome 7 q11.23. WS is characterized by vascular stenosis, hypertension, elfin-like facies, developmental delay, and typical behavioral features. Endocrine abnormalities including hypercalcemia, diabetes mellitus, and subclinical hypothyroidism might be present. About 20 % of affected children may present with congenital anomalies of the kidney and

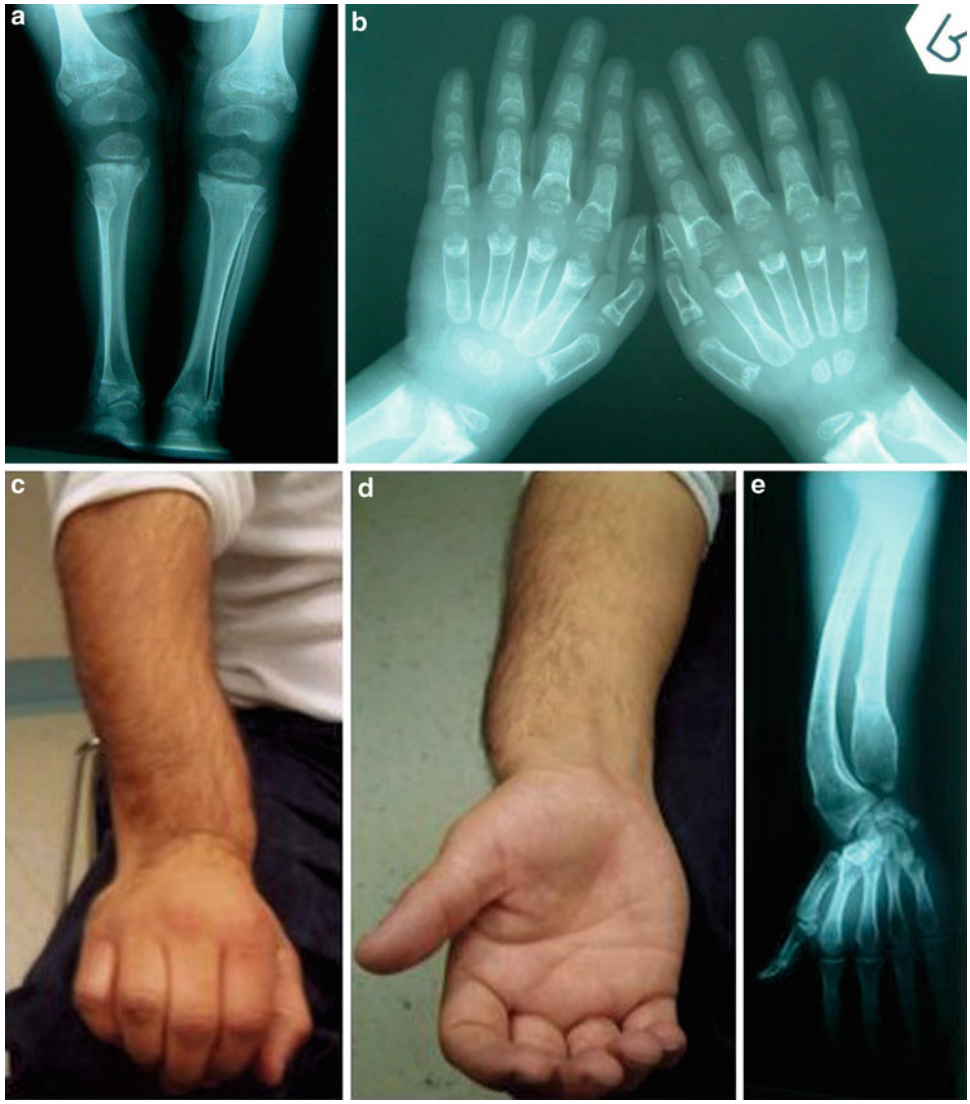

Fig. 6 Radio- and photographs of patients with a relatively mild form of Jansen's disease (From [125] with permission)

urinary tract, hypercalciuria, or dysfunctional voiding [127].

Of the deleted genes, elastin is the most important. The ablation of elastin gene in mice results in vascular abnormalities similar to those observed in WS patients [128]. Homozygous deletion at the elastin locus was found in over 90 % of patients with the classical Williams phenotype [129], and a series of 235 WS patients revealed submicroscopic deletions of the elastin gene in 96 % of the investigated individuals [130], thus making it an important diagnostic tool. Other deleted proteins, like LIM-kinase [131], the cytoplasmic linker protein-115 (CYLN2), and the transcription factors GTF2I and GTF2IRD1 [132], may contribute to some of the distinct neurological and cognitive deficits. In contrast, *NCF1* deletions are protective against hypertension [133]. In addition, genes flanking aneuploid genes, some of which are located several megabases away from the deletion, may contribute to the observed phenotypic variation [134, 135].

The etiology of hypercalcemia is less clear. Although it is clinically not severe in most cases, some affected individuals require therapeutic interventions with bisphosphonates [136]. The calcitonin receptor gene, located on chromosome 7q21, is not included in the deletions identified in WS [137]. Increased calcium retention, sensitivity, or abnormal synthesis or degradation of 1,25 $(OH)_2$ vitamin D has been postulated to be causal [138, 139]. Claudin 3 and 4 though deleted were not found to be causative for hypercalcemia [140]. The transient receptor potential cation channel 3 (TRPC3) overexpressed in the intestines and kidneys of a WS patient has been shown to increase calcium absorption in the gut and reabsorption in the kidneys [141].

Infantile Hypercalcemia: CYP24A1 Deficiency

Initially referred to as idiopathic infantile hypercalcemia (IIH), this disorder was shown to be caused by homozygous or compound heterozygous mutations in the gene encoding the 24-hydroxylase (CYP24A1), the enzyme that metabolizes and thus inactivates the biologically active 1,25$(OH)_2$D [142–146]. Affected infants develop often severe hypercalcemia and hypercalciuria leading to nephrocalcinosis and failure to thrive. Besides elevated plasma and urinary calcium levels, 1,25$(OH)_2$D levels are increased, which was shown in one child to dramatically enhance intestinal calcium absorption [143], thereby suppressing circulating PTH concentrations through two mechanisms, i.e., elevated plasma calcium and 1,25$(OH)_2$ vitamin D concentration.

Hypocalcemia and Hyperphosphatemia Due to Reduced Parathyroid Hormone Activity

As for hypercalcemic disorders, patients who present with hypocalcemia require careful clinical evaluation, as well as the assessment of laboratory parameters in serum and urine, and a detailed review of the family history [147] (Fig. 7).

Hypoparathyroidism

Hypoparathyroidism comprises a heterogeneous group of disorders presenting with hypocalcemia

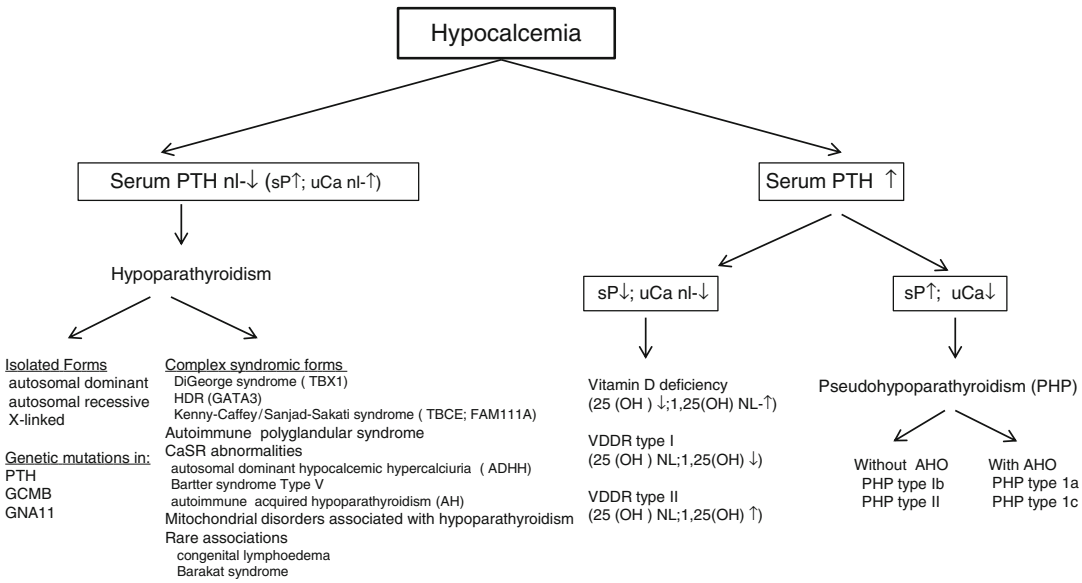

Fig. 7 Flow diagram for the work-up of patients with hypocalcemia

of varying severity, inappropriately normal or elevated urinary calcium excretion, and hyperphosphatemia, yet normal or diminished PTH levels. Hypoparathyroidism may be nonfamilial (sporadic) or familial, and it may occur as an isolated defect or as a component of disorders with additional manifestations, such as pluriglandular autoimmune disorder or various developmental abnormalities, e.g., DiGeorge syndrome (DGS). Familial isolated hypoparathyroidism can present anytime from early infancy well into adulthood.

The main treatment options available for patients with acute or chronic hypoparathyroidism are calcium salts, vitamin D or vitamin D analogues, and drugs that increase renal tubular reabsorption of calcium (i.e., thiazides). The parathyroid hormone-dependent renal production of 1,25-dihydroxyvitamin D is deficient in all hypoparathyroid states. Consequently, therapy with a vitamin D analogue is used to improve serum calcium levels. However, because of the absence of functional PTH and the lack of PTH-dependent calcium reabsorption in the distal renal tubules, patients affected by hypoparathyroidism frequently develop hypercalciuria and nephrolithiasis, and chronic kidney disease, even if attempts are made to maintain plasma calcium within the lower end of the normal range [148]. Considerable efforts were therefore made to treat patients with recombinant PTH(1-34) or PTH(1-84) [149–155]. Compared with twice-daily delivery, pump delivery of PTH(1-34) appears to provide the most promising modality for improving calcium homeostasis and bone turnover in children with severe congenital hypoparathyroidism [156, 157].

Parathyroid Hormone (PTH) Gene Abnormalities

Preproparathyroid hormone (preproPTH), the PTH precursor, contains a 25-residue amino-terminal signal sequence followed by a 6-residue pro-specific peptide and the mature hormone. The hydrophobic core of the human preproPTH signal peptide is composed of 12 contiguous uncharged amino acids (residues −5 to −16 of the signal peptide).

Several different PTH gene mutations were identified in patients with autosomal dominant or autosomal recessive isolated hypoparathyroidism. A single-base substitution (T → C) resulted in the substitution of arginine (CGT) at position 18 in the signal peptide for cysteine (TGT), thus disrupting the hydrophobic core of the signal sequence, which is required by the secreted proteins for efficient translocation across the endoplasmic reticulum [158]. Another single-point mutation changes cysteine to arginine at the −8 position of the signal peptide, which causes interference with the normal targeting and processing of secretory proteins, including the normal PTH precursor, suggesting that the mutant gene product exerts a dominant-negative effect in vitro by trapping the hormone intracellularly, predominantly in endoplasmic reticulum (ER) [159], thereby causing stress-induced cell death [160]. In another family, a single-base substitution (T → C) involving codon 23 of exon 2 was detected, which resulted in the substitution of proline (CCG) for the normal serine (TCG) in the signal peptide [161]. This mutation at the −3 position of the preproPTH protein cleavage site most likely disrupts cleavage of the mutant precursor molecule and prevents the efficient formation and secretion of PTH [161]. The affected individuals of one other kindred with autosomal recessive isolated hypoparathyroidism showed a single-base transition (G → C) at position 1 of intron 2 of the gene encoding PTH. This mutation resulted in the deletion of exon 2, which encodes the initiation codon and the signal peptide, thereby causing parathyroid hormone deficiency [162]. A nonsense mutation involving codon 23 (Ser23Stop) was recently reported in a girl with autosomal recessive isolated hypoparathyroidism [163], and a heterozygous T to C point mutation was identified that eliminates the initiator methionine, thereby deleting the first six amino acids of the signal peptide [164].

GCM2 Abnormalities

Glial cells missing 2 (GCM2), the mammalian homolog of the Drosophila Gcm2 gene, encodes a 506-amino acid parathyroid-specific transcription factor, which contributes to the regulation of

PTH gene expression [165]. Mice that are homozygous for the deletion of GCM2 (the murine homolog) lack parathyroid glands, and these animals develop hypocalcemia and hyperphosphatemia without a compensatory increase in PTHrP or $1,25(OH)_2$ vitamin D levels [166]. GCM2-null mice revealed a small cluster of PTH-expressing cells under the thymic capsule; however, the amount of PTH was insufficient to prevent hypocalcemia [167].

The gene encoding GCM2 is located on chromosome 6p23–24, and isolated hypoparathyroidism can be caused by inactivating mutations on both parental alleles or by a dominant-negative heterozygous mutation. The first GCM2 mutation, a large homozygous intragenic deletion, was identified in the proband of an extended kindred with an autosomal recessive form of isolated hypoparathyroidism [168]. Subsequently, homozygous mutations were identified as additional causes of hypoparathyroidism; these affect amino acid residues 63 (G63S) [169] or 47 (R47L) [170], as well as several other residues [171–174]. Two closely related heterozygous GCM2 mutations were furthermore identified in two families in which hypoparathyroidism follows an autosomal dominant mode of inheritance [175, 176]. Both mutations lead to a shift in the open reading frame and the replacement of the putative transactivation domain within the carboxyl-terminal region by unrelated amino acid sequence, and both mutant proteins have a dominant-negative effect on the wild-type GCM2 protein. A similar mechanism may apply to the Asn502His mutation, which localizes to the nucleus and retains the ability to bind to the GCM-consensus DNA recognition motif but shows impaired gene transactivation and a dominant-negative effect on the wild-type protein [173]. For a large number of patients with isolated hypoparathyroidism, however, no disease-causing mutation has yet been identified [171], making it likely that mutations in additional as-of-yet unidentified genes can also cause hypoparathyroidism.

X-Linked Recessive Hypoparathyroidism

X-linked recessive hypoparathyroidism has been reported in two related multigenerational kindreds [177]. The relatedness of these two kindreds was established by demonstrating an identical mitochondrial DNA sequence, inherited via the maternal lineage, in affected males from the two families [178]. Affected males suffered from infantile onset of epilepsy and hypocalcemia [179]. Studies utilizing X-linked polymorphic markers in these families localized the mutant gene to chromosome Xq26-q27 [180].

Characterization of 906 kb region on Xq27 by combined analysis of single nucleotide polymorphisms and sequence-tagged site identified a 23–25 kb deletion, which did not contain genes. However, DNA fiber-FISH and pulsed-field gel electrophoresis revealed an approximately 340 kb insertion that replaced the deleted fragment and a molecular deletional-insertion that involved chromosome 2p25 and Xq27 [181]. This complex deletion-insertion {del(X) (q27.1) inv ins (X;2) (q27.1; p25.3)} is located 67 kb downstream of the SOX3 gene. The developing parathyroid tissue of mouse embryos has strong SOX expression. Thus, this mutation may have a position effect on SOX3 expression. These findings added SOX3 to the growing list of transcription factors, including GCM2, GATA3, TBX1, HOXA3, PAX1, and PAX9, that operate in parathyroid development [181].

Autoimmune Pluriglandular Hypoparathyroidism

Autoimmune pluriglandular syndromes associated with hypoparathyroidism can be subdivided into three subtypes: (1) APS1, (2) APS3 (which is associated with thyroid autoimmunity), and (3) APS4 (which is associated with other autoimmune disorders).

APS1 or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive disease with a high incidence in isolated subpopulations in Central and Eastern Finland [182], which usually becomes manifest during childhood. Establishing the diagnosis requires the presence of at least two of three major components: hypoparathyroidism, candidiasis, and adrenal insufficiency; however, hypoparathyroidism may be the only manifestation of the syndrome. APS1 is caused by mutations within the autoimmune regulator (AIRE) gene

located on chromosome 21 (21q22). As part of this syndrome, autoantibodies against NACHT leucine-rich repeat protein 5 (NALP5Abs) can be detected. Non-APS forms of hypoparathyroidism show an association with class I human leukocyte antigen (HLA) allele A*2601 and with class II HLA alleles DRB1*01 and DRB1*09 [183].

Linkage studies of Finnish families mapped the APECED gene to chromosome 21q22.3 [184]. Further, positional cloning approaches led to the isolation AIRE (*a*uto*i*mmune *re*gulator), which encodes a 545-amino acid protein. Specific domains of AIRE protein indicate that it is involved in transcriptional processes, including (i) the amino-terminal HSR domain, (ii) nuclear localization signal (NLS), (iii) a SAND domain, (iv) two plant homeodomain (PHD) type zinc fingers, and (v) four LXXLL motifs [185]. To date, more than 50 different APS1-causing mutations have been established in affected patients. Though mutations are distributed throughout the coding region of the gene, most mutations are located in the amino-terminal HSR domain. The R257X mutation in SAND domain is the most prevalent mutation among Finnish patients, accounting for 83 % of the disease alleles [185, 186]. This particular mutation is also frequently found in Central and Eastern European and Northern Italian populations, indicating an early introduction of the mutation into Caucasian populations [186, 187]. Characteristic mutations have been reported also for various other ethnicities [188–192]. Recently, a novel mechanism of AIRE dysregulation has been described in which miR-220b inhibits AIRE gene translation through the 3'UTR [193].

AIRE has been shown to regulate the elimination of organ-specific T cells in the thymus and thus failure to delete forbidden T cells [194] and to disrupt of the nuclear organization [195], thereby resulting in failure to establish immunologic tolerance. A unique G228W variant in the SAND domain appears to inhibit wild-type AIRE from reaching the sites of active transcription in medullary thymic epithelial cells. This resulted in the failure to delete T cells reactive against antigens specific for the thymus, leading to autoimmunity. Thus, the AIRE-mediated dominant-negative effect may cause autoimmune predisposition to phenotypes distinct from APS [196]. In addition, there is a downstream abnormality as activated $CD4^+$ T cells of APECED demonstrate a selective IL-22 defect [197].

APS1 patients with hypoparathyroidism can have antibodies directed against the CaSR, which leads to a decrease in PTH secretion and thus hypocalcemia [198]. The NACHT leucine-rich repeat protein 5 (NALP5), which is predominantly expressed in the cytoplasm of parathyroid chief cells, is another antigen, autoantibodies against which can be responsible for some forms of hypoparathyroidism. NALP5-specific autoantibodies were detected in almost half of the patients with APS1 and hypoparathyroidism, but were absent in all APS1 patients without hypoparathyroidism [199]. However, the pathological significance of these antibodies has been questioned [200]. Instead of seeking AIRE mutations, which is a cumbersome process, IgG-neutralizing autoantibodies against type I interferon can be used as a diagnostic criterion [201] as high titers of these antibodies were found in 100 % of Finnish and Norwegian patients with two prevalent AIRE truncations [202]. Furthermore, rising titers of anti-cytokine antibodies may precede clinical presentation [203].

DiGeorge Syndrome

DiGeorge syndrome (DGS) is associated with the absence or hypoplasia of the thymus and the parathyroid glands, cardiovascular anomalies, and craniofacial dysmorphism [204]. Most DGS cases that result from the deletion of the 250–3,000 kb critical region that contains approximately 30 genes [205, 206] are designated as DGS type 1 (DGS1) [207]. DGS2 is associated with the deletion locus on chromosome 10p [208]. Approximately 17 % of patients with the phenotypic features of DGS have no detectable genomic deletion [209].

Hypocalcemia, considered one of the cardinal features of DGS, is invariably due to hypoparathyroidism as originally described by DiGeorge in 1965 and documented by aplasia or hypoplasia of parathyroid glands at surgery or autopsy [210].

Hypocalcemia was noticed in 203/340 subjects from a large European cohort; the majority of affected individuals were found to have transient hypocalcemia [211]. Similar transient hypocalcemia occurs at birth due to the abrupt cessation of active maternal calcium supply in combination with birth stress. Increased demands on parathyroid reserve resolve as stress dissipates. Symptomatic or latent hypocalcemia may also be precipitated by the stress of surgery, pregnancy, or puberty [212]. Point prevalence of hypocalcemia outside the neonatal period was 30 % in 27 subjects of all ages [213]. EDTA infusion can be used to unmask latent hypocalcemia [214].

Treatment is aimed at keeping serum calcium in low-normal range since the absence of PTH leads to high or inappropriately normal urinary excretion of calcium, which increases the risk of renal calcification and nephrolithiasis.

The deleted region in DGS1 contains several genes [207, 215–217]. The ablation of several of these genes causes developmental abnormalities of the pharyngeal arches in transgenic mice [218–220]. Tbx1-ablated transgenic mice [220] and humans with point mutations of TBX1 have the DGS1 phenotype [221]; mutations in this gene are therefore likely to cause DGS1 [222]. TBX1 is a DNA-binding transcriptional factor of the T-Box family with an important role in organogenesis and pattern formation. Tbx1-null mutant mice ($Tbx1^{-/-}$) had all the developmental anomalies of DGS1, while haploinsufficiency ($Tbx1^{+/-}$) was associated with a milder phenotype. The spectrum of DGS1 malformations is thus elicited in a dose-dependent manner [223], suggesting that the Tbx1 dose can be modulated by other modifying genes, thus causing phenotypic variability [224–227].

Hypoparathyroidism, Deafness, and Renal Anomalies (HDR) Syndrome

The combined occurrence of hypoparathyroidism, deafness, and renal dysplasia (HDR) as an autosomal dominant trait was reported in one family in 1992 [228]. Patients had asymptomatic hypocalcemia with undetectable or inappropriately normal serum concentrations of PTH and normal brisk increases in plasma cAMP in response to the infusion of PTH. The patients also had bilateral, symmetrical, nonprogressive sensorineural deafness involving all frequencies. The renal abnormalities consisted mainly of bilateral cysts that compressed the glomeruli and tubules, leading to renal impairment in some patients. Cytogenetic abnormalities were not detected and abnormalities of the PTH gene were excluded.

Deletion mapping studies in two unrelated HDR patients showed cytogenic abnormalities involving chromosome 10p14-10pter [229]. These two patients suffered from hypoparathyroidism, deafness, and growth and mental retardation; one patient also had a solitary dysplastic kidney with vesicoureteric reflux and a uterus bicornuis unicollis, and the other HDR patient also had cartilaginous exostoses and was shown to have a complex reciprocal insertional translocation of chromosomes 10p and 8q. Neither of these patients had immunodeficiency or heart defects, which are key features of DGS2 (see above), and further studies defined two nonoverlapping regions; thus, the DGS2 region was located on 10p13-14 and HDR on 10p14-10pter. It is important to note that HDR patients with GATA3 haploinsufficiency do not have immune deficiency. Similarly, the facial dysmorphism, growth, and developmental delay, commonly seen in patients with larger 10p deletions, were absent in the HDR patients carrying GATA3 mutations, further indicating that these features were likely due to other genes on 10p [230]. Deletion mapping studies in two other HDR patients further defined a critical 200 kb region that contained GATA3 [230], which belongs to a family of zinc finger transcription factors that bind to the consensus DNA sequence and are involved in vertebrae embryonic development. DNA sequence analysis in other HDR patients identified mutations that resulted in a haploinsufficiency and loss of GATA3 function [230–232]. GATA3 has 2 zinc fingers. The C-terminal finger (ZnF2) binds DNA, while the N-terminal finger (ZnF1) stabilizes this DNA binding and interacts with other zinc finger proteins, such as the Friends of GATA (FOG) [233]. HDR-associated mutations involving GATA3 ZnF2 or the adjacent basic amino acids were found to result in a loss of DNA binding,

while those involving ZnF1 either lead to a loss of interaction with FOG2 ZnFs or altered DNA-binding affinity [232]. These findings are consistent with the proposed 3-dimensional model of GATA3 ZnF1, which has separate DNA and protein binding surfaces [232, 234]. Electrophoretic mobility shift assays (EMSAs) revealed three classes of GATA3 mutations: those that lead to a loss of DNA binding (over 90 % of all mutations), those that lead to a loss of the carboxyl-terminal zinc finger and result in reduced DNA-binding affinity, and those (e.g., Leu348Arg) that do not alter DNA binding or the affinity but likely induce conformational change in GATA3 [235]. Furthermore, a heterozygous mutation, 432insG, has been described, which introduces a premature stop codon at exon 4 (K302X), resulting in a loss of both zinc finger domains of the GATA3 protein [236]. No mutations were identified in patients with isolated hypoparathyroidism, indicating that GATA3 abnormalities are more likely to result in two or more of the phenotypic features of the HDR syndrome and not in isolated disease affecting only the regulation of calcium homeostasis [235]. The co-occurrence of the 22q11 deletion and the HDR due to a de novo deletion in chromosome 10p14 has been described in a Japanese boy with severe phenotype, including progressive renal failure and severe intellectual disabilities [237].

The HDR phenotype is consistent with the expression pattern of GATA3 during human and mouse embryogenesis in the developing kidney, otic vesicle, and parathyroids. Homozygous ablation of GATA3 in mice leads to CNS defects, but heterozygous GATA3-null animals were initially reported to have no abnormalities [238]. However, further studies have revealed that these heterozygous mice have a progressive hearing loss associated with continuous morphological degeneration of the cochlea [239, 240] and that they also have hypoparathyroidism [241].

Mitochondrial Disorders Associated with Hypoparathyroidism

Hypoparathyroidism has been reported to occur in three disorders associated with mitochondrial dysfunction:(1) Kearns-Sayre syndrome (KSS), (2) MELAS syndrome, and (3) mitochondrial trifunctional protein deficiency syndrome (MTPDS). Both the KSS and MELAS syndromes have been reported to occur with insulin-dependent diabetes mellitus and hypoparathyroidism [242, 243]. A point mutation in the mitochondrial gene tRNA leucine (UUR) has been reported in one patient with the MELAS syndrome who also suffered from hypoparathyroidism and diabetes mellitus [101]. Large deletions, consisting of 6,741 and 6,903 base pairs and involving >38 % of the mitochondrial genome, have been reported in other patients who suffered from hypoparathyroidism and sensorineural deafness [244]. Rearrangements and duplication of mitochondrial DNA have also been reported in KSS. MTPDS is a disorder of fatty acid oxidation that is associated with peripheral neuropathy, pigmentary retinopathy, and acute fatty liver degeneration in pregnant women who carry an affected fetus. Hypoparathyroidism has been observed with trifunctional protein deficiency [245, 246]. The role of these mitochondrial mutations in the etiology of hypoparathyroidism remains to be further elucidated.

Kenny-Caffey and Sanjad-Sakati Syndrome

Hypoparathyroidism has been reported to occur in over 50 % of patients with the Kenny-Caffey syndrome (KCS), which is associated with short stature, osteosclerosis, and cortical thickening of the long bones, delayed closure of the anterior fontanel, basal ganglia calcification, nanophthalmos, dental anomalies, and hyperopia [247]. Parathyroid tissue could not be found in a detailed postmortem examination of one patient [248], suggesting that hypoparathyroidism may be due to an embryological defect of parathyroid development. KCS, namely, KCS type 1 (KCS1), was convincingly demonstrated in 16 affected children in 6 unrelated sibships, born to healthy consanguineous parents of Bedouin ancestry [249]. In eight consanguineous Kuwaiti kindreds, linkage to a locus in the 1q42–q43 region was found for the autosomal recessive form of Kenny-Caffey syndrome [250]. This disease has been observed almost exclusively in the Middle East.

The only available data about its prevalence is from Saudi Arabia, where its frequency is estimated between 1:40,000 and 1:100,000 live births [247]. An analysis of DNA from 14 children with severe short stature of unknown etiology by whole exome sequencing identified one subject with Kenny-Caffey syndrome, highlighting the fact that rare syndromic causes of short stature may be under-recognized and underdiagnosed [251]. KCS1 is caused by mutations of the tubulin-specific chaperone (TBCE), whereas patients with KCS2 were recently shown to carry de novo mutations in FAM111A (family with sequence similarity 111A) [252]. There is close genotype-phenotype correlation.

Five individuals with KCS2 and five with more severe osteocraniostenosis (OCS) were found to have heterozygous mutations in FAM111A. This protein comprises 611 amino acids with homology to trypsin-like peptidases. Molecular modeling revealed that these mutations are close to the outer surface rather than on the active site, thus raising the possibility that decreased binding of FAM111A by its inactivating partner results in increased and/or deregulated FAM111A activity, a gain-of-function effect observed even in a heterozygous state [253]. FAM111A functions as a host range restriction factor which plausibly plays a role in embryonic morphogenesis and appears to be crucial for parathyroid gland formation and function [252]. Mother-to-daughter transmission of KCS2 was shown to be associated with a recurrent dominant FAM111A mutation, namely, pArg569His [254].

In the Sanjad-Sakati syndrome, hypoparathyroidism is associated with severe prenatal and postnatal growth failure and dysmorphic features, and this has been reported in 12 patients from Saudi Arabia [255]. The presenting complaint in all patients was hypocalcemic tetany or generalized convulsions, usually detected in the first few days or weeks of life. Consanguinity was noted in the families of 11 of the 12 patients, the majority of which originated from the Western province of Saudi Arabia. This syndrome, which is inherited as an autosomal recessive disorder, has also been identified in families of Bedouin origin, and homozygosity and linkage disequilibrium studies located this gene to chromosome 1q42–q43 [256]. Sanjad-Sakati syndrome resembles the autosomal recessive form of KCS with similar manifestations but lacking osteosclerosis. Eight Sanjad-Sakati families from Saudi Arabia were genotyped with polymorphic short tandem repeat markers from the SSS/KCS critical region. A maximum multipoint LOD score of 14.32 was obtained at marker D1S2649, confirming linkage of Sanjad-Sakati syndrome to the same region as autosomal recessive Kenny-Caffey syndrome. Haplotype analysis refined the critical region to 2.6 cM and identified a rare haplotype present in all the Sanjad-Sakati syndrome disease alleles, indicative of a common founder. In addition to the assignment of the Sanjad-Sakati syndrome in Saudi families and of the Kenny-Caffey syndrome in Kuwaiti families to overlapping genetic intervals, comparison of the haplotypes unexpectedly demonstrated that the diseases shared an identical haplotype. This finding, combined with the clinical similarity between the two syndromes, suggests that the two conditions are not only allelic but are also caused by the same ancestral mutation [257]. Molecular genetic investigations led to the conclusion that mutations of the tubulin-specific chaperone (TBCE) are associated with both syndromes [258]. TBCE encodes one of several chaperone proteins required for the proper folding of α-tubulin subunits and the formation of α-β tubulin heterodimers. In addition, deletion and truncation mutations in the gene encoding a tubulin-specific chaperone cofactor E (TBCE) have been shown to cause the hypoparathyroidism, mental retardation, and facial dysmorphism (HRD) syndrome which is associated with extreme growth failure. However, cryptic translational initiation at each of three out-of-frame AUG codons upstream of the genetic lesion can rescue a mutant HRD allele by producing a functional TBCE protein [259]. The defect in the tubulin folding and assembly pathway also has grave consequences on growth and PMN functions [260, 261].

Additional Familial Syndromes

Single familial syndromes in which hypoparathyroidism is a component have been reported. The inheritance of the disorder in some instances has

been established, and molecular genetic analysis of the PTH gene has revealed no abnormalities. Thus, an association of hypoparathyroidism, renal insufficiency, and developmental delay has been reported in one Asian family in whom autosomal recessive inheritance of the disorder was established [262]. An analysis of the PTH gene in this family revealed no abnormalities [262]. The occurrence of hypoparathyroidism, nerve deafness, and a steroid-resistant nephrosis leading to renal failure, which has been referred to as the Barakat syndrome [263], has been reported in four brothers from one family, and an association of hypoparathyroidism with congenital lymphoedema, nephropathy, mitral valve prolapse, and brachytelephalangy has been observed in two brothers from another family [264]. Molecular genetic studies have not been reported from these two families.

Abnormalities at the Calcium-Sensing Receptor (CaSR) and the Downstream Signaling Molecules

Abnormalities at the CaSR are associated with several different hypocalcemic disorders. These include (1) autosomal dominant forms of hypocalcemic hypercalciuria (ADHH), (2) Bartter syndrome type V (i.e., ADHH with a Bartter-like syndrome), and (3) autoimmune hypoparathyroidism (AH).

Autosomal Dominant Hypocalcemic Hypercalciuria (ADHH) Due to CaSR and Gα11 Mutations

ADHH, although rare, in index cases may comprise a sizeable fraction of cases of idiopathic hypoparathyroidism, perhaps representing as many as one-third of such cases [265]. CaSR mutations that result in a loss-of-function are associated with familial benign (hypocalciuric) hypercalcemia [87–92, 102]. It was therefore postulated that gain-of-function mutations in CaSR lead to hypocalcemia with hypercalciuria, and the investigation of kindreds with autosomal dominant forms of hypocalcemia has indeed identified such CaSR mutations [102, 266–270]. Soon after the cloning of the CaSR, investigators showed linkage of ADHH to a locus on chromosome 3q13 [267], i.e., the same locus as for the gene encoding the CaSR. Shortly afterward, a heterozygous missense mutation, Q127A, was identified as the cause of ADHH in an unrelated family [266]. The majority (>80 %) of CaSR mutations that result in a functional gain are located within the extracellular domain [102, 266–270], which is different from the findings in other disorders that are the result of activating mutations in G protein-coupled receptors. A second hotspot for mutations is transmembrane domains 6 and 7 and the intervening third extracellular loop, a site which maintains the CaSR in an inactive conformation and also is critical for the binding and/or action of allosteric modulators including calcimimetics of the phenylalkylamine class to which Cinacalcet belongs [271]. In addition, two deletion mutations have been described. Most ADHH patients are heterozygous for the activating mutation. In one family, a homozygous mutation was described, but it was not associated with a more severe phenotype [272], and although there is a spectrum of phenotypic severity for a given genotype, the symptoms present in affected members of the same family tend to be similar. Thus, one mutated allele may be enough to shift the set point to left, and the presence of second mutated allele makes no change in the phenotype perhaps due to the "dominant-positive" effect of the mutant receptor.

In addition to heterozygous gain-of-function mutations in the CaSR (*ADHH1*), ADHH cases were recently identified that are associated with heterozygous mutations in *GNA11 (ADHH2)*, the gene encoding Gα11 [93, 273]. Gα11 is one of two heterotrimeric G proteins that couple the CaSR to the Ca^{2+}/IP3/PKC signaling pathway in parathyroid cells [274]. Functional studies of the Gα11 mutation R60L revealed a significantly decreased EC_{50} and MAP kinase activity. Compared with subjects with CaSR mutations, patients with *GNA11* mutations lacked significant hypercalciuria and had normal serum magnesium levels [274]. FHH3 is caused by loss-of-function AP2σ1 mutations [95]; however, 19 patients (including 6 familial cases) with ADHH, who

did not have *CaSR* or *GNA11* mutations, were found not to have AP2σ1 mutations [275], indicating that gain-of-function AP2σ1 mutations are not a cause of ADHH.

Bartter Syndrome Type V

Bartter syndrome is a heterozygous group of autosomal recessive disorders of electrolyte homeostasis characterized by hypokalemic alkalosis, renal salt wasting that may lead to hypotension, hyperreninemic hyperaldosteronism, increased urinary prostaglandin excretion, and hypercalciuria with nephrocalcinosis [276, 277]. Mutations of several ion transporters and channels have been associated with Bartter syndrome, and five types are now recognized [277]. The CaSR-related cases of Bartter's syndrome identified to date have been inherited in an autosomal dominant manner, unlike other subtypes that are inherited as autosomal recessive traits.

Bartter syndrome type V is due to activating mutations of the CaSR. Activating mutations of the CaSR gene in three patients involving L125P, C131W, and A843E, which inhibited the activity of the ROMK channel, provided the missing link that explains why some activating mutations of CaSR can cause the Bartter syndrome phenotype [278, 279]. Another recent mutation in monozygotic twins involving the K29E in the ECD of the CaSR described mild hypokalemia, minimal aldosterone and renin production, and absent alkalosis but notable hypocalcemia [280]. The K29E mutation is an activating mutation of the CaSR [281] and buttresses previous observations that the phenotype of Bartter syndrome is variable and not directly related to the in vitro potency of the known genetic changes associated with this syndrome [282]. CaSR mutations causing type V Bartter syndrome have been shown to increase ER to cytosol calcium gradient, thus explaining the higher sensitivity of CaSR gain-of-function variants to external calcium [283].

Autoimmune Acquired Hypoparathyroidism (AH)

Twenty percent of patients, who had acquired hypoparathyroidism (*AH*) in association with autoimmune hypothyroidism, were found to have autoantibodies to the extracellular domain of the CaSR [111, 112, 284]. The CaSR autoantibodies are not persistent [284]. The majority of the patients who had CaSR autoantibodies were females, a finding that is similar to that found in other autoantibody-mediated diseases. Indeed a few AH patients have also had features of autoimmune polyglandular syndrome type 1 (APS1). These findings establish that the CaSR is an autoantigen in AH [111, 284]. CaSR autoantibodies bind to the CaSR ECD and have, in some cases, been shown to enhance receptor function, thereby reducing PTH secretion. Thus, hypoparathyroidism associated with activating CaSR autoantibodies results from activated parathyroid CaSR function and not from immune-mediated destruction of the parathyroid glands and is of varying severity [284].

Pseudohypoparathyroidism (PHP)

The term pseudohypoparathyroidism (PHP) was first introduced to describe patients with hypocalcemia and hyperphosphatemia due to PTH resistance rather than PTH deficiency [285]. Affected individuals show partial or complete resistance to biologically active exogenous PTH as demonstrated by a lack of increase in urinary cyclic AMP and urinary phosphate excretion; this condition is now referred to as PHP type I [286–288]. If associated with other endocrine deficiencies and characteristic physical stigmata, now collectively termed Albright's hereditary osteodystrophy (AHO), the condition is referred to as PHP type Ia. This latter syndrome is caused by heterozygous inactivating mutations within exons 1–13 of *GNAS* located on chromosome 20q13.3, which encode the stimulatory G protein ($G_s\alpha$) (for review, see [288, 289]). These mutations were shown to lead to an approximately 50 % reduction in $G_s\alpha$ activity/protein in readily accessible tissues, like erythrocytes and fibroblasts, and explain, at least partially, the resistance toward PTH and other hormones that mediate their actions through G protein-coupled receptors [286–288]. A similar reduction in $G_s\alpha$ activity/protein is also found in patients with

pseudopseudohypoparathyroidism (PPHP), who often show the same physical appearance as individuals with PHP-Ia, but lack endocrine abnormalities [286, 290–295]. However, contrary to previous reports, recent studies have shown that not all AHO features are observed in PPHP patients. For example, obesity, which was thought to be a hallmark of PHP-Ia and PPHP, was not evident in a large number of PPHP patients [296].

Patients affected by PHP-Ia or PPHP are typically found within the same kindred, but not within the same sibship, and hormonal resistance is parentally imprinted, i.e., PHP-Ia occurs only if the genetic defect is located on the maternal allele, while PPHP occurs only if the defect is located on the paternal allele [297, 298]. Observations consistent with these findings in humans were made in mice that are heterozygous for the ablation of exons 1 or 2 of the *Gnas* locus [299–301]. Animals that inherited the mutant allele from a female showed much reduced $G_s\alpha$ protein in the renal cortex and decreased plasma calcium concentration due to resistance toward PTH. In contrast, offspring that had obtained the mutant allele from a male showed no evidence for abnormalities in the regulation of mineral ion homeostasis. These findings in mice with ablation of *Gnas* exon 1 or 2 and in humans with inactivating mutations in *GNAS* exons 1–13 indicate that certain tissues, such as the proximal renal tubules, express $G_s\alpha$ predominantly from the maternal allele; expression from the paternal allele is silenced through some unknown mechanisms. These data provided a reasonable explanation for the finding that heterozygous *GNAS* mutations result in a dominant phenotype with regard to the mineral ion abnormalities, if inherited through females.

Progressive osseous heteroplasia (POH) is caused also by heterozygous inactivating mutations in the *GNAS* exons encoding $G_s\alpha$ [302–305]. Interestingly, POH became apparent predominantly when a $G_s\alpha$ mutation was inherited from a male. Furthermore, the majority of mutations occurred in *GNAS* exons 2–13, thus implicating XLαs rather than $G_s\alpha$ in the pathogenesis of POH. Recent evidence, however, indicated that the abnormal bone formation process followed a dermomyotomal distribution pattern, suggesting that a somatic mutation is required in addition to heterozygosity at the *GNAS* locus [306].

Mutations in the *GNAS* gene encoding $G_s\alpha$ have not been detected in patients with PHP type Ib (PHP-Ib), a disorder in which affected individuals show PTH-resistant hypocalcemia and hyperphosphatemia, but usually lack developmental defects. Initially it was therefore thought that this variant of PHP is caused by PTH/PTHrP receptor mutations; however, mutations in its gene and mRNA could not be identified [307–310]. Furthermore, it was shown that there is an increased incidence of TSH resistance in PHP-Ib patients [261, 287, 311, 312] and that some individuals affected by this disease variant show some shortening of the fourth metacarpals, suggesting some overlap between the developmental features of PHP-Ia and PHP-Ib [313, 314].

A genome-wide search to identify the location of the "PHP-Ib gene" mapped the PHP-Ib locus to chromosome 20q13.3, which contains the *GNAS* locus [315], and it was furthermore shown that the genetic defect is parentally imprinted, i.e., it is inherited in the same mode as the PTH-resistant hypocalcemia in kindreds with PHP-Ia and/or PPHP [297, 298]. Patients affected by PHP-Ib furthermore show a loss of methylation on the maternal allele, which is usually restricted to *GNAS* exon A/B [316, 317]. In most families with the autosomal dominant form of PHP-Ib with parental imprinting (AD-PHP-Ib), affected individuals and healthy carriers were shown to carry a 3 kb deletion located with the syntaxin 16 (*STX16*) gene about 220 kb upstream of exon A/B [318–321] (Fig. 8). Other AD-PHP-Ib kindreds, in which the affected members show a loss of A/B methylation alone, revealed either a 4.4 kb deletion within *STX16* overlapping with the 3 kb deletion by 1,286 bp [322] or a 24.6 kb deletion comprising most *STX16* exons [323]. Methylation changes at *GNAS* exon A/B alone were furthermore observed in the affected members of a family with a 18.9 kb deletion comprising exon NESP55 and a large part of AS intron 4 [324]. In affected individuals with either mutation, the deletion is always found on the maternal allele, while it occurs on the paternal allele in unaffected healthy carriers.

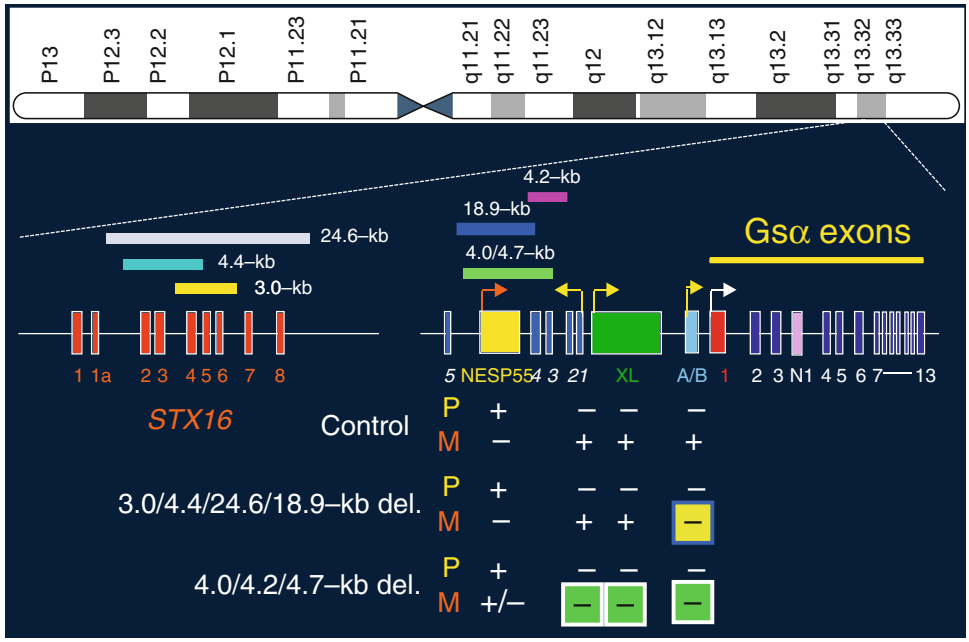

Fig. 8 Genomic structure of PHP-Ib locus to chromosome 20q13.3. This locus contains *GNAS*, encoding the stimulatory G protein ($G_s\alpha$). The pathophysiological mechanisms related to the defect of GNAS are described in the text

The affected members of two families with broader methylation changes within the *GNAS* locus were shown to carry two distinct deletions on the maternal allele that remove *GNAS* exon NESP55 and the antisense exons 3 and 4 [325], a third deletion removes only antisense exons 3 and 4 [326]. Although indistinguishable broad methylation changes were observed in most patients with sporadic PHP-Ib, no deletions or point mutations have yet been identified in these individuals [327]. In fact, only patients with paternal uniparental isodisomy involving either the long arm of chromosome 20 (patUPD20q) or the entire chromosome (patUPD20) have provided a molecular explanation for this variant of PHP-Ib [328]. Taken together, these findings suggest that several different deletions upstream or within the *GNAS* locus or patUPD20q lead to indistinguishable clinical and laboratory findings. However, it remains uncertain how the deletion affecting *STX16* results in a loss of exon A/B methylation alone, while the deletion of *GNAS* exon NESP results in a broader loss of methylation. Furthermore, it remains uncertain how the different deletions affect signaling through the PTH/PTHrP receptor in the proximal renal tubules, but not in most other tissues. Mice lacking the murine homolog of exon A/B were recently shown to have biallelic and thus increased $G_s\alpha$ transcription [329] (Fig. 8). Loss of exon A/B methylation on the maternal allele allowing active transcription from the promoters of both parental alleles and this transcript therefore seems to have a prominent role in suppressing $G_s\alpha$ expression.

Blomstrand's Disease

Blomstrand's chondrodysplasia is an autosomal recessive human disorder characterized by early lethality, dramatically advanced bone maturation, and accelerated chondrocyte differentiation [330]. Affected infants are typically born to consanguineous healthy parents (only in one instance did unrelated healthy parents have two affected offspring) [331–335] and show pronounced hyperdensity of the entire skeleton (Fig. 9) [336] and markedly advanced ossification, and

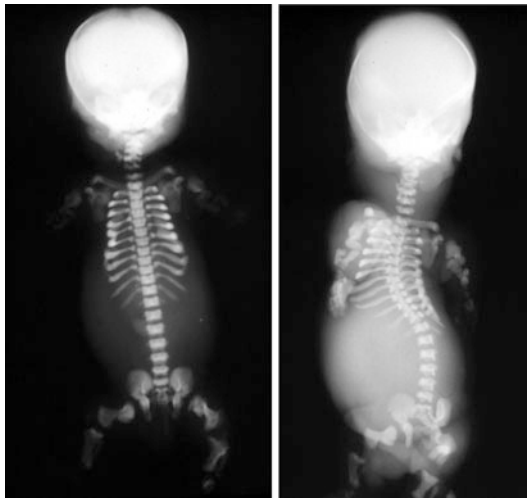

Fig. 9 Radiological findings in a patient with Blomstrand's disease. (From [333], with permission from Loshkajian with permission). Note the markedly advanced ossification of all skeletal elements, and extremely short limbs, despite comparatively normal size and shape of hands and feet. In addition, notice that the clavicles are relatively long and abnormally shaped

particularly the long bones are extremely short and poorly modeled. PTH/PTHrP receptor mutations that impair its functional properties were identified as the most likely cause of Blomstrand's disease. One of these defects is caused by a nucleotide exchange in exon M5 of the maternal PTH/PTHrP receptor allele, which introduces a novel splice acceptor site and thus leads to the synthesis of a receptor mutant that does not mediate, despite seemingly normal cell surface expression, the actions of PTH or PTHrP; the patient's paternal PTH/PTHrP receptor allele is, for yet unknown reasons, only poorly expressed [336]. In a second patient with Blomstrand's disease, the product of a consanguineous marriage, a nucleotide exchange was identified that changes proline at position 132 to leucine [337, 338]. The resulting PTH/PTHrP receptor mutant despite reasonable cell surface expression had severely impaired binding to radiolabeled PTH and PTHrP analogues, resulting in greatly reduced agonist-stimulated cAMP accumulation and no measurable inositol phosphate response. Additional loss-of-function mutations of the PTH/PTHrP receptor have recently been identified in three unrelated patients with Blomstrand's disease. Two of these frameshift mutations secondary to a homozygous single nucleotide deletion in exon EL2 [339] and 27 bp insertion between exon M4 and EL2 led to a truncated receptor protein [340]. The other defect, a nonsense mutation at residue 104, also resulted in the same receptor protein defect [341]. Affected infants show abnormalities in other organs, including secondary hyperplasia of the parathyroid glands (presumably due to hypocalcemia), besides the described skeletal defects. In addition, analysis of fetuses with Blomstrand's disease revealed abnormal breast development and tooth impaction, highlighting the involvement of the PTH/PTHrP receptor in the normal development of breast and tooth [342].

Hyperphosphatemic Disorders with Reduced Secretion of Biologically Active FGF23

Hyperphosphatemic Familial Tumoral Calcinosis (HFTC)

HFTC needs to be differentiated from sporadic and secondary TC. It is a rare autosomal recessive disorder [343], which can be severe, sometimes fatal, and is typically characterized by hyperphosphatemia and often massive calcium deposits in skin and subcutaneous tissues; in some patients, however, only few minor abnormalities are noted [344]. The biochemical hallmark of tumoral calcinosis is hyperphosphatemia caused by loss-of-function mutations in genes relevant to the production of an intact bioactive form of FGF23, i.e., mutations in (1) FGF23 [40], (2) GALNT3 [345], or resistance to the end-organ effects of FGF23 bioactivity (αKlotho) [346]. Homozygous or compound heterozygous mutations in GALNT3, which encodes a glycosyltransferase responsible for initiating mucin-type O-glycosylation, appear to occur more frequently. Furthermore, the disorder can be caused by loss-of-function mutations in FGF23. Mutations in either gene lead to indistinguishable changes in FGF23, namely, low serum intact FGF23, but significantly elevated C-terminal FGF23 concentrations [347, 348].

In contrast, HFTC caused by mutations in αKL is characterized by profound increases of both forms of FGF23.

Hyperostosis with Hyperphosphatemia (HHS)

HHS is an autosomal recessive disorder, which shares several clinical and metabolic features with HFTC. The combination of hyperostosis with hyperphosphatemia was first described in 1970 [349, 350]. Most cases appear to be sporadic, but consanguineous parents were described for some patients, implying that the disease can be recessive. All affected individuals in two unrelated Arab-Israeli HHS families were found to harbor a previously described splice site mutation in GALNT3, indicating that HFTC and HHS are allelic variants [351]. Four novel GALNT3 gene mutations were found in additional unrelated subjects with considerable phenotypic overlap, again underscoring the fact that these two disorders are variants of the same disease [352]. The molecular reasons for the enhanced skeletal involvement in HHS are currently unknown, but could potentially be due to modifier gene interactions.

Hypophosphatemic Disorders

The different forms of hypophosphatemia represent the most common cause of hereditary rickets, which can be divided into two main groups according to the predominant metabolic abnormality [353, 354]. In the first group, hypophosphatemia is the result of a renal tubular defect, which may consist of either a single (isolated) defect in renal phosphate handling, as it occurs in the X-linked hypophosphatemia (XLH), or of multiple tubular defects as encountered in Fanconi syndrome. In the second group, vitamin D metabolism is abnormal, either because of a defect in the 1α-hydroxylase enzyme or because of defects in the 1,25-dihydroxyvitamin D_3 receptor (VDR) leading to end-organ resistance. The application of molecular genetics approaches has helped to elucidate some of the mechanisms underlying these disorders of hereditary hypophosphatemic rickets (Table 1).

Hypophosphatemic Disorders with Increased FGF23 Activity

Autosomal Dominant Hypophosphatemic Rickets (ADHR)

Autosomal dominant hypophosphatemic rickets is characterized by FGF23 excess due to "activating" mutations in the FGF23 gene. Genetic linkage studies mapped the ADHR locus to chromosome 12p13.3 [355] and defined a 1.5 Mb critical region that contained 12 genes. Positional cloning in affected members of four unrelated families identified three different missense mutations involving a new member of the fibroblast growth factor (FGF) family [38].

The C-terminal and the N-terminal portions of FGF23 are connected by an "RXXR" motif, which is the recognition site for a furin-like protease. At this site, FGF23 can be cleaved and thus inactivated. Missense mutations that replace the arginine (R) residue at either position 176 or 179 with glutamine (Q) or tryptophan (W) disrupt the cleavage site, thus making FGF23 resistant to enzymatic cleavage (Fig. 2), thereby stabilizing the intact bioactive FGF23 molecule [6, 39, 48, 356, 357]. Iron deficiency stimulates FGF23 expression and leads mice engineered to carry one of the ADHR mutations to hypophosphatemia [358], and similar observations were made in human with ADHR [359].

Oncogenic Osteomalacia (OOM)

OOM (also referred to as tumor-induced osteomalacia (TIO)) is a rare disorder characterized by hypophosphatemia, phosphaturia, low circulating levels of 1,25-dihydroxyvitamin D, and osteomalacia that develops in previously unaffected individuals [360]. Similarities between OOM, ADHR, and XLH suggested that they may involve the same phosphate-regulating pathway, and it is important to note that OOM tumors do express PHEX [361, 362], which is mutated in XLH (see below). The possibility that FGF23,

Table 1 Biochemical findings in several inherited hypo- and hyperphosphatemic disorders and underlying genetic defects

	FGF-23	TRP or TmP/GFR	1,25$(OH)_2$D	PTH	Serum calcium	Urinary calcium	Mutant gene
Hypophosphatemic disorders							
FGF23 dependent							
XLH	Increased/ inappropriately normal	Low	Low/ inappropriately normal	Normal/ increased	Normal	Normal	**PHEX**
ADHR	Increased/ inappropriately normal	Low	Low/ inappropriately normal	Normal	Normal	Normal	**FGF23**
ARHP	Increased/ inappropriately normal	Low	Low/ inappropriately normal	Normal	Normal	Normal	**DMP1, ENPP1, FAM20C**
Hypophosphatemic disorders							
FGF23 independent							
HHRH	Low/normal	Low	High	Low	Normal/ increased	High	**NPT2c**
Renal Fanconi syndrome	Low/normal	Low	High	Low	Normal/ increased	High	**NPT2a**
Hyperphosphatemic disorders							
Tumoral calcinosis	Intact: low C-terminal: very high	High	Normal-high	Low	Normal/ increased	Increased	**FGF23 or GALNT3 (glycosyltransferase)**
	Extremely high (intact and C-terminal)	High	Normal-high	Elevated	Normal/ increased	Increased	**Klotho**
Isolated hypoparathyroidism	Normal-increased	Elevated	Low-normal	Low-normal	Low	Increased or inappropriately normal	**Calcium-sensing receptor, PTH, GCM2, GNA11, and unknown genetic defects**
Pseudohypoparathyroidism type Ia (PHP-Ia) or Ib (PHP-Ib)	Normal-increased	Elevated	Low-normal	High	Low	Low	**PHP-Ia: *GNAS* exons encoding Gsα** **PHP-Ib: microdeletions within or upstream of *GNAS***

which is mutated in ADHR, may also be expressed in OOM tumors and that FGF23 may be a secreted protein was therefore explored [39, 65, 356, 363]. Indeed, OOM tumors were found by Northern blot analysis to contain high levels of FGF23 mRNA and protein. Consistent with this finding, FGF23 plasma concentrations can be increased considerably in OOM patients, until successful tumor removal [356, 357, 364, 365].

Tumors responsible for oncogenic osteomalacia produce two molecular forms of FGF23 (~32 and ~12 kDa), and both variants were also observed when assessing conditioned medium from different cell lines expressing full-length wild-type FGF23 [39]. When conditioned medium from cells expressing R176Q FGF23 or R179Q FGF23 was investigated by Western blot analysis, only the larger protein band was observed [7, 8, 366]. These findings showed that the ADHR mutations impair FGF23 degradation, thus enhancing and/or prolonging its biological activity. In addition to FGF23, these tumors have also been shown to express other factors, including DMP1, sFRP4, and MEPE [367].

X-Linked Hypophosphatemia (XLH)

Like ADHR, patients with XLH present with hypophosphatemia, hyperphosphaturia, low circulating 1,25-dihydroxyvitamin D levels, and osteomalacia. XLH is caused by inactivating mutations in PHEX, a gene located on Xp22.1 [368, 369], which shows significant amino acid sequence homology to the M13 family of zinc metallopeptidases. In the past, substrates for PHEX considered were FGF23, matrix extracellular phosphoglycoprotein (MEPE) [68, 370], and secreted frizzled-related protein 4 (sFRP4) [65, 67]. Among these proteins, FGF23 levels were found to be elevated in about two-thirds of XLH patients [78, 261, 356] and more than tenfold in Hyp mice, the murine homolog of XLH [63, 371]. Although PHEX-dependent cleavage of FGF23 was observed in one study in vitro [372], these findings were not confirmed by others [40]. However, genetic ablation of FGF23 in male Hyp mice, i.e., animals that are null for FGF23 and PHEX, led to blood phosphate levels that are indistinguishable from those in mice lacking FGF23 alone [45, 46], indicating that FGF23 resides genetically downstream of PHEX. Furthermore, recent studies have shown that Hyp mice normalize their plasma phosphate concentration and heal their rachitic changes, when injected with inactivating antibodies to FGF23, indicating that FGF23 is indeed the phosphaturic principle in XLH [373]. XLH patients exhibited a similar response to a single injection of anti-FGF23 antibodies [374].

Autosomal Recessive Hypophosphatemia (ARHP)

There are different forms of autosomal recessive hypophosphatemia (*ARHP*) characterized by renal phosphate wasting. ARHP can be caused by mutations in DMP1 (Dentin matrix protein 1), which belongs to the family of integrin-binding ligand N-linked glycoproteins (SIBLING proteins) that are secreted phosphoproteins involved in bone mineralization [375]. DMP1 mutations lead to increased FGF23 expression and thus increased urinary phosphate excretion and defective osteocyte maturation [376, 377]. ARHP was first reported in consanguineous kindreds, suggesting an autosomal recessive form of hypophosphatemia [378–380]. Patients affected by ARHP have FGF23 levels that are either elevated or inappropriately normal for the level of serum phosphorous [48, 51]. Of the several different DMP1 mutations identified thus far, one mutation alters the translation initiation codon (M1V), two mutations are located in different intron-exon boundaries, and three are frameshift mutations within exon 6. All mutations appear to be inactivating, suggesting that the loss of DMP1 causes increased FGF23 production leading to hypophosphatemia. Accordingly, Dmp1-null mice show severe defects in dentine, bone, and cartilage, as well as hypophosphatemia and osteomalacia [381, 382]. Furthermore, FGF23 levels in osteocytes and in serum are drastically elevated in these animals [48]. Given the established importance of DMP1 in osteoblast function, loss of DMP1 actions in osteoblasts and extracellular matrix may also contribute to the phenotype of patients with ARHR. Consistent with this hypothesis, a high-calcium/high-phosphate diet which is capable to rescue osteomalacia in

VDR-null mice does not seem to prevent bone and dentine mineralization defect in Dmp1-null mice [383]. Other forms of ARHP are caused by mutation in the gene encoding ENPP1 gene (ectonucleotide pyrophosphatase/phosphodiesterase), which catalyzes phosphoester cleavage of adenosine triphosphate, thereby generating pyrophosphate, a mineralization inhibitor. All forms of hypophosphatemia are often associated with ossification of the posterior spinal ligaments, and ENPP1 mutations can also be associated with calcifications of the vascular endothelium, as observed in GACI (generalized arterial calcification of infancy) [51, 54, 384].

Hypophosphatemic Disorders with Normal or Suppressed FGF23 Activity

Nephrolithiasis and Osteoporosis Associated with Hypophosphatemia

Two different heterozygous mutations (A48P and V147M) in *NPT2a*, the gene encoding a sodium-dependent phosphate transporter, have been reported in patients with urolithiasis or osteoporosis and persistent idiopathic hypophosphatemia due to decreased tubular phosphate reabsorption [385]. When expressed in *Xenopus laevis* oocytes, the mutant NPT2a showed impaired function and, when co-injected, dominant-negative properties. However, these in vitro findings were not confirmed in another study using oocytes and OK cells, raising the concern that the identified NPT2a mutation alone cannot explain the findings in the described patients [386]. On the other hand, additional heterozygous NPT2a variations (in-frame deletion or missense change) have recently been identified upon analyzing a large cohort of hypercalciuric stone-forming kindreds; however, these genetic variations do not seem to cause functional abnormalities [387]. Homozygous in-frame duplication of 21 bp in SLC34A1 resulting in complete loss of function of the mutant NPT2a, one of two sodium-dependent phosphate cotransporters expressed in the proximal renal tubules, was identified in two siblings from a consanguineous family with autosomal recessive Fanconi syndrome and hypophosphatemic rickets [388].

These findings are similar to those observed in mice with homozygous ablation of Npt2a ($Npt2a^{-/-}$) [389]. Due to hypophosphatemia, $Npt2a^{-/-}$ mice show an appropriate elevation in the serum levels of 1,25-dihydroxyvitamin D, leading to hypercalcemia, hypercalciuria and decreased serum parathyroid hormone levels, and increased serum alkaline phosphatase activity.

Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH)

Homozygous or compound heterozygous mutations in the sodium phosphate cotransporter NPT2c (*SLC34A3)* are the cause of HHRH, an autosomal recessive disorder affecting renal tubular phosphate reabsorption, leading to hypophosphatemia, increased $1,25(OH)_2$ vitamin D levels, and hypercalciuria, which lead in a considerable number of patients to nephrolithiasis [390–393]; even individuals with heterozygous NPT2c mutations can show laboratory abnormalities and nephrolithiasis. Long-term phosphate supplementation as the sole therapy leads, with the exception of persistently decreased TmP/GFR, to reversal of the clinical and biochemical abnormalities [390]. Treatment with calcitriol is contraindicated since it can further increase urinary calcium excretion.

Vitamin D-Dependent Rickets (VDDR)

Patients with VDDR type I (pseudo-vitamin D-resistant rickets) show clinical and laboratory findings that are similar to patients with vitamin D-deficient rickets but do not respond to treatment with 25(OH) vitamin D; instead treatment with $1,25(OH)_2$ vitamin D is required [394]. Clarification of the abnormal vitamin D metabolism [395] led to the recognition of two different forms of rickets: VDDR type I (defect in the 1-α-hydroxylation) and vitamin D-dependent rickets type II (VDDR type II) (end-organ resistance to $1,25(OH)_2D$).

1-Alpha Hydroxylase Deficiency (VDDR Type I)

Patients affected by *VDDR type I* (autosomal recessive) show almost all the clinical and

biochemical features of vitamin D-deficient rickets except that vitamin D intake is usually adequate. The permanent teeth show marked enamel hypoplasia unlike in *XLH* [396]. The serum concentration of $1,25(OH)_2$ vitamin D is low in untreated patients [397] and in vitamin D-sufficient patients with normal or elevated serum 25(OH)D3 levels, which provided the first hint that the renal 1α-hydroxylase is deficient [398–400]; molecular genetic studies later confirmed this conclusion. Indeed, genetic linkage studies in affected French-Canadian families mapped VDDR type I to a region on chromosome 12q13.3 [401], which is the location of the gene encoding the 25(OH)D 1α-hydroxylase (CYP27B). DNA sequence analysis of patients affected by VDDR type 1 identified more than 20 different mutations of CYP27B [402–406] in 26 kindreds. All patients with VDDR type 1 were found to carry homozygous or compound heterozygous mutations, while the obligate carriers were heterozygous for the mutant allele. Mutations that confer partial enzyme activity in vitro were found in the two patents with mild laboratory abnormalities, suggesting that such mutations contribute to the phenotypic variation observed in patients with 1α-hydroxylase deficiency [407].

End-Organ Resistance (VDR Mutations, VDDR Type II)

Vitamin D-dependent rickets type II is an autosomal recessive disorder caused by end-organ resistance to $1,25(OH)_2$ vitamin D [408–410]. Alopecia, ectodermal defects like oligodontia, and epidermal cysts might be present. The disease varies in its clinical and biochemical manifestations, which suggest heterogeneity in the underlying molecular defects [410]. Most of the patients have early-onset rickets, but the first reported patient was a 22-year-old woman who had skeletal pain for 7 years [408], and another patient presented at the age of 50 years following 5 years of symptoms [411]. Alopecia in some cases is associated with poor therapeutic response to the 1α-(OH) vitamin D [412, 413].

$1,25(OH)_2$ vitamin D actions are mediated by an intracellular receptor that binds DNA and concentrates the hormone in the nucleus [414], analogous to the classical steroid hormones [415]. The interactions between $1,25(OH)_2$ vitamin D and its intracellular receptor have been studied using cultured skin fibroblasts from control subjects and VDDR type II patients [416, 417]. Several defects were identified, including absent receptors, a decreased number of receptors with normal affinity, a normal receptor-hormone binding but a subsequent failure to translocate the hormone to the nucleus, and a post-receptor defect, in which normal receptors are present, but there is a deficiency in the induction of the 25-OHD-24 hydroxylase enzyme in response to $1,25(OH)_2$ vitamin D. Thus, the heterogeneity suggested from clinical observations in VDDR type II patients could be demonstrated at the cellular level with various combinations of defective receptor-hormone binding and expression. Vitamin D receptor (VDR) is an intracellular protein, which has a molecular weight of 60,000 Daltons. The binding site for $1,25(OH)_2$ vitamin D resides in the C-terminal part of the protein, while the N-terminal part of the molecule possesses the DNA-binding domain [418]. This hormone-receptor complex binds to a DNA region, which is located upstream of the promoter of genes encoding calcium-binding proteins and other proteins.

The availability of cDNAs encoding the avian and human VDR [419] helped to clarify the molecular basis of VDDR type II [420]. Nucleotide sequence analysis of genomic DNA revealed that the human VDR gene consists of nine exons; exons 2 and 3 encode the DNA-binding domain, while exons 7, 8, and 9 encode the vitamin D-binding domain. The gene is located on chromosome 12q12–q14 in man [401], i.e., in a region that comprises the gene encoding the 1-α-hydroxylase. Mutational analysis of the VDR gene in VDDR type II patients demonstrated the presence of nonsense and missense mutations affecting different parts of the receptor. The expression of these mutations in COS-1 monkey kidney cells demonstrated that these mutations result in a reduction or a loss of VDR function similar to the heterogeneous effects observed in cultured fibroblasts from VDDR type II patients. Furthermore, null mutant, i.e., "knockout" mice

for VDR produced by targeted gene disruption [421, 422], was found to have features consistent with those observed in patients with VDDR type II. The severity of resistance to $1,25(OH)_2$ vitamin D is variable, and some patients have improved following therapy with very large doses of vitamin D [423] or $1,25(OH)_2$ vitamin D [424–426]. However, currently most patients are treated with long-term nocturnal intravenous calcium infusions followed by oral calcium supplementation [427, 428]; cinacalcet to reduce PTH secretion has been tried with some success [429].

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, which is caused by mutations in *CLCN5* encoding the chloride/proton antiporter, chloride channel CLC-5 [430, 431], and Lowe syndrome (oculocerebrorenal syndrome) [432], another X-linked recessive disorder that is caused by mutations in OCRL1 [433, 434]. Other rare diseases that can be associated with severe hypophosphatemia are the Fanconi-Bickel syndrome, which is caused by homozygous or compound heterozygous mutations in GLUT2 [435, 436], a glucose transporter localized on the basolateral membrane of the proximal renal tubules. The hallmarks of this disorder are severe failure to thrive, hepatomegaly, and proximal renal tubular dysfunction with massive glycosuria, fasting hypoglycemia, and postprandial hyperglycemia, in addition to variable phosphaturia, acidosis, and aminoaciduria. Other hypophosphatemic disorders include osteoglophonic dysplasia (OGD) [437], an autosomal dominant disorder, which was shown to be caused by different heterozygous missense mutations in the FGFR1 [438, 439], and linear nevus sebaceous syndrome (LNSS), also known as epidermal nevus syndrome (ENS) or Schimmelpenning-Feuerstein-Mims syndrome, in which elevated FGF23 was observed [440, 441]. Somatic activating mutations of HRAS or NRAS (mitogen-activated protein kinase) associated with giant epidermal or melanocytic nevi cause increased endogenous FGF23 from bone, thus causing hypophosphatemia and osteomalacia [442]. Furthermore, fibrous dysplasia can be associated with increased urinary phosphate excretion. This disorder is caused by heterozygous activating, post-zygotic mutations in exon 8 of *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein ($G_s\alpha$) [443, 444]. These mutations lead in the dysplastic regions to a cAMP-dependent increase in FGF23 production by osteoblasts/osteocytes and fibrous cells [44, 445].

Acute and Chronic Treatment of Calcium and Phosphorus Disorders

Goals of acute and chronic therapy are dependent upon the specific clinical setting in which the disturbance occurs, and management decisions usually require individual attention to the underlying pathophysiology of each patient's underlying disorder. Broad principles for correcting calcium and phosphorus abnormalities are discussed.

Hypercalcemia

Acute Intervention

Hypercalcemia is the biochemical hallmark of increased PTH or $1,25(OH)_2$ vitamin D levels, less frequently in patients with fat necrosis or malignancies. When severe it can be life-threatening and requires urgent medical intervention. If cardiac and renal function is normal, increasing sodium clearance, maximizing glomerular filtration rate, and correcting dehydration increase calcium excretion. Other available pharmacological options are calcitonin, bisphosphonates, and cinacalcet. Calcitonin causes rapid reduction in serum calcium level by inhibiting bone resorption and enhancing urinary calcium excretion, but its use is limited by the requirement for frequent dosing and tachyphylaxis. Bisphosphonates inhibit osteoclast activity. Typically, a clinical response is seen within 1–4 days, with nadir in calcium observed by 4–7 days. Caution is required, because acute renal failure and osteonecrosis of the jaw can be encountered as rare side effects. Cinacalcet is an allosteric activator

of CaSR (calcimimetic) that increases the receptor's affinity for calcium, leading to a reduction in PTH synthesis and an increase in renal calcium excretion because of reduced distal tubular calcium reabsorption. Peritoneal or hemodialysis with low calcium concentration in the dialysis fluid might be required in severe cases. Corticosteroids to reduce intestinal calcium absorption are not always effective.

Chronic Intervention

Chronic treatment is guided by the underlying disorder. Primary hyperparathyroidism (PHPT), e.g., parathyroid tumors, NSPHT, and MEN, respond well to surgical removal of the parathyroid glands. No effective medical therapy for the long-term management of PHPT is currently approved for children. In some NSHPT patients, pamidronate [446] has been used to manage life-threatening hypercalcemia and skeletal demineralization prior to parathyroidectomy. Intraoperative PTH measurements have been shown to be effective for monitoring whether parathyroidectomy is complete [447]. Cinacalcet has been used as well, but with equivocal results, since CaSR mutations can disrupt interaction with this drug. Heterozygous loss-of-function mutations of the CaSR (FHH) usually cause mild-to-moderate hypercalcemia that is not driven by excess PTH. FHH is a benign disorder characteristically associated with hypocalciuria, which unlike PHPT requires no treatment except reassurance. Parathyroidectomy is not indicated.

Hypercalcemia driven by increased intestinal calcium absorption, e.g., Williams syndrome, usually responds to a low-calcium diet with elimination of vitamin D. Low-calcium milk (Locasol) and protection from the sunlight can be useful [148]. Corticosteroids may be a useful adjunct to lower plasma calcium levels by decreasing absorption from the gut. Steroids can be usually discontinued after a few days when dietary changes have shown to be effective. Treatment of infantile hypercalcemia consists of calcium- and vitamin D-restricted diets, steroids, and bisphosphonates, if necessary. Cellulose phosphate has also been used to decrease calcium absorption.

Hypercalcemia associated with AHH may improve following glucocorticoid administration in some, but not all, patients [118].

Hypocalcemia

A decrease in ionized calcium is frequently a manifestation of defective vitamin D homeostasis or inadequate PTH secretion or action. The PTH-dependent renal production of 1,25-dihydroxyvitamin D is deficient in all hypoparathyroid states.

Acute Intervention

Symptomatic hypocalcemia or severe asymptomatic hypocalcemia is a medical emergency and often requires intravenous 10 % calcium gluconate or calcium chloride infusion. Concomitant hypomagnesemia and hyperkalemia, if present, should be corrected. The transition from acute management of hypocalcemia to chronic maintenance is highly dependent on the individual clinical situation. It is often possible to begin oral supplementation within a few days of intravenous therapy with a few days of overlap. Some children with abnormal parathyroid development, e.g., DGS, maintain normal calcium when healthy, but have decreased parathyroid reserve and therefore develop symptomatic hypocalcemia when stressed, for example, due to surgery or infections, or when normal intestinal calcium intake is reduced because of diarrhea or vomiting.

Chronic Intervention

The main treatment options available for patients with acute or chronic hypoparathyroidism are calcium salts, vitamin D or vitamin D analogues, and drugs that increase renal tubular reabsorption of calcium (i.e., thiazides). The selection of the dose and type of the vitamin D analogue varies with the underlying condition and the response to therapy. Calcitriol is the preferred metabolite as it is consistently effective at nontoxic doses and has a short half-life, thus allowing rapid correction should hypercalcemia develop. Monitoring of therapy is essential to avoid hypercalcemia, hypercalciuria, and nephrocalcinosis. Furthermore, recombinant

PTH has been used in some cases of severe hypoparathyroidism. Compared with twice-daily delivery, pump delivery of PTH(1-34) appears to provide the most promising modality for improving calcium homeostasis and bone turnover in these children [154]. The absence of functional PTH and the resulting lack of PTH-dependent calcium reabsorption in the distal renal tubules predispose to hypercalciuria, nephrolithiasis, and chronic kidney disease. Maintaining serum calcium at the lower end of the normal range avoids clinical symptoms and minimizes the risk of hypercalciuria. This is exactly important, and if the hypocalcemia is not symptomatic, maintenance of lower serum Ca level is recommended. Hypercalciuria, if it occurs, may respond to oral hydrochlorothiazide. Monitoring for these complications at regular intervals is the key to avoid complications.

Hypocalcemia due to vitamin D deficiency is treated with cholecalciferol or related analogues. It is important to ensure an adequate calcium supply with the vitamin D replacement, as rapid mineralization of the skeleton may follow initial treatment, potentially causing a precipitous drop in serum calcium (hungry bone syndrome). Treatment of VDDR I (1α-hydroxylase deficiency) requires lifelong replacement with calcitriol or alphacalcidiol, thus bypassing the 1-α-hydroxylation step. Some patients with VDDR II (end-organ resistance to $1,25(OH_2)$ vitamin D) may respond to very high doses of calcitriol or alphacalcidiol, but most pediatric patients require regular intravenous calcium infusions or high doses of oral calcium.

Hypocalcemia due to calcium-sensing receptor (CaSR) mutations is due to increased CaSR sensitivity (ADHH). These patients therefore have serum PTH levels that are in the low-normal range, which is different from patients with hypoparathyroidism, who often have undetectable serum PTH levels or patients with pseudohypoparathyroidism, who typically have major PTH elevations. Treatment with active metabolites of vitamin D to correct the hypocalcemia can result in marked hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal impairment, which may be only partially reversible after cessation of the vitamin D treatment.

Bartter syndrome is characterized by increased prostaglandin E2 production, which stimulates the 1α-hydroxylase activity, thereby increasing $1,25(OH)_2D$ levels. Indomethacin (or other COX2 inhibitors) decreases prostaglandin levels, which furthermore restricts intestinal calcium and vitamin D absorption from the diet, thus helping to correct hypercalciuria and nephrocalcinosis. However, indomethacin itself possesses serious nephrotoxicity; appropriate dose in each patient should be considered.

Long-term therapy of hypocalcemia due to pseudohypoparathyroidism (PHP) is similar to other forms of hypoparathyroidism, namely, oral calcium and calcitriol. However, PHP patients are at little risk of developing increased urinary calcium excretion, unless medications are not sufficiently reduced after the skeleton is fully mineralized after pubertal development. Treatment with calcitriol can thus be usually more aggressive than that of other forms of hypocalcemia, and normocalcemia and normal or close-to-normal PTH should be achieved. Patients with PHP-Ia (and PHP-Ib) should furthermore be routinely screened and eventually treated for any associated endocrinopathy, in particular, hypothyroidism. In addition, careful physical examination and, when necessary, specific psychological investigations should be performed annually to detect and follow up the presence/evolution of specific AHO features (heterotopic ossifications, cognitive delay, brachydactyly). Increasing evidence suggests that children should be screened with appropriate provocative tests for GH deficiency [448]; note that PHP-Ia patients often show "normal" growth rates early in life, but fuse their growth plates prematurely, making it necessarily to start treatment with rhGH as soon as possible. Finally, there are no specific treatments for the various manifestations of AHO.

Hyperphosphatemia

Acute Intervention

Acute hyperphosphatemia usually does not cause symptoms unless reciprocal reduction in serum calcium leads to hypocalcemia. In the setting of

normal kidney function, hyperphosphatemia is usually self-limited because of the capacity of kidney to excrete the phosphorus load. In the setting of markedly compromised renal function, dialysis can be required, in addition to oral phosphate binders.

Chronic Intervention

Chronic hyperphosphatemia management is dependent on the underlying disorder. Acetazolamide has been used to treat hyperphosphatemia and tumor-like extraosseous calcifications due to inactivating mutations in FGF23 [449] or GALNT3 in patients with FTC. This treatment induces mild metabolic acidosis, thus improving calcium-phosphate complex solubility. In severe cases, regular hemodialysis has been prescribed with reasonable success.

Secondary hyperparathyroidism seen in chronic kidney disease is driven by hyperphosphatemia, reduced $1,25(OH)_2D$ production and thus hypocalcemia, and possibly elevated FGF23 levels. The cornerstone of management is dietary phosphate restriction, use of phosphate binders, and dialysis to aid with phosphate removal. Cinacalcet has been shown in EVOLVE trial to decrease bone turnover and tissue fibrosis [450]. Parathyroidectomy is often reserved for ESRD patients, who have profound PTH elevations and thus increased bone resorption.

Hypophosphatemia

Acute Intervention

Acute severe hypophosphatemia particularly presenting as hemolysis, rhabdomyolysis, flaccid paralysis, or cardiac dysfunction is a medical emergency that should be corrected promptly with intravenous sodium- or potassium-phosphate, as appropriate. Cumulative phosphate deficit cannot be accurately predicted from serum levels. Once the levels are above 1.5 mg/dL, transition to oral replacement should be attempted.

Chronic Intervention

The cornerstone of management is oral phosphorus replacement, which needs to be administered in 4–5 daily doses; high doses of phosphate are associated with diarrhea. Other adjunctive therapy is guided by the underlying disorder. Furthermore, anti-FGF23 antibodies may become available for FGF23-dependent hypophosphatemic disorders.

In patients with oncogenic osteomalacia (OOM), complete resection of the FGF23-secreting tumor leads to rapid correction of the biochemical abnormalities. Somatostatin and cinacalcet has been tried with some success if tumor resection is incomplete. Anti-FGF23 antibodies are likely to ameliorate potentially harmful effects of long-standing phosphorus and vitamin D therapy before the tumor is found and resected.

The primary goal for the treatment or X-linked hypophosphatemia (XLH) and other FGF23-dependent forms of hypophosphatemia is to correct or minimize rachitic changes and aim for an acceptable height velocity; in addition, meticulous dental care is advised because of the high incidence of dental abscesses. Serum alkaline phosphatase is the most useful laboratory biomarker to gauge the success of therapy, in addition to radiographs. The current therapy consists of the oral administration of phosphate and calcitriol. Cinacalcet and calcitonin have been tried with some success as adjunctive therapies. Anti-FGF23 antibodies were recently shown to normalize blood phosphate levels in adult XLH patients [374]. Treatment with recombinant human growth hormone (rhGH) is controversial given the lack of adequately controlled trials. Lower limb corrective osteotomies or minimally invasive hemiepiphysiodesis are needed for severe bony deformities in older children. For all patients with inherited forms of hypophosphatemia, iron stores should be replenished, if deficient.

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is a hypophosphatemic disorder characterized by normal or suppressed FGF23 activity and thus elevated $1,25(OH)_2$ vitamin D levels. This disorder is therefore managed differently from the hypophosphatemia such as XLH, ARHP, or ADHR. Oral phosphate supplements are effective. Calcitriol is contraindicated, as $1,25(OH)_2$ vitamin D levels are elevated.

Fanconi-Bickel syndrome is a disorder of generalized proximal tubular dysfunction that is

caused by GLUT2 mutations. Treatment aims at correcting acidosis, treating the hypophosphatemic rickets, and using fructose-based diets to circumvent hypoglycemia. Long-term prognosis is unknown, but there is a risk of atherosclerotic vascular disease, repeated fractures from generalized osteopenia, and markedly short stature.

Concluding Remarks

Remarkable advances have been made in identifying key proteins that are involved, either directly or indirectly, in the regulation of calcium and phosphate homeostasis, the hormones that are involved in these mechanisms, and receptors that mediate these hormonal actions in the different target tissues. Although most of these conditions are rare, their molecular definition resulted in the identification of several proteins that are involved in the normal regulation of mineral ion homeostasis and/or bone development. These advances have added to targeted therapy for some of these disorders.

References

1. Segawa H, Kawakami E, Kaneko I, Kuwahata M, Ito M, Kusano K, et al. Effect of hydrolysis-resistant FGF23-R179Q on dietary phosphate regulation of the renal type-II Na/Pi transporter. Pflugers Arch. 2003;446(5):585–92.
2. Segawa H, Yamanaka S, Onitsuka A, Tomoe Y, Kuwahata M, Ito M, et al. Parathyroid hormone-dependent endocytosis of renal type IIc Na-Pi cotransporter. Am J Physiol Renal Physiol. 2007;292(1):F395–403.
3. Miyamoto K, Ito M, Tatsumi S, Kuwahata M, Segawa H. New aspect of renal phosphate reabsorption: the type IIc sodium-dependent phosphate transporter. Am J Nephrol. 2007;27(5):503–15.
4. Shimada T, Urakawa I, Yamazaki Y, Hasegawa H, Hino R, Yoneya T, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. Biochem Biophys Res Commun. 2004;314(2): 409–14.
5. Larsson T, Marsell R, Schipani E, Ohlsson C, Ljunggren O, Tenenhouse HS, et al. Transgenic mice expressing fibroblast growth factor 23 under the control of the alpha1(I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. Endocrinology. 2004; 145(7):3087–94.
6. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci USA. 2001;98(11): 6500–5.
7. Shimada T, Muto T, Urakawa I, Yoneya T, Yamazaki Y, Okawa K, et al. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. Endocrinology. 2002;143:3179–82.
8. Bai XY, Miao D, Goltzman D, Karaplis AC. The autosomal dominant hypophosphatemic rickets R176Q mutation in fibroblast growth factor 23 resists proteolytic cleavage and enhances in vivo biological potency. J Biol Chem. 2003;278(11):9843–9.
9. Jueppner H, Thakker RV. In: Pollack M, editor. The Kidney. Philadelphia: WB Saunders; 2008. p. 311–45.
10. Gardella TJ, Jüppner H, Brown EM, Kronenberg HM, Potts Jr JT. Parathyroid hormone and parathyroid hormone-related peptide in the regulation of calcium homeostasis and bone development. In: DeGroot LJ, Jameson JL, editors. Endocrinology, vol. 1. 6th ed. Philadelphia: W.B. Saunders; 2010. p. 1040–73.
11. Okazaki T, Igarashi T, Kronenberg HM. 5'-Flanking region of the parathyroid hormone gene mediates negative regulation by $1,25(OH)_2$ vitamin D_3. J Biol Chem. 1989;263:2203–8.
12. Demay MB, Kiernan MS, DeLuca HF, Kronenberg HM. Sequences in the human parathyroid hormone gene that bind the 1,25- dihydroxyvitamin D3 receptor and mediate transcriptional repression in response to 1,25-dihydroxyvitamin D3. Proc Natl Acad Sci USA. 1992;89(17):8097–101.
13. Naveh-Many T, Rahaminov R, Livini N, Silver J. Parathyroid cell proliferation in normal and chronic renal failure in rats. The effects of calcium, phosphate, and vitamin D. J Clin Invest. 1995;96:1786–93.
14. Almaden Y, Canalejo A, Hernandez A, Ballesteros E, Garcia-Navarro S, Torres A, et al. Direct effect of phosphorus on PTH secretion from whole rat parathyroid glands in vitro. J Bone Miner Res Off J Am Soc Bone Miner Res. 1996;11(7):970–6.
15. Slatopolsky E, Finch J, Denda M, Ritter C, Zhong M, Dusso A, et al. Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. J Clin Invest. 1996;97:2534–40.
16. Hebert SC. Extracellular calcium-sensing receptor: implications for calcium and magnesium handling in the kidney. Kidney Int. 1996;50(6):2129–39.
17. Suva LJ, Winslow GA, Wettenhall RE, Hammonds RG, Moseley JM, Diefenbach-Jagger H, et al. A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. Science. 1987;237:893–6.

18. Mangin M, Webb AC, Dreyer BE, Posillico JT, Ikeda K, Weir EC, et al. Identification of a cDNA encoding a parathyroid hormone-like peptide from a human tumor associated with humoral hypercalcemia of malignancy. Proc Natl Acad Sci U S A. 1988;85:597–601.
19. Strewler GJ, Stern PH, Jacobs JW, Eveloff J, Klein RF, Leung SC, et al. Parathyroid hormone-like protein from human renal carcinoma cells. Structural and functional homology with parathyroid hormone. J Clin Invest. 1987;80:1803–7.
20. Broadus AE, Stewart AF. Parathyroid hormone-related protein: structure, processing, and physiological actions. In: Bilezikian JP, Levine MA, Marcus R, editors. The parathyroids basic and clinical concepts. New York: Raven; 1994. p. 259–94.
21. Strewler GJ. Mechanisms of disease: the physiology of parathyroid hormone-related protein. New Engl J Med. 2000;342:177–85.
22. Kronenberg H. Developmental regulation of the growth plate. Nature. 2003;423:332–6.
23. VanHouten J, Dann P, McGeoch G, Brown EM, Krapcho K, Neville M, et al. The calcium-sensing receptor regulates mammary gland parathyroid hormone-related protein production and calcium transport. J Clin Invest. 2004;113(4):598–608.
24. Hiremath M, Wysolmerski J. Parathyroid hormone-related protein specifies the mammary mesenchyme and regulates embryonic mammary development. J Mammary Gland Biol Neoplasia. 2013;18(2):171–7.
25. Jüppner H, Abou-Samra AB, Freeman MW, Kong XF, Schipani E, Richards J, et al. A G protein-linked receptor for parathyroid hormone and parathyroid hormone-related peptide. Science. 1991;254:1024–6.
26. Abou-Samra AB, Jüppner H, Force T, Freeman MW, Kong XF, Schipani E, et al. Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: a single receptor stimulates intracellular accumulation of both cAMP and inositol triphosphates and increases intracellular free calcium. Proc Natl Acad Sci U S A. 1992;89:2732–6.
27. Lee K, Deeds JD, Segre GV. Expression of parathyroid hormone-related peptide and its receptor messenger ribonucleic acid during fetal development of rats. Endocrinology. 1995;136:453–63.
28. Usdin TB, Gruber C, Bonner TI. Identification and functional expression of a receptor selectively recognizing parathyroid hormone, the PTH2 receptor. J Biol Chem. 1995;270:15455–8.
29. Usdin TB, Hoare SRJ, Wang T, Mezey E, Kowalak JA. Tip39: a new neuropeptide and PTH2-receptor agonist from hypothalamus. Nat Neurosci. 1999;2:941–3.
30. Dimitrov EL, Petrus E, Usdin TB. Tuberoinfundibular peptide of 39 residues (TIP39) signaling modulates acute and tonic nociception. Exp Neurol. 2010;226(1):68–83.
31. Coutellier L, Usdin TB. Enhanced long-term fear memory and increased anxiety and depression-like behavior after exposure to an aversive event in mice lacking TIP39 signaling. Behav Brain Res. 2011;222(1):265–9.
32. Whyte MP. Rickets and osteomalacia. In: Wass J, Shalet S, editors. Oxford textbook of endocrinology, Oxford: Oxford University Press; 2002. p. 697–715.
33. Liberman U, Marx SJ. Vitamin D and other calciferols. In: Beaudlt A, Sly W, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th ed. New York: McGraw-Hill; 2001. p. 4223–40.
34. Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW. Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc Natl Acad Sci U S A. 2004;101(20):7711–5.
35. Al Mutair AN, Nasrat GH, Russell DW. Mutation of the CYP2R1 vitamin D 25-hydroxylase in a Saudi Arabian family with severe vitamin D deficiency. J Clin Endocrinol Metab. 2012;97(10):E2022–5.
36. White KE, Larsson TE, Econs MJ. The roles of specific genes implicated as circulating factors involved in normal and disordered phosphate homeostasis: frizzled related protein-4, matrix extracellular phosphoglycoprotein, and fibroblast growth factor 23. Endocr Rev. 2006;27(3):221–41.
37. Haussler MR, Haussler CA, Jurutka PW, Thompson PD, Hsieh JC, Remus LS, et al. The vitamin D hormone and its nuclear receptor: molecular actions and disease states. J Endocrinol. 1997;154(Suppl):S57–73.
38. ADHR Consortium T, White KE, Evans WE, O'Riordan JLH, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meittinger T, Strom TM. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet. 2000;26:345–8.
39. White KE, Jonsson KB, Carn G, Hampson G, Spector TD, Mannstadt M, et al. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. J Clin Endocrinol Metabol. 2001;86(2):497–500.
40. Benet-Pages A, Lorenz-Depiereux B, Zischka H, White K, Econs M, Strom T. FGF23 is processed by proprotein convertases but not by PHEX. Bone. 2004;35:455–62.
41. Tagliabracci VS, Engel JL, Wiley SE, Xiao J, Gonzalez DJ, Nidumanda Appaiah H, et al. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proc Natl Acad Sci U S A. 2014;111(15):5520–5.
42. Goetz R, Nakada Y, Hu MC, Kurosu H, Wang L, Nakatani T, et al. Isolated C-terminal tail of FGF23 alleviates hypophosphatemia by inhibiting FGF23-FGFR-Klotho complex formation. Proc Natl Acad Sci U S A. 2010;107:407–12.

43. Shimada T, Yoneya T, Hino R, Takeuchi Y, Fukumoto S, Yamashita T, editors. Transgenic mice expressing fibroblast growth factor 23 (FGF23) demonstrate hypophosphatemia with low serum 1,25-dihydroxyvitamin D [1,25(OH)2D] and rickets/osteomalacia. Twenty-third Annual Meeting of the American Society for Bone and Mineral Research, Phoenix; 2001; J Bone Mineral Res
44. Riminucci M, Collins M, Fedarko N, Cherman N, Corsi A, White K, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003;112:683–92.
45. Sitara D, Razzaque MS, Hesse M, Yoganathan S, Taguchi T, Erben RG, et al. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. Matrix Biol. 2004;23:421–32.
46. Liu S, Zhou J, Tang W, Jiang X, Rowe DW, Quarles LD. Pathogenic role of Fgf23 in Hyp mice. Am J Physiol Endocrinol Metab. 2006;291(1):E38–49.
47. Bonewald LF. The amazing osteocyte. J Bone Miner Res Off J Am Soc Bone Miner Res. 2011;26(2):229–38.
48. Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet. 2006;38(11):1310–5.
49. Wang X, Wang S, Li C, Gao T, Liu Y, Rangiani A, et al. Inactivation of a novel FGF23 regulator, FAM20C, leads to hypophosphatemic rickets in mice. PLoS Genet. 2012;8(5):e1002708.
50. Mackenzie NC, Zhu D, Milne EM, Van't Hof R, Martin A, Darryl Quarles L, et al. Altered bone development and an increase in FGF-23 expression in Enpp1(−/−) mice. PLoS One. 2012;7(2):e32177.
51. Lorenz-Depiereux B, Bastepe M, Benet-Pages A, Amyere M, Wagenstaller J, Muller-Barth U, et al. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. Nat Genet. 2006;38(11):1248–50.
52. Mäkitie O, Pereira RC, Kaitila I, Turan S, Bastepe M, Laine T, et al. Long-term clinical outcome and carrier phenotype in autosomal recessive hypophosphatemia caused by a novel DMP1 mutation. J Bone Miner Res. 2010;25:2165–174.
53. Turan S, Aydin C, Bereket A, Akcay T, Guran T, Yaralioglu BA, et al. Identification of a novel dentin matrix protein-1 (DMP-1) mutation and dental anomalies in a kindred with autosomal recessive hypophosphatemia. Bone. 2010;46(2):402–9.
54. Lorenz-Depiereux B, Schnabel D, Tiosano D, Hausler G, Strom TM. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010;86(2):267–72.
55. Nitschke Y, Baujat G, Botschen U, Wittkampf T, du Moulin M, Stella J, et al. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either ENPP1 or ABCC6. Am J Hum Genet. 2012;90(1):25–39.
56. Ishikawa HO, Xu A, Ogura E, Manning G, Irvine KD. The Raine syndrome protein FAM20C is a Golgi kinase that phosphorylates bio-mineralization proteins. PLoS One. 2012;7(8):e42988.
57. Rafaelsen SH, Raeder H, Fagerheim AK, Knappskog P, Carpenter TO, Johansson S, et al. Exome sequencing reveals FAM20c mutations associated with fibroblast growth factor 23-related hypophosphatemia, dental anomalies, and ectopic calcification. J Bone Miner Res Off J Am Soc Bone Miner Res. 2013;28(6):1378–85.
58. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997;390(6655):45–51.
59. Kuro-o M. Klotho as a regulator of fibroblast growth factor signaling and phosphate/calcium metabolism. Curr Opin Nephrol Hypertens. 2006;15(4):437–41.
60. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006;444:770–4.
61. Ohnishi M, Nakatani T, Lanske B, Razzaque MS. Reversal of mineral ion homeostasis and soft-tissue calcification of klotho knockout mice by deletion of vitamin D 1alpha-hydroxylase. Kidney Int. 2009;75(11):1166–72.
62. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004;113(4):561–8.
63. Liu S, Brown T, Zhou J, Xiao Z, Awad H, Guilak F, et al. Role of matrix extracellular phosphoglycoprotein in the pathogenesis of X-linked hypophosphatemia. J Am Soc Nephrol. 2005;16:1645–53.
64. Shimada T, Yamazaki Y, Takahashi M, Hasegawa H, Urakawa I, Oshima T, et al. Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. Am J Physiol Renal Physiol. 2005;289(5):F1088–95.
65. Jan De Beur S, Finnegan R, Vassiliadis J, Cook B, Barberio D, Estes S, et al. Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. J Bone Miner Res Off J Am Soc Bone Miner Res. 2002;17:1102–10.
66. Carpenter TO, Ellis BK, Insogna KL, Philbrick WM, Sterpka J, Shimkets R. Fibroblast growth factor 7: an inhibitor of phosphate transport derived from oncogenic osteomalacia-causing tumors. J Clin Endocrinol Metab. 2005;90(2):1012–20.
67. Berndt T, Craig T, Bowe A, Vassiliadis J, Reczek D, Finnegan R, et al. Secreted frizzled-related protein 4 is

a potent tumor-derived phosphaturic agent. J Clin Invest. 2003;112:785–94.
68. Rowe P, Kumagai Y, Gutierrez G, Garrett I, Blacher R, Rosen D, et al. MEPE has the properties of an osteoblastic phosphatonin and minhibin. Bone. 2004;34:303–19.
69. Christov M, Koren S, Yuan Q, Baron R, Lanske B. Genetic ablation of sfrp4 in mice does not affect serum phosphate homeostasis. Endocrinology. 2012;152(5):2031–6.
70. Thakker RV. Molecular genetics of parathyroid disease. Curr Opin Endocrinol Diabetes Obes. 1996;3:521–8.
71. Szabo J, Heath B, Hill VM, Jackson CE, Zarbo RJ, Mallette LE, et al. Hereditary hyperparathyroidism-jaw tumor syndrome: the endocrine tumor gene HRPT2 maps to chromosome 1q21-q31. Am J Hum Genet. 1995;56(4):944–50.
72. Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet. 2002;32(4):676–80.
73. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9): 2990–3011.
74. Hsu SC, Levine MA. Primary hyperparathyroidism in children and adolescents: the Johns Hopkins Children's Center experience 1984–2001. J Bone Miner Res Off J Am Soc Bone Miner Res. 2002;17 Suppl 2: N44–50.
75. Arnold A, Brown MF, Urena P, Gaz RD, Sarfati E, Drueke TB. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. J Clin Invest. 1995;95(5):2047–53.
76. Buchwald PC, Akerstrom G, Westin G. Reduced p18INK4c, p21CIP1/WAF1 and p27KIP1 mRNA levels in tumours of primary and secondary hyperparathyroidism. Clin Endocrinol (Oxf). 2004;60(3): 389–93.
77. Bjorklund P, Åkerstrom G, Westin G. Accumulation of nonphosphorylated beta-catenin and c-myc in primary and uremic secondary hyperparathyroid tumors. J Clin Endocrinol Metab. 2007;92(1):338–44.
78. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. New Engl J Med. 2003;348(17): 1656–63.
79. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584–92.
80. Shimada T, Urakawa I, Isakova T, Yamazaki Y, Epstein M, Wesseling-Perry K, et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. J Clin Endocrinol Metab. 2010;95(2):578–85.
81. Smith ER, Cai MM, McMahon LP, Holt SG. Biological variability of plasma intact and C-terminal FGF23 measurements. J Clin Endocrinol Metab. 2012;97(9): 3357–65.
82. Larsson T, Zahradnik R, Lavigne J, Ljunggren Ö, Jüppner H, Jonsson K. Immunohistochemical detection of FGF-23 protein in tumors that cause oncogenic osteomalacia. Eur J Endocrinol. 2003;148:269–76.
83. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol. 2005;16(7):2205–15.
84. Portale A, Wolf M, Jüppner H, Cayetano S, Kumar J, Wesseling-Perry K, et al. Disordered FGF23 and mineral metabolism in the chronic kidney disease in children (CKiD) cohort. Clin J Am Soc Nephrol. 2014;9:344–53.
85. Au AY, McDonald K, Gill A, Sywak M, Diamond T, Conigrave AD, et al. PTH mutation with primary hyperparathyroidism and undetectable intact PTH. N Engl J Med. 2008;359(11):1184–6.
86. Janicic N, Soliman E, Pausova Z, Seldin MF, Riviere M, Szpirer J, et al. Mapping of the calcium-sensing receptor gene (CASR) to human chromosome 3q13.3-21 by fluorescence in situ hybridization, and localization to rat chromosome 11 and mouse chromosome 16. Mamm Genome Off J Int Mamm Genome Soc. 1995;6(11):798–801.
87. Pollak MR, Brown EM, WuChou YH, Hebert SC, Marx SJ, Steinmann B, et al. Mutations in the human Ca^{2+}-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Cell. 1993;75:1297–303.
88. Chou YH, Pollak MR, Brandi ML, Toss G, Arnqvist H, Atkinson AB, et al. Mutations in the human Ca(2+)-sensing-receptor gene that cause familial hypocalciuric hypercalcemia. Am J Hum Genet. 1995;56(5):1075–9.
89. Pearce S, Trump D, Wooding C, Besser G, Chew S, Grant D, et al. Calcium-sensing receptor mutations in familial benign hypercalcaemia and neonatal hyperparathyroidism. J Clin Invest. 1995;96:2683–92.
90. Janicic N, Pausova Z, Cole DE, Hendy GN. Insertion of an Alu sequence in the Ca(2+)-sensing receptor gene in familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Am J Hum Genet. 1995;56(4):880–6.
91. Aida K, Koishi S, Inoue M, Nakazato M, Tawata M, Onaya T. Familial hypocalciuric hypercalcemia associated with mutation in the human Ca(2+)-sensing receptor gene. J Clin Endocrinol Metab. 1995;80(9): 2594–8.
92. Heath III H, Odelberg S, Jackson CE, Teh BT, Hayward N, Larsson C, et al. Clustered inactivating mutations and benign polymorphisms of the calcium receptor gene in familial benign hypocalciuric

hypercalcemia suggest receptor functional domains. J Clin Endocrinol Metab. 1996;81:1312–7.
93. Nesbit MA, Hannan FM, Howles SA, Babinsky VN, Head RA, Cranston T, et al. Mutations affecting G-protein subunit alpha11 in hypercalcemia and hypocalcemia. N Engl J Med. 2013;368(26): 2476–86.
94. Mannstadt M, Harris M, Bravenboer B, Chitturi S, Dreijerink KM, Lambright DG, et al. Germline mutations affecting Galpha11 in hypoparathyroidism. N Engl J Med. 2013;368(26):2532–4.
95. Nesbit MA, Hannan FM, Howles SA, Reed AA, Cranston T, Thakker CE, et al. Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. Nat Genet. 2013;45(1):93–7.
96. Lloyd SE, Pannett AA, Dixon PH, Whyte MP, Thakker RV. Localization of familial benign hypercalcemia, Oklahoma variant (FBHOk), to chromosome 19q13. Am J Hum Genet. 1999;64(1): 189–95.
97. McMurtry CT, Schranck FW, Walkenhorst DA, Murphy WA, Kocher DB, Teitelbaum SL, et al. Significant developmental elevation in serum parathyroid hormone levels in a large kindred with familial benign (hypocalciuric) hypercalcemia. Am J Med. 1992;93(3):247–58.
98. Trump D, Whyte MP, Wooding C, Pang JT, Pearce SH, Kocher DB, et al. Linkage studies in a kindred from Oklahoma, with familial benign (hypocalciuric) hypercalcaemia (FBH) and developmental elevations in serum parathyroid hormone levels, indicate a third locus for FBH. Hum Genet. 1995;96(2):183–7.
99. Pearce SH, Bai M, Quinn SJ, Kifor O, Brown EM, Thakker RV. Functional characterization of calcium-sensing receptor mutations expressed in human embryonic kidney cells. J Clin Invest. 1996;98(8): 1860–6.
100. Bai M, Quinn S, Trivedi S, Kifor O, Pearce SH, Pollak MR, et al. Expression and characterization of inactivating and activating mutations in the human Ca^{2+}-sensing receptor. J Biol Chem. 1996;271(32): 19537–45.
101. Morten KJ, Cooper JM, Brown GK, Lake BD, Pike D, Poulton J. A new point mutation associated with mitochondrial encephalomyopathy. Hum Mol Genet. 1993;2(12):2081–7.
102. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev. 2001;81(1):239–97.
103. Zajickova K, Vrbikova J, Canaff L, Pawelek PD, Goltzman D, Hendy GN. Identification and functional characterization of a novel mutation in the calcium-sensing receptor gene in familial hypocalciuric hypercalcemia: modulation of clinical severity by vitamin D status. J Clin Endocrinol Metab. 2007;92(7): 2616–23.
104. Felderbauer P, Klein W, Bulut K, Ansorge N, Dekomien G, Werner I, et al. Mutations in the calcium-sensing receptor: a new genetic risk factor for chronic pancreatitis? Scand J Gastroenterol. 2006;41(3):343–8.
105. Pollak MR, Chou YH, Marx SJ, Steinmann B, Cole DE, Brandi ML, et al. Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Effects of mutant gene dosage on phenotype. J Clin Invest. 1994;93(3):1108–12.
106. Bai M, Pearce SH, Kifor O, Trivedi S, Stauffer UG, Thakker RV, et al. In vivo and in vitro characterization of neonatal hyperparathyroidism resulting from a de novo, heterozygous mutation in the Ca2+−sensing receptor gene: normal maternal calcium homeostasis as a cause of secondary hyperparathyroidism in familial benign hypocalciuric hypercalcemia. J Clin Invest. 1997;99(1):88–96.
107. Ward BK, Cameron FJ, Magno AL, McDonnell CM, Stuckey BG, Ratajczak T. A novel homozygous deletion in the calcium-sensing receptor ligand-binding domain associated with neonatal severe hyperparathyroidism. J Pediat Endocrinol Metab. 2006;19(1): 93–100.
108. Marx SJ, Fraser D, Rapoport A. Familial hypocalciuric hypercalcemia. Mild expression of the gene in heterozygotes and severe expression in homozygotes. Am J Med. 1985;78(1):15–22.
109. Cole D, Forsythe CR, Dooley JM, Grantmyre EB, Salisbury SR. Primary neonatal hyperparathyroidism: a devastating neurodevelopmental disorder if left untreated. J Craniofac Genet Dev Biol. 1990;10(2): 205–14.
110. Toke J, Czirjak G, Patocs A, Enyedi B, Gergics P, Csakvary V, et al. Neonatal severe hyperparathyroidism associated with a novel de novo heterozygous R551K inactivating mutation and a heterozygous A986S polymorphism of the calcium-sensing receptor gene. Clin Endocrinol (Oxf). 2007;67(3):385–92.
111. Kifor O, Moore Jr FD, Delaney M, Garber J, Hendy GN, Butters R, et al. A syndrome of hypocalciuric hypercalcemia caused by autoantibodies directed at the calcium-sensing receptor. J Clin Endocrinol Metab. 2003;88(1):60–72.
112. Pallais J, Kifor O, Chen Y, Slovik D, Brown E. Acquired hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor. N Engl J Med. 2004;351:362–9.
113. Makita N, Sato J, Manaka K, Shoji Y, Oishi A, Hashimoto M, et al. An acquired hypocalciuric hypercalcemia autoantibody induces allosteric transition among active human Ca-sensing receptor conformations. Proc Natl Acad Sci U S A. 2007;104(13): 5443–8.
114. Frame B, Poznanski AK. Conditions that may be confused with rickets. In: DeLuca HF, Anast AS, editor. Pediatric diseases related to calcium. New York: Elsevier; 1980. p. 269–89.
115. Jüppner H, Schipani E, Silve C. Jansen's metaphyseal chondrodysplasia and Blomstrand's lethal chondrodysplasia: two genetic disorders caused by PTH/PTHrP receptor mutations. In: Bilezikian J,

Raisz L, Rodan G, editors. Principles of bone biology, vol. 2. San Diego: Academic; 2002. p. 1117–35.
116. Schipani E, Kruse K, Jüppner H. A constitutively active mutant PTH-PTHrP receptor in Jansen-type metaphyseal chondrodysplasia. Science. 1995;268: 98–100.
117. Schipani E, Langman CB, Parfitt AM, Jensen GS, Kikuchi S, Kooh SW, et al. Constitutively activated receptors for parathyroid hormone and parathyroid hormone-related peptide in Jansen's metaphyseal chondrodysplasia. N Engl J Med. 1996;335:708–14.
118. Schipani E, Langman CB, Hunzelman J, LeMerrer M, Loke KY, Dillon MJ, et al. A novel PTH/PTHrP receptor mutation in Jansen's metaphyseal chondrodysplasia. J Clin Endocrinol Metab. 1999;84:3052–7.
119. Minagawa M, Arakawa K, Minamitani K, Yasuda T, Niimi H. Jansen-type metaphyseal chondrodysplasia: analysis of PTH/PTH-related protein receptor messenger RNA by the reverse transcription-polymerase chain method. Endocr J. 1997;44:493–9.
120. Brown WW, Jüppner H, Langman CB, Price H, Farrow EG, White KE, et al. Hypophosphatemia with elevations in serum fibroblast growth factor 23 in a child with Jansen's metaphyseal chondrodysplasia. J Clin Endocrinol Metab. 2009;94(1):17–20.
121. Onuchic L, Ferraz-de-Souza B, Mendonca BB, Correa PH, Martin RM. Potential effects of alendronate on fibroblast growth factor 23 levels and effective control of hypercalciuria in an adult with Jansen's metaphyseal chondrodysplasia. J Clin Endocrinol Metab. 2012;97(4):1098–103.
122. Savoldi G, Izzi C, Signorelli M, Bondioni MP, Romani C, Lanzi G, et al. Prenatal presentation and postnatal evolution of a patient with Jansen metaphyseal dysplasia with a novel missense mutation in PTH1R. Am J Med Genet A. 2013;161(10): 2614–9.
123. Schipani E, Lanske B, Hunzelman J, Kovacs CS, Lee K, Pirro A, et al. Targeted expression of constitutively active PTH/PTHrP receptors delays endochondral bone formation and rescues PTHrP-less mice. Proc Natl Acad Sci U S A. 1997;94:13689–94.
124. Beier F, LuValle P. The cyclin D1 and cyclin a genes are targets of activated PTH/PTHrP receptors in Jansen's metaphyseal chondrodysplasia. Mol Endocrinol. 2002;16(9):2163–73.
125. Bastepe M, Raas-Rothschild A, Silver J, Weissman I, Jüppner H, Gillis D. A form of Jansen's metaphyseal chondrodysplasia with limited metabolic and skeletal abnormalities is caused by a novel activating PTH/PTHrP receptor mutation. J Clin Endocrinol Metab. 2004;89:3595–600.
126. Schipani E, Jensen GS, Pincus J, Nissenson RA, Gardella TJ, Jüppner H. Constitutive activation of the cAMP signaling pathway by parathyroid hormone (PTH)/PTH-related peptide (PTHrP) receptors mutated at the two loci for Jansen's metaphyseal chondrodysplasia. Mol Endocrinol. 1997;11:851–8.
127. Pober BR. Williams-Beuren syndrome. N Engl J Med. 2010;362(3):239–52.
128. Li D, Brooke B, Davis E, Mecham R, Sorensen L, Boak B, et al. Elastin is an essential determinant of arterial morphogenesis. Nature. 1998;393:276–80.
129. Ewart AK, Morris CA, Atkinson DL, Jin W, Sternes K, Spallone P, et al. Hemizygosity at the elastin locus in a developmental disorder. Williams syndrome. Nat Genet. 1993;5:11–6.
130. Lowery MC, Morris CA, Ewart A, Brothman LJ, Zhu XL, Leonard CO, et al. Strong correlation of elastin deletions, detected by FISH, with Williams syndrome: evaluation of 235 patients. Am J Hum Genet. 1995;57(1):49–53.
131. Tassabehji M, Metcalfe K, Fergusson WD, Carette MJ, Dore JK, Donnai D, et al. LIM-kinase deleted in Williams syndrome. Nat Genet. 1996;13 (3):272–3.
132. van Hagen JM, van der Geest JN, van der Giessen RS, Lagers-van Haselen GC, Eussen HJ, Gille JJ, et al. Contribution of CYLN2 and GTF2IRD1 to neurological and cognitive symptoms in Williams syndrome. Neurobiol Dis. 2007;26(1):112–24.
133. Del Campo M, Antonell A, Magano LF, Munoz FJ, Flores R, Bayes M, et al. Hemizygosity at the NCF1 gene in patients with Williams-Beuren syndrome decreases their risk of hypertension. Am J Hum Genet. 2006;78(4):533–42.
134. Edelmann L, Prosnitz A, Pardo S, Bhatt J, Cohen N, Lauriat T, et al. An atypical deletion of the Williams-Beuren syndrome interval implicates genes associated with defective visuospatial processing and autism. J Med Genet. 2007;44(2):136–43.
135. Merla G, Howald C, Henrichsen CN, Lyle R, Wyss C, Zabot MT, et al. Submicroscopic deletion in patients with Williams-Beuren syndrome influences expression levels of the nonhemizygous flanking genes. Am J Hum Genet. 2006;79(2):332–41.
136. Cagle AP, Waguespack SG, Buckingham BA, Shankar RR, Dimeglio LA. Severe infantile hypercalcemia associated with Williams syndrome successfully treated with intravenously administered pamidronate. Pediatrics. 2004;114(4):1091–5.
137. Perez Jurado LA, Li X, Francke U. The human calcitonin receptor gene (CALCR) at 7q21.3 is outside the deletion associated with the Williams syndrome. Cytogenet Cell Genet. 1995;70(3–4):246–9.
138. Garabedian M, Jacqz E, Guillozo H, Grimberg R, Guillot M, Gagnadoux MF, et al. Elevated plasma 1,25-dihydroxyvitamin D concentrations in infants with hypercalcemia and an elfin facies. N Engl J Med. 1985;312(15):948–52.
139. Taylor AB, Stern PH, Bell NH. Abnormal regulation of circulating 25-hydroxyvitamin D in the Williams syndrome. N Engl J Med. 1982;306(16):972–5.
140. Lameris AL, Huybers S, Burke JR, Monnens LA, Bindels RJ, Hoenderop JG. Involvement of claudin 3 and claudin 4 in idiopathic infantile hypercalcaemia: a novel hypothesis? Nephrol Dial

Transplant Off Publ Eur Dial Transplant Assoc Eur Ren Assoc. 2010;25(11):3504–9.
141. Letavernier E, Rodenas A, Guerrot D, Haymann JP. Williams-Beuren syndrome hypercalcemia: is TRPC3 a novel mediator in calcium homeostasis? Pediatrics. 2012;129(6):e1626–30.
142. Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med. 2011;365:410–21.
143. Dauber A, Nguyen TT, Sochett E, Cole DE, Horst R, Abrams SA, et al. Genetic defect in CYP24A1, the vitamin D 24-hydroxylase gene, in a patient with severe infantile hypercalcemia. J Clin Endocrinol Metab. 2012;97(2):E268–74.
144. Fencl F, Blahova K, Schlingmann KP, Konrad M, Seeman T. Severe hypercalcemic crisis in an infant with idiopathic infantile hypercalcemia caused by mutation in CYP24A1 gene. Eur J Pediatr. 2013;172(1):45–9.
145. Tebben PJ, Milliner DS, Horst RL, Harris PC, Singh RJ, Wu Y, et al. Hypercalcemia, hypercalciuria, and elevated calcitriol concentrations with autosomal dominant transmission due to CYP24A1 mutations: effects of ketoconazole therapy. J Clin Endocrinol Metab. 2012;97(3):E423–7.
146. Castanet M, Mallet E, Kottler ML. Lightwood syndrome revisited with a novel mutation in CYP24 and vitamin D supplement recommendations. J Pediatr. 2013;163(4):1208–10.
147. Zwermann O, Piepkorn B, Engelbach M, Beyer J, Kann P. Abnormal pentagastrin response in a patient with pseudohypoparathyroidism. Exp Clin Endocrinol Diabetes. 2002;110(2):86–91.
148. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(12):4507–14.
149. Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1–34) versus calcitriol and calcium. J Clin Endocrinol Metab. 2003;88(9):4214–20.
150. Winer KK, Sinaii N, Peterson D, Sainz Jr B, Cutler Jr GB. Effects of once versus twice-daily parathyroid hormone 1–34 therapy in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008;93(9):3389–95.
151. Winer KK, Sinaii N, Reynolds J, Peterson D, Dowdy K, Cutler Jr GB. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1–34 versus calcitriol and calcium. J Clin Endocrinol Metab. 2010;95(6):2680–8.
152. Winer KK, Yanovski JA, Cutler Jr GB. Synthetic human parathyroid hormone 1–34 vs calcitriol and calcium in the treatment of hypoparathyroidism. JAMA. 1996;276(8):631–6.
153. Winer KK, Yanovski JA, Sarani B, Cutler Jr GB. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1–34 in treatment of hypoparathyroidism. J Clin Endocrinol Metab. 1998;83(10):3480–6.
154. Winer KK, Zhang B, Shrader JA, Peterson D, Smith M, Albert PS, et al. Synthetic human parathyroid hormone 1–34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(2):391–9.
155. Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, et al. Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol. 2013;1(4):275–83.
156. Winer KK, Fulton KA, Albert PS, Cutler GB, Jr. Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. J Pediatr. 2014;165:556–63.
157. Linglart A, Rothenbuhler A, Gueorgieva I, Lucchini P, Silve C, Bougneres P. Long-term results of continuous subcutaneous recombinant PTH (1–34) infusion in children with refractory hypoparathyroidism. J Clin Endocrinol Metab. 2011;96(11):3308–12.
158. Arnold A, Horst SA, Gardella TJ, Baba H, Levine MA, Kronenberg HM. Mutation of the signal peptide-encoding region of the preproparathyroid hormone gene in familial isolated hypoparathyroidism. J Clin Invest. 1990;86:1084–7.
159. Karaplis AC, Lim SK, Baba H, Arnold A, Kronenberg HM. Inefficient membrane targeting, translocation, and proteolytic processing by signal peptidase of a mutant preproparathyroid hormone protein. J Biol Chem. 1995;270:1629–35.
160. Datta R, Waheed A, Shah GN, Sly WS. Signal sequence mutation in autosomal dominant form of hypoparathyroidism induces apoptosis that is corrected by a chemical chaperone. Proc Natl Acad Sci U S A. 2007;104(50):19989–94.
161. Sunthornthepvarakul T, Churesigaew S, Ngowngarmratana S. A novel mutation of the signal peptide of the preproparathyroid hormone gene associated with autosomal recessive familial isolated hypoparathyroidism. J Clin Endocrinol Metab. 1999;84(10):3792–6.
162. Parkinson D, Thakker R. A donor splice site mutation in the parathyroid hormone gene is associated with autosomal recessive hypoparathyroidism. Nat Genet. 1992;1:149–53.
163. Ertl DA, Stary S, Streubel B, Raimann A, Haeusler G. A novel homozygous mutation in the parathyroid hormone gene (PTH) in a girl with isolated hypoparathyroidism. Bone. 2012;51(3):629–32.
164. Tomar N, Gupta N, Goswami R. Calcium-sensing receptor autoantibodies and idiopathic

hypoparathyroidism. J Clin Endocrinol Metab. 2013;98(9):3884–91.
165. Kawahara M, Iwasaki Y, Sakaguchi K, Taguchi T, Nishiyama M, Nigawara T, et al. Involvement of GCMB in the transcriptional regulation of the human parathyroid hormone gene in a parathyroid-derived cell line PT-r: effects of calcium and 1,25(OH)2D3. Bone. 2010;47(3):534–41.
166. Günther T, Chen ZF, Kim J, Priemel M, Rueger JM, Amling M, et al. Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. Nature. 2000;406(6792):199–203.
167. Liu Z, Yu S, Manley NR. Gcm2 is required for the differentiation and survival of parathyroid precursor cells in the parathyroid/thymus primordia. Dev Biol. 2007;305(1):333–46.
168. Ding C, Buckingham B, Levine MA. Familial isolated hypoparathyroidism caused by a mutation in the gene for the transcription factor GCMB. J Clin Invest. 2001;108(8):1215–20.
169. Thomee C, Schubert SW, Parma J, Le PQ, Hashemolhosseini S, Wegner M, et al. GCMB mutation in familial isolated hypoparathyroidism with residual secretion of parathyroid hormone. J Clin Endocrinol Metab. 2005;90(5):2487–92.
170. Baumber L, Tufarelli C, Patel S, King P, Johnson CA, Maher ER, et al. Identification of a novel mutation disrupting the DNA binding activity of GCM2 in autosomal recessive familial isolated hypoparathyroidism. J Med Genet. 2005;42(5):443–8.
171. Maret A, Ding C, Kornfield SL, Levine MA. Analysis of the GCM2 gene in isolated hypoparathyroidism: a molecular and biochemical study. J Clin Endocrinol Metab. 2008;93(4):1426–32.
172. Bowl MR, Mirczuk SM, Grigorieva IV, Piret SE, Cranston T, Southam L, et al. Identification and characterization of novel parathyroid-specific transcription factor Glial Cells Missing Homolog B (GCMB) mutations in eight families with autosomal recessive hypoparathyroidism. Hum Mol Genet. 2010;19(10):2028–38.
173. Mirczuk SM, Bowl MR, Nesbit MA, Cranston T, Fratter C, Allgrove J, et al. A missense glial cells missing homolog B (GCMB) mutation, Asn502His, causes autosomal dominant hypoparathyroidism. J Clin Endocrinol Metab. 2010;95(7):3512–6.
174. Tomar N, Bora H, Singh R, Gupta N, Kaur P, Chauhan SS, et al. Presence and significance of a R110W mutation in the DNA-binding domain of GCM2 gene in patients with isolated hypoparathyroidism and their family members. Eur J Endocrinol. 2010;162(2):407–21.
175. Mannstadt M, Bertrand G, Muresan M, Weryha G, Leheup B, Pulusani SR, et al. Dominant-negative GCMB mutations cause an autosomal dominant form of hypoparathyroidism. J Clin Endocrinol Metab. 2008;93(9):3568–76.
176. Canaff L, Zhou X, Mosesova I, Cole DE, Hendy GN. Glial Cells Missing-2 (GCM2) transactivates the calcium-sensing receptor gene: effect of a dominant-negative GCM2 mutant associated with autosomal dominant hypoparathyroidism. Hum Mutat. 2009;30(1):85–92.
177. Peden VH. True idiopathic hypoparathyroidism as a sex-linked recessive trait. Am J Hum Genet. 1960;12:323–37.
178. Mumm S, Whyte MP, Thakker RV, Buetow KH, Schlessinger D. mtDNA analysis shows common ancestry in two kindreds with X-linked recessive hypoparathyroidism and reveals a heteroplasmic silent mutation. Am J Hum Genet. 1997;60(1):153–9.
179. Whyte M, Kim G, Kosanovich M. Absence of parathyroid tissue in sex-linked recessive hypoparathyroidism. J Paediatr. 1986;109:915.
180. Thakker RV, Davies KE, Whyte MP, Wooding C, O'Riordan JL. Mapping the gene causing X-linked recessive idiopathic hypoparathyroidism to Xq26-Xq27 by linkage studies. J Clin Invest. 1990;86(1):40–5.
181. Bowl M, Nesbit M, Harding B, Levy E, Jefferson A, Volpi E, et al. An interstitial deletion-insertion involving chromosomes 2p25.3 and Xq27.1, near SOX3, causes X-linked recessive hypoparathyroidism. J Clin Invest. 2005;115:2822–31.
182. Ahonen P. Autoimmune polyendocrinopathy–candidosis–ectodermal dystrophy (APECED): autosomal recessive inheritance. Clin Genet. 1985;27(6):535–42.
183. Goswami R, Singh A, Gupta N, Rani R. Presence of strong association of the major histocompatibility complex (MHC) class I allele HLA-A*26:01 with idiopathic hypoparathyroidism. J Clin Endocrinol Metab. 2012;97(9):E1820–4.
184. Aaltonen J, Bjorses P, Sandkuijl L, Perheentupa J, Peltonen L. An autosomal locus causing autoimmune disease: autoimmune polyglandular disease type I assigned to chromosome 21. Nat Genet. 1994;8(1):83–7.
185. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, et al. Positional cloning of the APECED gene. Nat Genet. 1997;17(4):393–8.
186. Scott HS, Heino M, Peterson P, Mittaz L, Lalioti MD, Betterle C, et al. Common mutations in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients of different origins. Mol Endocrinol. 1998;12(8):1112–9.
187. Cihakova D, Trebusak K, Heino M, Fadeyev V, Tiulpakov A, Battelino T, et al. Novel AIRE mutations and P450 cytochrome autoantibodies in Central and Eastern European patients with APECED. Hum Mutat. 2001;18(3):225–32.
188. Wang CY, Davoodi-Semiromi A, Huang W, Connor E, Shi JD, She JX. Characterization of mutations in patients with autoimmune polyglandular syndrome type 1 (APS1). Hum Genet. 1998;103(6):681–5.
189. Heino M, Scott HS, Chen Q, Peterson P, Maebpaa U, Papasavvas MP, et al. Mutation analyses of North

American APS-1 patients. Hum Mutat. 1999;13(1): 69–74.
190. Pearce SH, Cheetham T, Imrie H, Vaidya B, Barnes ND, Bilous RW, et al. A common and recurrent 13-bp deletion in the autoimmune regulator gene in British kindreds with autoimmune polyendocrinopathy type 1. Am J Hum Genet. 1998;63(6):1675–84.
191. Bjorses P, Halonen M, Palvimo JJ, Kolmer M, Aaltonen J, Ellonen P, et al. Mutations in the AIRE gene: effects on subcellular location and transactivation function of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy protein. Am J Hum Genet. 2000;66(2):378–92.
192. Rosatelli MC, Meloni A, Devoto M, Cao A, Scott HS, Peterson P, et al. A common mutation in Sardinian autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients. Hum Genet. 1998;103 (4):428–34.
193. Matsuo T, Noguchi Y, Shindo M, Morita Y, Oda Y, Yoshida E, et al. Regulation of human autoimmune regulator (AIRE) gene translation by miR-220b. Gene. 2013;530(1):19–25.
194. Liston A, Lesage S, Wilson J, Peltonen L, Goodnow CC. Aire regulates negative selection of organ-specific T cells. Nat Immunol. 2003;4(4):350–4.
195. Meloni A, Incani F, Corda D, Cao A, Rosatelli MC. Role of PHD fingers and COOH-terminal 30 amino acids in AIRE transactivation activity. Mol Immunol. 2008;45(3):805–9.
196. Su MA, Giang K, Zumer K, Jiang H, Oven I, Rinn JL, et al. Mechanisms of an autoimmunity syndrome in mice caused by a dominant mutation in Aire. J Clin Invest. 2008;118(5):1712–26.
197. Laakso SM, Kekalainen E, Heikkila N, Mannerstrom H, Kisand K, Peterson P, et al. In vivo analysis of helper T cell responses in patients with autoimmune polyendocrinopathy – candidiasis – ectodermal dystrophy provides evidence in support of an IL-22 defect. Autoimmunity. 2014;47:556–62.
198. Gavalas NG, Kemp EH, Krohn KJ, Brown EM, Watson PF, Weetman AP. The calcium-sensing receptor is a target of autoantibodies in patients with autoimmune polyendocrine syndrome type 1. J Clin Endocrinol Metab. 2007;92(6):2107–14.
199. Alimohammadi M, Bjorklund P, Hallgren A, Pontynen N, Szinnai G, Shikama N, et al. Autoimmune polyendocrine syndrome type 1 and NALP5, a parathyroid autoantigen. N Engl J Med. 2008;358(10):1018–28.
200. Kemp EH, Habibullah M, Kluger N, Ranki A, Sandhu HK, Krohn KJ, et al. Prevalence and clinical associations of calcium-sensing receptor and NALP5 autoantibodies in Finnish APECED patients. J Clin Endocrinol Metab. 2014;99(3):1064–71.
201. Meloni A, Furcas M, Cetani F, Marcocci C, Falorni A, Perniola R, et al. Autoantibodies against type I interferons as an additional diagnostic criterion for autoimmune polyendocrine syndrome type I. J Clin Endocrinol Metab. 2008;93(11):4389–97.
202. Meager A, Visvalingam K, Peterson P, Moll K, Murumagi A, Krohn K, et al. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. PLoS Med. 2006;3(7):e289.
203. Wolff AS, Sarkadi AK, Marodi L, Karner J, Orlova E, Oftedal BE, et al. Anti-cytokine autoantibodies preceding onset of autoimmune polyendocrine syndrome type I features in early childhood. J Clin Immunol. 2013;33(8):1341–8.
204. Lammer EJ, Opitz JM. The DiGeorge anomaly as a developmental field defect. Am J Med Genet Suppl. 1986;2:113–27.
205. Gong W, Emanuel BS, Collins J, Kim DH, Wang Z, Chen F, et al. A transcription map of the DiGeorge and velo-cardio-facial syndrome minimal critical region on 22q11. Hum Mol Genet. 1996;5(6): 789–800.
206. Scambler PJ. The 22q11 deletion syndromes. Hum Mol Genet. 2000;9(16):2421–6.
207. Scambler PJ, Carey AH, Wyse RK, Roach S, Dumanski JP, Nordenskjold M, et al. Microdeletions within 22q11 associated with sporadic and familial DiGeorge syndrome. Genomics. 1991;10(1):201–6.
208. Monaco G, Pignata C, Rossi E, Mascellaro O, Cocozza S, Ciccimarra F. DiGeorge anomaly associated with 10p deletion. Am J Med Genet. 1991;39(2): 215–6.
209. Stoller JZ, Epstein JA. Identification of a novel nuclear localization signal in Tbx1 that is deleted in DiGeorge syndrome patients harboring the 1223delC mutation. Hum Mol Genet. 2005;14(7):885–92.
210. Conley ME, Beckwith JB, Mancer JF, Tenckhoff L. The spectrum of the DiGeorge syndrome. J Pediatr. 1979;94(6):883–90.
211. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet. 1997;34(10):798–804.
212. Cuneo BF, Langman CB, Ilbawi MN, Ramakrishnan V, Cutilletta A, Driscoll DA. Latent hypoparathyroidism in children with conotruncal cardiac defects. Circulation. 1996;93(9):1702–8.
213. Taylor SC, Morris G, Wilson D, Davies SJ, Gregory JW. Hypoparathyroidism and 22q11 deletion syndrome. Arch Dis Child. 2003;88(6):520–2.
214. Gidding SS, Minciotti AL, Langman CB. Unmasking of hypoparathyroidism in familial partial DiGeorge syndrome by challenge with disodium edetate. N Engl J Med. 1988;319(24):1589–91.
215. Augusseau S, Jouk S, Jalbert P, Prieur M. DiGeorge syndrome and 22q11 rearrangements. Hum Genet. 1986;74(2):206.
216. Budarf ML, Collins J, Gong W, Roe B, Wang Z, Bailey LC, et al. Cloning a balanced translocation associated with DiGeorge syndrome and identification of a disrupted candidate gene. Nat Genet. 1995;10(3):269–78.

217. Yamagishi H, Garg V, Matsuoka R, Thomas T, Srivastava D. A molecular pathway revealing a genetic basis for human cardiac and craniofacial defects. Science. 1999;283(5405):1158–61.
218. Lindsay EA, Botta A, Jurecic V, Carattini-Rivera S, Cheah YC, Rosenblatt HM, et al. Congenital heart disease in mice deficient for the DiGeorge syndrome region. Nature. 1999;401(6751):379–83.
219. Magnaghi P, Roberts C, Lorain S, Lipinski M, Scambler PJ. HIRA, a mammalian homologue of Saccharomyces cerevisiae transcriptional co-repressors, interacts with Pax3. Nat Genet. 1998;20(1):74–7.
220. Jerome LA, Papaioannou VE. DiGeorge syndrome phenotype in mice mutant for the T-box gene, Tbx1. Nat Genet. 2001;27(3):286–91.
221. Yagi H, Furutani Y, Hamada H, Sasaki T, Asakawa S, Minoshima S, et al. Role of TBX1 in human del22q11.2 syndrome. Lancet. 2003;362(9393): 1366–73.
222. Baldini A. DiGeorge's syndrome: a gene at last. Lancet. 2003;362(9393):1342–3.
223. Liao J, Kochilas L, Nowotschin S, Arnold JS, Aggarwal VS, Epstein JA, et al. Full spectrum of malformations in velo-cardio-facial syndrome/DiGeorge syndrome mouse models by altering Tbx1 dosage. Hum Mol Genet. 2004;13(15):1577–85.
224. Guris DL, Fantes J, Tara D, Druker BJ, Imamoto A. Mice lacking the homologue of the human 22q11.2 gene CRKL phenocopy neurocristopathies of DiGeorge syndrome. Nat Genet. 2001;27(3): 293–8.
225. Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobotka A, et al. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. Proc Natl Acad Sci U S A. 2006;103(20):7729–34.
226. Gogos JA, Santha M, Takacs Z, Beck KD, Luine V, Lucas LR, et al. The gene encoding proline dehydrogenase modulates sensorimotor gating in mice. Nat Genet. 1999;21(4):434–9.
227. Maynard TM, Meechan DW, Dudevoir ML, Gopalakrishna D, Peters AZ, Heindel CC, et al. Mitochondrial localization and function of a subset of 22q11 deletion syndrome candidate genes. Mol Cell Neurosci. 2008;39(3):439–51.
228. Bilous R, Murty G, Parkinson D, Thakker R, Coulthard M, Burn J, et al. Autosomal dominant familial hypoparathyroidism, sensineural deafness and renal dysplasia. N Engl J Med. 1992;327: 1069–84.
229. Lichtner P, Konig R, Hasegawa T, Van Esch H, Meitinger T, Schuffenhauer S. An HDR (hypoparathyroidism, deafness, renal dysplasia) syndrome locus maps distal to the DiGeorge syndrome region on 10p13/14. J Med Genet. 2000;37(1):33–7.
230. Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, Vanderlinden G, et al. GATA3 haploinsufficiency causes human HDR syndrome. Nature. 2000;406(6794):419–22.
231. Muroya K, Hasegawa T, Ito Y, Nagai T, Isotani H, Iwata Y, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. J Med Genet. 2001;38(6):374–80.
232. Nesbit MA, Bowl MR, Harding B, Ali A, Ayala A, Crowe C, et al. Characterization of GATA3 mutations in the hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome. J Biol Chem. 2004;279(21): 22624–34.
233. Tsang AP, Visvader JE, Turner CA, Fujiwara Y, Yu C, Weiss MJ, et al. FOG, a multitype zinc finger protein, acts as a cofactor for transcription factor GATA-1 in erythroid and megakaryocytic differentiation. Cell. 1997;90(1):109–19.
234. Dai YS, Markham BE. p300 Functions as a coactivator of transcription factor GATA-4. J Biol Chem. 2001;276(40):37178–85.
235. Ali A, Christie PT, Grigorieva IV, Harding B, Van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: insight into mechanisms of DNA binding by the GATA3 transcription factor. Hum Mol Genet. 2007;16(3):265–75.
236. Saito T, Fukumoto S, Ito N, Suzuki H, Igarashi T, Fujita T. A novel mutation in the GATA3 gene of a Japanese patient with PTH-deficient hypoparathyroidism. J Bone Miner Metab. 2009;27(3): 386–9.
237. Fukai R, Ochi N, Murakami A, Nakashima M, Tsurusaki Y, Saitsu H, et al. Co-occurrence of 22q11 deletion syndrome and HDR syndrome. Am J Med Genet A. 2013;161(10):2576–81.
238. Pandolfi PP, Roth ME, Karis A, Leonard MW, Dzierzak E, Grosveld FG, et al. Targeted disruption of the GATA3 gene causes severe abnormalities in the nervous system and in fetal liver haematopoiesis. Nat Genet. 1995;11(1):40–4.
239. van der Wees J, van Looij MA, de Ruiter MM, Elias H, van der Burg H, Liem SS, et al. Hearing loss following Gata3 haploinsufficiency is caused by cochlear disorder. Neurobiol Dis. 2004;16(1): 169–78.
240. van Looij MA, van der Burg H, van der Giessen RS, de Ruiter MM, van der Wees J, van Doorninck JH, et al. GATA3 haploinsufficiency causes a rapid deterioration of distortion product otoacoustic emissions (DPOAEs) in mice. Neurobiol Dis. 2005;20(3): 890–7.
241. Grigorieva IV, Mirczuk S, Gaynor KU, Nesbit MA, Grigorieva EF, Wei Q, et al. Gata3-deficient mice develop parathyroid abnormalities due to dysregulation of the parathyroid-specific transcription factor Gcm2. J Clin Invest. 2010;120(6):2144–55.
242. Moraes CT, DiMauro S, Zeviani M, Lombes A, Shanske S, Miranda AF, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. N Engl J Med. 1989;320(20):1293–9.

243. Zupanc ML, Moraes CT, Shanske S, Langman CB, Ciafaloni E, DiMauro S. Deletion of mitochondrial DNA in patients with combined features of Kearns-Sayre and MELAS syndromes. Ann Neurol. 1991;29(6):680–3.
244. Isotani H, Fukumoto Y, Kawamura H, Furukawa K, Ohsawa N, Goto Y, et al. Hypoparathyroidism and insulin-dependent diabetes mellitus in a patient with Kearns-Sayre syndrome harbouring a mitochondrial DNA deletion. Clin Endocrinol (Oxf). 1996;45(5):637–41.
245. Dionisi-Vici C, Garavaglia B, Burlina AB, Bertini E, Saponara I, Sabetta G, et al. Hypoparathyroidism in mitochondrial trifunctional protein deficiency. J Pediatr. 1996;129(1):159–62.
246. Labarthe F, Benoist JF, Brivet M, Vianey-Saban C, Despert F, de Baulny HO. Partial hypoparathyroidism associated with mitochondrial trifunctional protein deficiency. Eur J Pediatr. 2006;165(6):389–91.
247. Franceschini P, Testa A, Bogetti G, Girardo E, Guala A, Lopez-Bell G, et al. Kenny-Caffey syndrome in two sibs born to consanguineous parents: evidence for an autosomal recessive variant. Am J Med Genet. 1992;42(1):112–6.
248. Boynton JR, Pheasant TR, Johnson BL, Levin DB, Streeten BW. Ocular findings in Kenny's syndrome. Arch Ophthalmol. 1979;97(5):896–900.
249. Tahseen K, Khan S, Uma R, Usha R, Al Ghanem MM, Al Awadi SA, et al. Kenny-Caffey syndrome in six Bedouin sibships: autosomal recessive inheritance is confirmed. Am J Med Genet. 1997;69(2):126–32.
250. Diaz GA, Khan KT, Gelb BD. The autosomal recessive Kenny-Caffey syndrome locus maps to chromosome 1q42-q43. Genomics. 1998;54(1):13–8.
251. Guo MH, Shen Y, Walvoord EC, Miller TC, Moon JE, Hirschhorn JN, et al. Whole exome sequencing to identify genetic causes of short stature. Horm Res Paediatr. 2014;82(1):44–52.
252. Unger S, Gorna MW, Le Bechec A, Do Vale-Pereira S, Bedeschi MF, Geiberger S, et al. FAM111A mutations result in hypoparathyroidism and impaired skeletal development. Am J Hum Genet. 2013;92(6):990–5.
253. Fine DA, Rozenblatt-Rosen O, Padi M, Korkhin A, James RL, Adelmant G, et al. Identification of FAM111A as an SV40 host range restriction and adenovirus helper factor. PLoS Pathog. 2012;8(10):e1002949.
254. Nikkel S, Ahmed A, Smith A, Marcadier J, Bulman D, Boycott K. Mother-to-daughter transmission of Kenny-Caffey syndrome associated with the recurrent, dominant FAM111A mutation p.Arg569His. Clin Genet. 2014;86:394–95.
255. Sanjad SA, Sakati NA, Abu-Osba YK, Kaddoura R, Milner RD. A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features. Arch Dis Child. 1991;66(2):193–6.
256. Parvari R, Hershkovitz E, Kanis A, Gorodischer R, Shalitin S, Sheffield VC, et al. Homozygosity and linkage-disequilibrium mapping of the syndrome of congenital hypoparathyroidism, growth and mental retardation, and dysmorphism to a 1-cM interval on chromosome 1q42-43. Am J Hum Genet. 1998;63(1):163–9.
257. Diaz GA, Gelb BD, Ali F, Sakati N, Sanjad S, Meyer BF, et al. Sanjad-Sakati and autosomal recessive Kenny-Caffey syndromes are allelic: evidence for an ancestral founder mutation and locus refinement. Am J Med Genet. 1999;85(1):48–52.
258. Parvari R, Hershkovitz E, Grossman N, Gorodischer R, Loeys B, Zecic A, et al. Mutation of TBCE causes hypoparathyroidism-retardation-dysmorphism and autosomal recessive Kenny-Caffey syndrome. Nat Genet. 2002;32(3):448–52.
259. Tian G, Huang MC, Parvari R, Diaz GA, Cowan NJ. Cryptic out-of-frame translational initiation of TBCE rescues tubulin formation in compound heterozygous HRD. Proc Natl Acad Sci U S A. 2006;103(36):13491–6.
260. Hershkovitz E, Rozin I, Limony Y, Golan H, Hadad N, Gorodischer R, et al. Hypoparathyroidism, retardation, and dysmorphism syndrome: impaired early growth and increased susceptibility to severe infections due to hyposplenism and impaired polymorphonuclear cell functions. Pediatr Res. 2007;62(4):505–9.
261. Weber T, Liu S, Indridason O, Quarles L. Serum FGF23 levels in normal and disordered phosphorus homeostasis. J Bone Miner Res. 2003;18:1227–34.
262. Parkinson DB, Shaw NJ, Himsworth RL, Thakker RV. Parathyroid hormone gene analysis in autosomal hypoparathyroidism using an intragenic tetranucleotide (AAAT)n polymorphism. Hum Genet. 1993;91(3):281–4.
263. Barakat AY, D'Albora JB, Martin MM, Jose PA. Familial nephrosis, nerve deafness, and hypoparathyroidism. J Pediatr. 1977;91(1):61–4.
264. Dahlberg PJ, Borer WZ, Newcomer KL, Yutuc WR. Autosomal or X-linked recessive syndrome of congenital lymphedema, hypoparathyroidism, nephropathy, prolapsing mitral valve, and brachytelephalangy. Am J Med Genet. 1983;16(1):99–104.
265. Lienhardt A, Bai M, Lagarde JP, Rigaud M, Zhang Z, Jiang Y, et al. Activating mutations of the calcium-sensing receptor: management of hypocalcemia. J Clin Endocrinol Metab. 2001;86(11):5313–23.
266. Pollak MR, Brown EM, Estep HL, McLaine PN, Kifor O, Park J, et al. Autosomal dominant hypocalcaemia caused by a Ca^{2+}-sensing receptor gene mutation. Nat Genet. 1994;8:303–7.
267. Finegold DN, Armitage MM, Galiani M, Matise TC, Pandian MR, Perry YM, et al. Preliminary localization of a gene for autosomal dominant hypoparathyroidism to chromosome 3q13. Pediatr Res. 1994;36(3):414–7.
268. Pearce SH, Williamson C, Kifor O, Bai M, Coulthard MG, Davies M, et al. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the

calcium-sensing receptor. N Engl J Med. 1996;335 (15):1115–22.
269. Baron J, Winer K, Yanovski J, Cunningham A, Laue L, Zimmerman D, et al. Mutations in the Ca(2+)-sensing receptor gene cause autosomal dominant and sporadic hypoparathyroidism. Hum Mol Genet. 1996;5:601–6.
270. Okazaki R, Chikatsu N, Nakatsu M, Takeuchi Y, Ajima M, Miki J, et al. A novel activating mutation in calcium-sensing receptor gene associated with a family of autosomal dominant hypocalcemia. J Clin Endocrinol Metab. 1999;84:363–6.
271. Hu J, McLarnon SJ, Mora S, Jiang J, Thomas C, Jacobson KA, et al. A region in the seven-transmembrane domain of the human Ca2+ receptor critical for response to Ca2+. J Biol Chem. 2005;280(6):5113–20.
272. Lienhardt A, Garabedian M, Bai M, Sinding C, Zhang Z, Lagarde JP, et al. A large homozygous or heterozygous in-frame deletion within the calcium-sensing receptor's carboxylterminal cytoplasmic tail that causes autosomal dominant hypocalcemia. J Clin Endocrinol Metab. 2000;85(4):1695–702.
273. Hannan FM, Nesbit MA, Zhang C, Cranston T, Curley AJ, Harding B, et al. Identification of 70 calcium-sensing receptor mutations in hyper- and hypo-calcaemic patients: evidence for clustering of extracellular domain mutations at calcium-binding sites. Hum Mol Genet. 2012;21(12):2768–78.
274. Li D, Opas EE, Tuluc F, Metzger DL, Hou C, Hakonarson H, et al. Autosomal dominant hypoparathyroidism caused by germline mutation in GNA11: phenotypic and molecular characterization. J Clin Endocrinol Metab. 2014;99:E1774–83.
275. Rogers A, Nesbit MA, Hannan FM, Howles SA, Gorvin CM, Cranston T, et al. Mutational analysis of the adaptor protein 2 sigma subunit (AP2S1) gene: search for autosomal dominant hypocalcemia type 3 (ADH3). J Clin Endocrinol Metab. 2014;99(7): E1300–5.
276. Thakker RV. Molecular pathology of renal chloride channels in Dent's disease and Bartter's syndrome. Exp Nephrol. 2000;8(6):351–60.
277. Hebert SC. Bartter syndrome. Curr Opin Nephrol Hypertens. 2003;12(5):527–32.
278. Watanabe S, Fukumoto S, Chang H, Takeuchi Y, Hasegawa Y, Okazaki R, et al. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. Lancet. 2002;360(9334):692–4.
279. Vargas-Poussou R, Huang C, Hulin P, Houillier P, Jeunemaitre X, Paillard M, et al. Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. J Am Soc Nephrol. 2002;13(9):2259–66.
280. Vezzoli G, Arcidiacono T, Paloschi V, Terranegra A, Biasion R, Weber G, et al. Autosomal dominant hypocalcemia with mild type 5 Bartter syndrome. J Nephrol. 2006;19(4):525–8.
281. Hu J, Mora S, Weber G, Zamproni I, Proverbio MC, Spiegel AM. Autosomal dominant hypocalcemia in monozygotic twins caused by a de novo germline mutation near the amino-terminus of the human calcium receptor. J Bone Miner Res Off J Am Soc Bone Miner Res. 2004;19(4):578–86.
282. Bettinelli A, Vezzoli G, Colussi G, Bianchetti MG, Sereni F, Casari G. Genotype-phenotype correlations in normotensive patients with primary renal tubular hypokalemic metabolic alkalosis. J Nephrol. 1998;11(2):61–9.
283. Ranieri M, Tamma G, Di Mise A, Vezzoli G, Soldati L, Svelto M, et al. Excessive signal transduction of gain-of-function variants of the calcium-sensing receptor (CaSR) are associated with increased ER to cytosol calcium gradient. PLoS One. 2013;8(11):e79113.
284. Li Y, Song YH, Rais N, Connor E, Schatz D, Muir A, et al. Autoantibodies to the extracellular domain of the calcium sensing receptor in patients with acquired hypoparathyroidism. J Clin Invest. 1996;97(4): 910–4.
285. Albright F, Burnett CH, Smith PH, Parson W. Pseudohypoparathyroidism – an example of "Seabright-Bantam syndrome". Endocrinology. 1942;30:922–32.
286. Weinstein LS. Albright hereditary osteodystrophy, pseudohypoparathyroidism, and G_s deficiency. In: Spiegel AM, editor. G proteins, receptors, and disease. Totowa: Humana Press; 1998. p. 23–56.
287. de Jan Beur S, Levine M. Pseudohypoparathyroidism: clinical, biochemical, and molecular features. In: Bilezikian JP, Markus R, Levine MA, editors. The parathyroids: basic and clinical concepts. New York: Academic; 2001. p. 807–25.
288. Bastepe M, Jüppner H. Pseudohypoparathyroidism, Albright's hereditary osteodystrophy, and progressive osseous heteroplasia: disorders caused by inactivating GNAS mutations. In: DeGroot LJ, Jameson JL, editors. Endocrinology, 1. 6th ed. Philadelphia: W.B. Saunders; 2010. p. 1223–35.
289. Bastepe M, Jüppner H. Pseudohypoparathyroidism, Gsα, and the *GNAS* locus. BoneKEy. 2005;2:20–32.
290. Levine MA. Pseudohypoparathyroidism. In: Bilezikian JP, Raisz LG, Rodan GA, editors. Principles of bone biology. New York: Academic; 1996. p. 853–76.
291. Schuster V, Eschenhagen T, Kruse K, Gierschik P, Kreth HW. Endocrine and molecular biological studies in a German family with Albright hereditary osteodystrophy. Eur J Pediatr. 1993;152:185–9.
292. Miric A, Vechio JD, Levine MA. Heterogeneous mutations in the gene encoding the α-subunit of the stimulatory G protein of adenylyl cyclase in Albright hereditary osteodystrophy. J Clin Endocrinol Metab. 1993;76:1560–8.
293. Weinstein LS, Gejman PV, Friedman E, Kadowaki T, Collins RM, Gershon ES, et al. Mutations of the Gs α−subunit gene in Albright hereditary

osteodystrophy detected by denaturing gradient gel electrophoresis. Proc Natl Acad Sci U S A. 1990;87:8287–90.
294. Ahrens W, Hiort O, Staedt P, Kirschner T, Marschke C, Kruse K. Analysis of the GNAS1 gene in Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 2001;86(10):4630–4.
295. Linglart A, Carel JC, Garabedian M, Le T, Mallet E, Kottler ML. GNAS1 lesions in pseudohypoparathyroidism Ia and Ic: genotype phenotype relationship and evidence of the maternal transmission of the hormonal resistance. J Clin Endocrinol Metab. 2002;87(1):189–97.
296. Long DN, McGuire S, Levine MA, Weinstein LS, Germain-Lee EL. Body mass index differences in pseudohypoparathyroidism type 1a versus pseudopseudohypoparathyroidism may implicate paternal imprinting of Galpha(s) in the development of human obesity. J Clin Endocrinol Metab. 2007;92(3):1073–9.
297. Davies AJ, Hughes HE. Imprinting in Albright's hereditary osteodystrophy. J Med Genet. 1993;30:101–3.
298. Wilson LC, Oude-Luttikhuis MEM, Clayton PT, Fraser WD, Trembath RC. Parental origin of Gsα gene mutations in Albright's hereditary osteodystrophy. J Med Genet. 1994;31:835–9.
299. Germain-Lee EL, Schwindinger W, Crane JL, Zewdu R, Zweifel LS, Wand G, et al. A mouse model of Albright hereditary osteodystrophy generated by targeted disruption of exon 1 of the Gnas gene. Endocrinology. 2005;146(11):4697–709.
300. Yu S, Yu D, Lee E, Eckhaus M, Lee R, Corria Z, et al. Variable and tissue-specific hormone resistance in heterotrimeric Gs protein alpha-subunit ($G_s\alpha$) knockout mice is due to tissue-specific imprinting of the $G_s\alpha$ gene. Proc Natl Acad Sci U S A. 1998;95(15):8715–20.
301. Yu S, Gavrilova O, Chen H, Lee R, Liu J, Pacak K, et al. Paternal versus maternal transmission of a stimulatory G-protein alpha subunit knockout produces opposite effects on energy metabolism. J Clin Invest. 2000;105:615–23.
302. Eddy MC, De Jan Beur SM, Yandow SM, McAlister WH, Shore EM, Kaplan FS, et al. Deficiency of the alpha-subunit of the stimulatory G protein and severe extraskeletal ossification. J Bone Miner Res Off J Am Soc Bone Miner Res. 2000;15(11):2074–83.
303. Yeh GL, Mathur S, Wivel A, Li M, Gannon FH, Ulied A, et al. GNAS1 mutation and Cbfa1 misexpression in a child with severe congenital plate-like osteoma cutis. J Bone Miner Res Off J Am Soc Bone Miner Res. 2000;15(11):2063–73.
304. Shore E, Ahn J, de Jan Beur S, Li M, Xu M, Gardner RM, et al. Paternally-inherited inactivating mutations of the *GNAS1* gene in progressive osseous heteroplasia. N Engl J Med. 2002;346:99–106.
305. Adegbite NS, Xu M, Kaplan FS, Shore EM, Pignolo RJ. Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification. Am J Med Genet A. 2008;146A(14):1788–96.
306. Cairns DM, Pignolo RJ, Uchimura T, Brennan TA, Lindborg CM, Xu M, et al. Somitic disruption of GNAS in chick embryos mimics progressive osseous heteroplasia. J Clin Invest. 2013;123(8):3624–33.
307. Schipani E, Weinstein LS, Bergwitz C, Iida-Klein A, Kong XF, Stuhrmann M, et al. Pseudohypoparathyroidism type Ib is not caused by mutations in the coding exons of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene. J Clin Endocrinol Metab. 1995;80:1611–21.
308. Bettoun JD, Minagawa M, Kwan MY, Lee HS, Yasuda T, Hendy GN, et al. Cloning and characterization of the promoter regions of the human parathyroid hormone (PTH)/PTH-related peptide receptor gene: analysis of deoxyribonucleic acid from normal subjects and patients with pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 1997;82:1031–40.
309. Suarez F, Lebrun JJ, Lecossier D, Escoubet B, Coureau C, Silve C. Expression and modulation of the parathyroid hormone (PTH)/PTH-related peptide receptor messenger ribonucleic acid in skin fibroblasts from patients with type Ib pseudohypoparathyroidism. J Clin Endocrinol Metab. 1995;80:965–70.
310. Fukumoto S, Suzawa M, Takeuchi Y, Nakayama K, Kodama Y, Ogata E, et al. Absence of mutations in parathyroid hormone (PTH)/PTH-related protein receptor complementary deoxyribonucleic acid in patients with pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 1996;81:2554–8.
311. Bastepe M, Lane AH, Jüppner H. Paternal uniparental isodisomy of chromosome 20q (patUPD20q) – and the resulting changes in *GNAS1* methylation – as a plausible cause of pseudohypoparathyroidism. Am J Hum Genet. 2001;68:1283–9.
312. Bastepe M, Jüppner H. Pseudohypoparathyroidism: new insights into an old disease. In: Strewler GJ, editor. Endocrinology and Metabolism Clinics of North America: Hormones and disorders of mineral metabolism, vol. 29. Philadelphia: W. B. Saunders; 2000. p. 569–89.
313. de Pérez Nanclares G, Fernández-Rebollo E, Santin I, Garcia-Cuartero B, Gaztambide S, Menendez E, et al. Epigenetic defects of GNAS in patients with pseudohypoparathyroidism and mild features of Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 2007;92(6):2370–3.
314. Unluturk U, Harmanci A, Babaoglu M, Yasar U, Varli K, Bastepe M, et al. Molecular diagnosis and clinical characterization of pseudohypoparathyroidism type-Ib in a patient with mild Albright's hereditary osteodystrophy-like features, epileptic seizures, and defective renal handling of uric acid. Am J Med Sci. 2008;336(1):84–90.
315. Jüppner H, Schipani E, Bastepe M, Cole DEC, Lawson ML, Mannstadt M, et al. The gene

responsible for pseudohypoparathyroidism type Ib is paternally imprinted and maps in four unrelated kindreds to chromosome 20q13.3. Proc Natl Acad Sci U S A. 1998;95:11798–803.
316. Liu J, Litman D, Rosenberg M, Yu S, Biesecker L, Weinstein L. A GNAS1 imprinting defect in pseudohypoparathyroidism type IB. J Clin Invest. 2000;106:1167–74.
317. Bastepe M, Pincus JE, Sugimoto T, Tojo K, Kanatani M, Azuma Y, et al. Positional dissociation between the genetic mutation responsible for pseudohypoparathyroidism type Ib and the associated methylation defect at exon A/B: evidence for a long-range regulatory element within the imprinted *GNAS1* locus. Hum Mol Genet. 2001;10:1231–41.
318. Bastepe M, Fröhlich LF, Hendy GN, Indridason OS, Josse RG, Koshiyama H, et al. Autosomal dominant pseudohypoparathyroidism type Ib is associated with a heterozygous microdeletion that likely disrupts a putative imprinting control element of *GNAS*. J Clin Invest. 2003;112(8):1255–63.
319. Laspa E, Bastepe M, Jüppner H, Tsatsoulis A. Phenotypic and molecular genetic aspects of pseudohypoparathyroidism type Ib in a Greek kindred: evidence for enhanced uric acid excretion due to parathyroid hormone resistance. J Clin Endocrinol Metab. 2004;89:5942–7.
320. Mahmud FH, Linglart A, Bastepe M, Jüppner H, Lteif AN. Molecular diagnosis of pseudohypoparathyroidism type Ib in a family with presumed paroxysmal dyskinesia. Pediatrics. 2005;115(2):e242–4.
321. Liu J, Nealon J, Weinstein L. Distinct patterns of abnormal GNAS imprinting in familial and sporadic pseudohypoparathyroidism type IB. Hum Mol Genet. 2005;14:95–102.
322. Linglart A, Gensure RC, Olney RC, Jüppner H, Bastepe M. A novel *STX16* deletion in autosomal dominant pseudohypoparathyroidism type Ib redefines the boundaries of a cis-acting imprinting control element of *GNAS*. Am J Hum Genet. 2005;76:804–14.
323. Elli FM, de Sanctis L, Peverelli E, Bordogna P, Pivetta B, Miolo G, et al. Autosomal dominant pseudohypoparathyroidism type Ib: a novel inherited deletion ablating STX16 causes loss of imprinting at the A/B DMR. J Clin Endocrinol Metab. 2014;99:E724–28.
324. Richard N, Abeguile G, Coudray N, Mittre H, Gruchy N, Andrieux J, et al. A new deletion ablating NESP55 causes loss of maternal imprint of A/B GNAS and autosomal dominant pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 2012;97(5):E863–7.
325. Bastepe M, Jüppner H. The GNAS locus and pseudohypoparathyroidism. Horm Res. 2005;63:65–74.
326. Chillambhi S, Turan S, Hwang DY, Chen HC, Jüppner H, Bastepe M. Deletion of the noncoding *GNAS* antisense transcript causes pseudohypoparathyroidism type Ib and biparental defects of *GNAS* methylation in *cis*. J Clin Endocrinol Metab. 2010;95:3993–4002.
327. Linglart A, Bastepe M, Jüppner H. Similar clinical and laboratory findings in patients with symptomatic autosomal dominant and sporadic pseudohypoparathyroidism type Ib despite different epigenetic changes at the *GNAS* locus. Clin Endocrinol (Oxf). 2007;67(6):822–31.
328. Dixit A, Chandler KE, Lever M, Poole RL, Bullman H, Mughal MZ, et al. Pseudohypoparathyroidism type 1b due to paternal uniparental disomy of chromosome 20q. J Clin Endocrinol Metab. 2013;98(1):E103–8.
329. Williamson CM, Ball ST, Nottingham WT, Skinner JA, Plagge A, Turner MD, et al. A cis-acting control region is required exclusively for the tissue-specific imprinting of Gnas. Nat Genet. 2004;36(8):894–9.
330. Blomstrand S, Claësson I, Säve-Söderbergh J. A case of lethal congenital dwarfism with accelerated skeletal maturation. Pediatr Radiol. 1985;15:141–3.
331. Young ID, Zuccollo JM, Broderick NJ. A lethal skeletal dysplasia with generalised sclerosis and advanced skeletal maturation: Blomstrand chondrodysplasia. J Med Genet. 1993;30:155–7.
332. Leroy JG, Keersmaeckers G, Coppens M, Dumon JE, Roels H. Blomstrand lethal chondrodysplasia. Am J Med Genet. 1996;63:84–9.
333. Loshkajian A, Roume J, Stanescu V, Delezoide AL, Stampf F, Maroteaux P. Familial Blomstrand Chondrodysplasia with advanced skeletal maturation: further delineation. Am J Med Genet. 1997;71:283–8.
334. den Hollander NS, van der Harten HJ, Vermeij-Keers-C, Niermeijer MF, Wladimiroff JW. First-trimester diagnosis of Blomstrand lethal osteochondrodysplasia. Am J Med Genet. 1997;73:345–50.
335. Oostra RJ, Baljet B, Dijkstra PF, Hennekam RCM. Congenital anomalies in the teratological collection of museum Vrolik in Amsterdam, The Netherlands. II: Skeletal dysplasia. Am J Med Genet. 1998;77:116–34.
336. Jobert AS, Zhang P, Couvineau A, Bonaventure J, Roume J, Le Merrer M, et al. Absence of functional receptors for parathyroid hormone and parathyroid hormone-related peptide in Blomstrand chondrodysplasia. J Clin Invest. 1998;102(1):34–40.
337. Zhang P, Jobert AS, Couvineau A, Silve C. A homozygous inactivating mutation in the parathyroid hormone/parathyroid hormone-related peptide receptor causing Blomstrand chondrodysplasia. J Clin Endocrinol Metab. 1998;83:3365–8.
338. Karaplis AC, Bin He MT, Nguyen A, Young ID, Semeraro D, Ozawa H, et al. Inactivating mutation in the human parathyroid hormone receptor type 1 gene in Blomstrand chondrodysplasia. Endocrinology. 1998;139:5255–8.
339. Karperien MC, van der Harten HJ, van Schooten R, Farih-Sips H, den Hollander NS, Kneppers ALJ, et al. A frame-shift mutation in the type I parathyroid

hormone/parathyroid hormone-related peptide receptor causing Blomstrand lethal osteochondrodysplasia. J Clin Endocrinol Metab. 1999;84:3713–20.
340. Karperien M, Sips H, Hvd H, Wijnaents L, Kindblom L, Papapoulos S, et al. Novel mutations in the type I PTH/PTHrP receptor causing Blomstrand lethal osteochondrodysplasia (abstract). J Bone Miner Res. 2001;16 Suppl 1:S549.
341. Hoogendam J, Farih-Sips H, Wynaendts LC, Lowik CW, Wit JM, Karperien M. Novel mutations in the parathyroid hormone (PTH)/PTH-related peptide receptor type 1 causing Blomstrand osteochondrodysplasia types I and II. J Clin Endocrinol Metab. 2007;92(3):1088–95.
342. Wysolmerski JJ, Cormier S, Philbrick W, Dann P, Zhang J, Roume J, et al. Absence of functional type 1 PTH/PTHrP receptors in humans is associated with abnormal breast development and tooth impactation. J Clin Endocrinol Metab. 2001;86:1788–94.
343. Ichikawa S, Lyles KW, Econs MJ. A novel GALNT3 mutation in a pseudoautosomal dominant form of tumoral calcinosis: evidence that the disorder is autosomal recessive. J Clin Endocrinol Metab. 2005;90(4):2420–3.
344. Ichikawa S, Imel EA, Sorenson AH, Severe R, Knudson P, Harris GJ, et al. Tumoral calcinosis presenting with eyelid calcifications due to novel missense mutations in the glycosyl transferase domain of the GALNT3 gene. J Clin Endocrinol Metab. 2006;91(11):4472–5.
345. Topaz O, Shurman DL, Bergman R, Indelman M, Ratajczak P, Mizrachi M, et al. Mutations in GALNT3, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. Nat Genet. 2004;36(6):579–81.
346. Ichikawa S, Imel EA, Kreiter ML, Yu X, Mackenzie DS, Sorenson AH, et al. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. J Clin Invest. 2007;117(9):2684–91.
347. Larsson T, Davis S, Garringer H, Mooney S, Draman M, Cullen M, et al. Fibroblast growth factor-23 mutants causing familial tumoral calcinosis are differentially processed. J Clin Endocrinol Metab. 2005;146:3883–91.
348. Araya K, Fukumoto S, Backenroth R, Takeuchi Y, Nakayama K, Ito N, et al. A novel mutation in fibroblast growth factor 23 gene as a cause of tumoral calcinosis. J Clin Endocrinol Metab. 2005;90(10):5523–7.
349. Melhem R, Najjar S, Khachadurian A. Cortical hyperostosis with hyperphosphatemia: a new syndrome? J Pediatr. 1970;77:986–90.
350. Narchi H. Hyperostosis with hyperphosphatemia: evidence of familial occurrence and association with tumoral calcinosis. Pediatrics. 1997;99:745–8.
351. Frishberg Y, Araya K, Rinat C, Topaz O, Yamazaki Y, Feinstein Y, et al., editors. Hyperostosis-hyperphosphatemia syndrome caused by mutations in *GALNT3* and associated with augmented processing of FGF-23. Philadelphia: American Society of Nephrology; 2004.
352. Ichikawa S, Baujat G, Seyahi A, Garoufali AG, Imel EA, Padgett LR, et al. Clinical variability of familial tumoral calcinosis caused by novel GALNT3 mutations. Am J Med Genet A. 2010;152a(4):896–903.
353. Trump D, Thakker R. Inherited hypophosphataemic rickets. In: Thakker R, editor. Molecular genetics of endocrine disorders. London: Chapman and Hall; 1997. p. 123–51.
354. Glorieux F, Karsenty G, Thakker R. Metabolic bone disease in children. In: Avioli LV, Krane SM, editors. Metabolic bone disease. 3rd ed. New York: Academic; 1997. p. 759–83.
355. Econs M, McEnery P, Lennon F, Speer M. Autosomal dominant hypophosphatemic rickets is linked to chromosome 12p13. J Clin Invest. 1997;100:2653–7.
356. Yamazaki Y, Okazaki R, Shibata M, Hasegawa Y, Satoh K, Tajima T, et al. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. J Clin Endocrinol Metab. 2002;87:4957–60.
357. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med. 2003;348(17):1656–63.
358. Farrow EG, Yu X, Summers LJ, Davis SI, Fleet JC, Allen MR, et al. Iron deficiency drives an autosomal dominant hypophosphatemic rickets (ADHR) phenotype in fibroblast growth factor-23 (Fgf23) knock-in mice. Proc Natl Acad Sci U S A. 2011;108(46):E1146–55.
359. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. J Clin Endocrinol Metab. 2011;96(11):3541–9.
360. Drezner MK. Phosphorus homeostasis and related disorders. In: Bilezikian JP, Raisz LG, Rodan GA, editors. Principles in bone biology, vol. 1. 2nd ed. - New York: Academic; 2002. p. 321–38.
361. Lipman M, Panda D, Bennett H, Henderson J, Shane E, Shen Y, et al. Cloning of human PEX cDNA. Expression, subcellular localization, and endopeptidase activity. J Biol Chem. 1998;273:13729–37.
362. John M, Wickert H, Zaar K, Jonsson K, Grauer A, Ruppersberger P, et al. A case of neuroendocrine oncogenic osteomalacia associated with a PHEX and fibroblast growth factor-23 expressing sinusidal malignant schwannoma. Bone. 2001;29:393–402.
363. Seufert J, Ebert K, Müller J, Eulert J, Hendrich C, Werner E, et al. Octreotide therapy for tumor-induced osteomalacia. N Engl J Med. 2001;345:1883–8.
364. Imel E, Peacock M, Pitukcheewanont P, Heller H, Ward L, Shulman D, et al. Sensitivity of fibroblast growth factor 23 measurements in tumor-induced

osteomalacia. J Clin Endocrinol Metab. 2006;91:2055–61.
365. van Boekel G, Ruinemans-Koerts J, Joosten F, Dijkhuizen P, van Sorge A, de Boer H. Tumor producing fibroblast growth factor 23 localized by two-staged venous sampling. Eur J Endocrinol. 2008;158(3):431–7.
366. White KE, Carn G, Lorenz-Depiereux B, Benet-Pages A, Strom TM, Econs MJ. Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. Kidney Int. 2001;60(6):2079–86.
367. Imanishi Y, Hashimoto J, Ando W, Kobayashi K, Ueda T, Nagata Y, et al. Matrix extracellular phosphoglycoprotein is expressed in causative tumors of oncogenic osteomalacia. J Bone Miner Metab. 2012;30(1):93–9.
368. Consortium TH. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet. 1995;11:130–6.
369. Holm IA, Huang X, Kunkel LM. Mutational analysis of the PEX gene in patients with X-linked hypophosphatemic rickets. Am J Hum Genet. 1997;60(4):790–7.
370. Rowe P, de Zoysa P, Dong R, Wang H, White K, Econs M, et al. MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. Genomics. 2000;67:54–68.
371. Aono Y, Shimada T, Yamazaki Y, Hino R, Takeuchi M, Fujita T, et al., editors. The neutralization of FGF-23 ameliorates hypophosphatemia and rickets in Hyp mice. Meeting of the American Society for Bone and Mineral Research, Minneapolis; 2003.
372. Bowe A, Finnegan R, Jan de Beur S, Cho J, Levine M, Kumar R. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. Biochem Biophys Res Commun. 2001;284:977–81.
373. Yamazaki Y, Tamada T, Kasai N, Urakawa I, Aono Y, Hasegawa H, et al. Anti-FGF23 neutralizing antibodies show the physiological role and structural features of FGF23. J Bone Miner Res Off J Am Soc Bone Miner Res. 2008;23(9):1509–18.
374. Carpenter TO, Imel EA, Ruppe MD, Weber TJ, Klausner MA, Wooddell MM, et al. Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. J Clin Invest. 2014;124(4):1587–97.
375. George A, Sabsay B, Simonian PA, Veis A. Characterization of a novel dentin matrix acidic phosphoprotein. Implications for induction of biomineralization. J Biol Chem. 1993;268(17):12624–30.
376. Narayanan K, Ramachandran A, Hao J, He G, Park KW, Cho M, et al. Dual functional roles of dentin matrix protein 1. Implications in biomineralization and gene transcription by activation of intracellular Ca2+ store. J Biol Chem. 2003;278(19):17500–8.
377. Chen JM, Cooper DN, Chuzhanova N, Ferec C, Patrinos GP. Gene conversion: mechanisms, evolution and human disease. Nat Rev Genet. 2007;8(10):762–75.
378. Perry W, Stamp T. Hereditary hypophosphataemic rickets with autosomal recessive inheritance and severe osteosclerosis. A report of two cases. J Bone Joint Surg Br. 1978;60-B:430–4.
379. Scriver C, Reade T, Halal F, Costa T, Cole D. Autosomal hypophosphataemic bone disease responds to 1,25-(OH)2D3. Arch Dis Child. 1981;56:203–7.
380. Bastepe M, Shlossberg H, Murdock H, Jüppner H, Rittmaster R. A lebanese family with osteosclerosis and hypophosphatemia. J Bone Miner Res. 1999;14 Suppl 1:S558.
381. Ye L, Mishina Y, Chen D, Huang H, Dallas S, Dallas M, et al. Dmp1-deficient mice display severe defects in cartilage formation responsible for a chondrodysplasia-like phenotype. J Biol Chem. 2005;280:6197–203.
382. Feng JQ, Scott G, Guo D, Jiang B, Harris M, Ward T, et al. Generation of a conditional null allele for Dmp1 in mouse. Genesis. 2008;46(2):87–91.
383. Liu S, Zhou J, Tang W, Menard R, Feng JQ, Quarles LD. Pathogenic role of Fgf23 in Dmp1-null mice. Am J Physiol Endocrinol Metab. 2008;295(2):E254–61.
384. Levy-Litan V, Hershkovitz E, Avizov L, Leventhal N, Bercovich D, Chalifa-Caspi V, et al. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. Am J Hum Genet. 2010;86(2):273–8.
385. Prié D, Huart V, Bakouh N, Planelles G, Dellis O, Gérard B, et al. Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. N Engl J Med. 2002;347:983–91.
386. Virkki L, Forster I, Hernando N, Biber J, Murer H. Functional characterization of two naturally occurring mutations in the human sodium-phosphate cotransporter type IIa. J Bone Miner Res Off J Am Soc Bone Miner Res. 2003;18:2135–41.
387. Lapointe JY, Tessier J, Paquette Y, Wallendorff B, Coady MJ, Pichette V, et al. NPT2a gene variation in calcium nephrolithiasis with renal phosphate leak. Kidney Int. 2006;69(12):2261–7.
388. Magen D, Berger L, Coady MJ, Ilivitzki A, Militianu D, Tieder M, et al. A loss-of-function mutation in NaPi-IIa and renal Fanconi's syndrome. N Engl J Med. 2010;362(12):1102–9.
389. Beck L, Karaplis AC, Amizuka N, Hewson AS, Ozawa H, Tenenhouse HS. Targeted inactivation of *Ntp2* in mice leads to severe renal phosphate wasting, hypercalciuria, and skeletal abnormalities. Proc Natl Acad Sci U S A. 1998;95:5372–7.
390. Tieder M, Modai D, Samuel R, Arie R, Halabe A, Bab I, et al. Hereditary hypophosphatemic rickets with hypercalciuria. N Engl J Med. 1985;312:611–7.
391. Bergwitz C, Roslin NM, Tieder M, Loredo-Osti JC, Bastepe M, Abu-Zahra H, et al. SLC34A3 mutations in patients with hereditary hypophosphatemic

rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaPi-IIc in maintaining phosphate homeostasis. Am J Hum Genet. 2006;78(2):179–92.
392. Lorenz-Depiereux B, Benet-Pages A, Eckstein G, Tenenbaum-Rakover Y, Wagenstaller J, Tiosano D, et al. Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am J Hum Genet. 2006;78(2):193–201.
393. Ichikawa S, Sorenson AH, Imel EA, Friedman NE, Gertner JM, Econs MJ. Intronic deletions in the SLC34A3 gene cause hereditary hypophosphatemic rickets with hypercalciuria. J Clin Endocrinol Metab. 2006;91(10):4022–7.
394. Prader A, Illig R, Heierli E. An unusual form of primary vitamin D-resistant rickets with hypocalcemia and autosomal-dominant hereditary transmission: hereditary pseudo-deficiency rickets. Helv Paediatr Acta. 1961;16:452–68.
395. Fraser D, Kooh SW, Kind HP, Holick MF, Tanaka Y, DeLuca HF. Pathogenesis of hereditary vitamin-D-dependent rickets. An inborn error of vitamin D metabolism involving defective conversion of 25-hydroxyvitamin D to 1 alpha,25-dihydroxyvitamin D. N Engl J Med. 1973;289(16):817–22.
396. Scriver CR. Vitamin D, dependency. Pediatrics. 1970;45(3):361–3.
397. Delvin EE, Glorieux FH, Marie PJ, Pettifor JM. Vitamin D dependency: replacement therapy with calcitriol? J Pediatr. 1981;99(1):26–34.
398. Scriver CR, Reade TM, DeLuca HF, Hamstra AJ. Serum 1,25-dihydroxyvitamin D levels in normal subjects and in patients with hereditary rickets or bone disease. N Engl J Med. 1978;299(18):976–9.
399. DeLuca HF. Vitamin D metabolism and function. Arch Intern Med. 1978;138(Spec No):836–47.
400. Chesney RW, Rosen JF, Hamstra AJ, DeLuca HF. Serum 1,25-dihydroxyvitamin D levels in normal children and in vitamin D disorders. Am J Dis Child. 1980;134(2):135–9.
401. Labuda M, Morgan K, Glorieux FH. Mapping autosomal recessive vitamin D dependency type I to chromosome 12q14 by linkage analysis. Am J Hum Genet. 1990;47(1):28–36.
402. St-Arnaud R, Messerlian S, Moir JM, Omdahl JL, Glorieux FH. The 25-hydroxyvitamin D 1-alpha-hydroxylase gene maps to the pseudovitamin D-deficiency rickets (PDDR) disease locus. J Bone Miner Res Off J Am Soc Bone Miner Res. 1997;12(10):1552–9.
403. Fu GK, Lin D, Zhang MY, Bikle DD, Shackleton CH, Miller WL, et al. Cloning of human 25-hydroxyvitamin D-1 alpha-hydroxylase and mutations causing vitamin D-dependent rickets type 1. Mol Endocrinol. 1997;11(13):1961–70.
404. Kitanaka S, Takeyama K, Murayama A, Sato T, Okumura K, Nogami M, et al. Inactivating mutations in the 25-hydroxyvitamin D3 1alpha-hydroxylase gene in patients with pseudovitamin D-deficiency rickets. N Engl J Med. 1998;338(10):653–61.
405. Yoshida T, Monkawa T, Tenenhouse HS, Goodyer P, Shinki T, Suda T, et al. Two novel 1alpha-hydroxylase mutations in French-Canadians with vitamin D dependency rickets type I1. Kidney Int. 1998;54(5):1437–43.
406. Wang JT, Lin CJ, Burridge SM, Fu GK, Labuda M, Portale AA, et al. Genetics of vitamin D 1alpha-hydroxylase deficiency in 17 families. Am J Hum Genet. 1998;63(6):1694–702.
407. Wang X, Zhang MY, Miller WL, Portale AA. Novel gene mutations in patients with 1alpha-hydroxylase deficiency that confer partial enzyme activity in vitro. J Clin Endocrinol Metab. 2002;87(6):2424–30.
408. Brooks MH, Bell NH, Love L, Stern PH, Orfei E, Queener SF, et al. Vitamin-D-dependent rickets type II. Resistance of target organs to 1,25-dihydroxyvitamin D. N Engl J Med. 1978;298(18):996–9.
409. Marx SJ, Spiegel AM, Brown EM, Gardner DG, Downs Jr RW, Attie M, et al. A familial syndrome of decrease in sensitivity to 1,25-dihydroxyvitamin D. J Clin Endocrinol Metab. 1978;47(6):1303–10.
410. Liberman UA, Samuel R, Halabe A, Kauli R, Edelstein S, Weisman Y, et al. End-organ resistance to 1,25-dihydroxycholecalciferol. Lancet. 1980;1(8167):504–6.
411. Fujita T, Nomura M, Okajima S, Furuya H. Adult-onset vitamin D-resistant osteomalacia with the unresponsiveness to parathyroid hormone. J Clin Endocrinol Metab. 1980;50(5):927–31.
412. Liberman UA, Eil C, Marx SJ. Resistance to Vitamin D. In: Cohn DV, Fujita T, Potts Jr JT, Talmage RV, editors. Endocrine control of bone and calcium metabolism, International congress series 619, vol. 8A. Amsterdam: Exerpta Medica; 1984. p. 32–40.
413. Fraher LJ, Karmali R, Hinde FR, Hendy GN, Jani H, Nicholson L, et al. Vitamin D-dependent rickets type II: extreme end organ resistance to 1,25-dihydroxy vitamin D3 in a patient without alopecia. Eur J Pediatr. 1986;145(5):389–95.
414. Haussler MR, Manolagas SC, Deftos LJ. Evidence for a 1,25-dihydroxyvitamin D3 receptor-like macromolecule in rat pituitary. J Biol Chem. 1980;255(11):5007–10.
415. O'Malley BW. Steroid hormone action in eucaryotic cells. J Clin Invest. 1984;74(2):307–12.
416. Eil C, Liberman UA, Rosen JF, Marx SJ. A cellular defect in hereditary vitamin-D-dependent rickets type II: defective nuclear uptake of 1,25-dihydroxyvitamin D in cultured skin fibroblasts. N Engl J Med. 1981;304(26):1588–91.
417. Eil C, Marx SJ. Nuclear uptake of 1,25-dihydroxy [3H]cholecalciferol in dispersed fibroblasts cultured from normal human skin. Proc Natl Acad Sci U S A. 1981;78(4):2562–6.
418. Haussler MR, Mangelsdorf DJ, Komm BS, et al. Molecular biology of the vitamin D hormone.

In: Cohn DV, Martin TJ, Mennier PJ, editors. Calcium regulation and bone metabolism: basic and clinic aspects, vol. 9. Amsterdam: Elsevier; 1987. p. 465–74.
419. McDonnell DP, Mangelsdorf DJ, Pike JW, Haussler MR, O'Malley BW. Molecular cloning of complementary DNA encoding the avian receptor for vitamin D. Science. 1987;235(4793):1214–7.
420. Hughes MR, Malloy PJ, Kieback DG, Kesterson RA, Pike JW, Feldman D, et al. Point mutations in the human vitamin D receptor gene associated with hypocalcemic rickets. Science. 1988;242(4886):1702–5.
421. Yoshizawa T, Handa Y, Uematsu Y, Sekine K, Takeda S, Yoshihara Y, et al. Disruption of the vitamin D receptor (VDR) in the mouse. J Bone Miner Res. 1996;11:S119.
422. Li YC, Amling M, Pirro AE, Priemel M, Meuse J, Baron R, et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor-ablated mice. Endocrinology. 1998;139:4391–6.
423. Tsuchiya Y, Matsuo N, Cho H, Kumagai M, Yasaka A, Suda T, et al. An unusual form of vitamin D-dependent rickets in a child: alopecia and marked end-organ hyposensitivity to biologically active vitamin D. J Clin Endocrinol Metab. 1980;51(4):685–90.
424. Rosen JF, Fleischman AR, Finberg L, Hamstra A, DeLuca HF. Rickets with alopecia: an inborn error of vitamin D metabolism. J Pediatr. 1979;94(5):729–35.
425. Liberman UA, Eil C, Marx SJ. Resistance to 1,25-dihydroxyvitamin D. Association with heterogeneous defects in cultured skin fibroblasts. J Clin Invest. 1983;71(2):192–200.
426. Castells G, Greig F, Fusi L, Finberg L, Yasmura A, Liberman U, et al. Vitamin D dependent rickets Type II (VDDRII) with alopecia. Treatment with mega doses of 1,25(OH)2D3 overcomes affinity defect in receptor for 1,25(OH)2D3. Pediatr Res. 1984;18:1174.
427. Balsan S, Garabédian M, Larchet M, Gorski AM, Cournot G, Tau C, et al. Long-term nocturnal calcium infusions can cure rickets and promote normal mineralization in hereditary resistance to 1,25-dihydroxyvitamin D. J Clin Invest. 1986;77(5):1661–7.
428. Tiosano D, Hadad S, Chen Z, Nemirovsky A, Gepstein V, Militianu D, et al. Calcium absorption, kinetics, bone density, and bone structure in patients with hereditary vitamin D-resistant rickets. J Clin Endocrinol Metab. 2011;96(12):3701–9.
429. Srivastava T, Alon US. Cinacalcet as adjunctive therapy for hereditary 1,25-dihydroxyvitamin D-resistant rickets. J Bone Miner Res Off J Am Soc Bone Miner Res. 2013;28(5):992–6.
430. Scheinman SJ, Guay-Woodford LM, Thakker RV, Warnock DG. Genetic disorders of renal electrolyte transport. N Engl J Med. 1999;340(15):1177–87.
431. Lloyd SE, Pearce SH, Fisher SE, Steinmeyer K, Schwappach B, Scheinman SJ, et al. A common molecular basis for three inherited kidney stone diseases. Nature. 1996;379(6564):445–9.
432. Lowe CU, Terrey M, Mac LE. Organic-aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation; a clinical entity. AMA Am J Dis Child. 1952;83(2):164–84.
433. Silver DN, Lewis RA, Nussbaum RL. Mapping the Lowe oculocerebrorenal syndrome to Xq24-q26 by use of restriction fragment length polymorphisms. J Clin Invest. 1987;79:282–5.
434. Leahey AM, Charnas LR, Nussbaum RL. Nonsense mutations in the OCRL-1 gene in patients with the oculocerebrorenal syndrome of Lowe. Hum Mol Genet. 1993;2(4):461–3.
435. Santer R, Schneppenheim R, Dombrowski A, Gotze H, Steinmann B, Schaub J. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat Genet. 1997;17(3):324–6.
436. Mannstadt M, Magen D, Segawa H, Stanley T, Sharma A, Sasaki S, et al. Fanconi-Bickel syndrome and autosomal recessive proximal tubulopathy with hypercalciuria (ARPTH) are allelic variants caused by GLUT2 mutations. J Clin Endocrinol Metab. 2012;97(10):E1978–86.
437. Beighton P. Osteoglophonic dysplasia. J Med Genet. 1989;26(9):572–6.
438. White K, Cabral J, Evans W, Ichikawa S, Davis S, Ornitz D, et al. A missense mutation in FGFR1 causes a novel syndrome: craniofacial dysplasia with hypophosphatemia (CFDH). Am J Hum Genet. 2005;76:361–67.
439. Farrow EG, Davis SI, Mooney SD, Beighton P, Mascarenhas L, Gutierrez YR, et al. Extended mutational analyses of FGFR1 in osteoglophonic dysplasia. Am J Med Genet A. 2006;140(5):537–9.
440. Hoffman W, Jüppner H, Deyoung B, O'dorisio M, Given K. Elevated fibroblast growth factor-23 in hypophosphatemic linear nevus sebaceous syndrome. Am J Med Genet A. 2005;134:233–6.
441. Heike C, Cunningham M, Steiner R, Wenkert D, Hornung R, Gruss J, et al. Skeletal changes in epidermal nevus syndrome: does focal bone disease harbor clues concerning pathogenesis? Am J Med Genet A. 2005;139:67–77.
442. Lim YH, Ovejero D, Sugarman JS, Deklotz CM, Maruri A, Eichenfield LF, et al. Multilineage somatic activating mutations in HRAS and NRAS cause mosaic cutaneous and skeletal lesions, elevated FGF23 and hypophosphatemia. Hum Mol Genet. 2014;23(2):397–407.
443. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med. 1991;325:1688–95.
444. Schwindinger W, Francomano C, Levine M. Identification of a mutation in the gene encoding the alpha

subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A. 1992;89:5152–6.
445. Kobayashi K, Imanishi Y, Koshiyama H, Miyauchi A, Wakasa K, Kawata T, et al. Expression of FGF23 is correlated with serum phosphate level in isolated fibrous dysplasia. Life Sci. 2006;78(20):2295–301.
446. Waller S, Kurzawinski T, Spitz L, Thakker R, Cranston T, Pearce S, et al. Neonatal severe hyperparathyroidism: genotype/phenotype correlation and the use of pamidronate as rescue therapy. Eur J Pediatr. 2004;163(10):589–94.
447. Garcia-Garcia E, Dominguez-Pascual I, Requena-Diaz M, Cabello-Laureano R, Fernandez-Pineda I, Sanchez-Martin MJ. Intraoperative parathyroid hormone monitoring in neonatal severe primary hyperparathyroidism. Pediatrics. 2014;134(4):e1203–5.
448. Germain-Lee EL, Groman J, Crane JL, de Beur SM J, Levine MA. Growth hormone deficiency in pseudohypoparathyroidism type 1a: another manifestation of multihormone resistance. J Clin Endocrinol Metab. 2003;88(9):4059–69.
449. Finer G, Price HE, Shore RM, White KE, Langman CB. Hyperphosphatemic familial tumoral calcinosis: response to acetazolamide and postulated mechanisms. Am J Med Genet A. 2014;164a(6):1545–9.
450. Parfrey PS, Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: the EVOLVE trial. J Clin Endocrinol Metab. 2013;98(12):4834–44.