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A Physiologic–Based Approach to the Evaluation of a Patient With Hyperphosphatemia

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Abstract

Phosphate is required for skeletal mineralization, cellular energy regulation, synthesis of cell membranes and nucleic acids, and a variety of cell signaling pathways. Extracellular serum phosphate concentration is determined by the balance of gastrointestinal phosphate absorption, skeletal turnover, distribution in intracellular compartments, and renal phosphate excretion. An integrated system of hormones, receptors, and phosphate transporters regulates phosphate homeostasis, and a variety of hereditary and acquired perturbations in these regulators can result in hyperphosphatemia. Although kidney failure is the most common cause of hyperphosphatemia encountered by nephrologists, hyperphosphatemia that presents in patients with early stages of chronic kidney disease or normal kidney function should prompt a detailed evaluation that can be diagnostically challenging. In this teaching case, we describe a case of hyperphosphatemia out of proportion to the degree of decrease in glomerular filtration rate. We present a practical parathyroid hormone-based diagnostic approach that illustrates the current understanding of phosphate regulation in clinically meaningful terms for the practicing nephrologist. Finally, we illustrate how measurement of fibroblast growth factor 23 could be integrated in the future when the test becomes more widely available.

INDEX WORDS

Hyperphosphatemia; calcium-sensing receptor; hypoparathyroidism; parathyroid hormone; fibroblast growth factor 23

INTRODUCTION

Phosphate homeostasis is orchestrated by a complex integrated system of hormones, including fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D; receptors, including the calcium-sensing receptor (CaSR) and

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receptors for FGF, PTH, and vitamin D; and sodium-dependent phosphate transporters in the gut and kidney. Perturbations in these factors can cause abnormal serum phosphate levels.

Hyperphosphatemia is one of the most common laboratory abnormalities encountered by practicing nephrologists, but it is seen most commonly in patients with advanced stages of chronic kidney disease (CKD) and end-stage kidney disease in whom the cause is almost always clear. In contrast, hyperphosphatemia in patients with intact or mild to moderately decreased kidney function can present a diagnostic challenge. We present a systematic approach to the evaluation of a patient with hyperphosphatemia that illustrates the complex mechanisms that regulate serum phosphate and the pathophysiology of hyperphosphatemic disorders.

CASE REPORT

Clinical History and Initial Laboratory Data

A 40-year-old woman is referred for evaluation of hyperphosphatemia and decreased kidney function. During a pre-employment health screening, laboratory testing showed a serum phosphate level of 6.3 mg/dL (2.0 mmol/L). The patient was a recent immigrant to the United States and had not seen a physician in several years. She had a history of nephrolithiasis and a poorly defined “calcium problem” for which she had been prescribed calcium and calcitriol several years earlier. She did not recall the doses, but had stopped taking the medications 3 months earlier when her supply was depleted. The patient reported that her mother also had taken calcium and vitamin D supplements before she died of a malignancy. She had no siblings and no other significant family history.

Physical examination findings were unremarkable. Laboratory testing showed an elevated serum creatinine level, hyperphosphatemia, hypocalcemia, hypercalciuria, hypomagnesemia, and a low-normal PTH level (Table 1). Blood cell counts, liver function test results, and lipid panels were all within reference ranges. Kidney ultrasound revealed symmetric 10.2-cm kidneys with evidence of nephrocalcinosis.

Additional Investigations

Given the clinical constellation and possible autosomal dominant inheritance, genetic testing was undertaken and revealed that the patient was heterozygous for an activating mutation in the gene encoding the CaSR, indicating autosomal dominant hypoparathyroidism.¹

Diagnosis

(1) Autosomal dominant hypoparathyroidism due to an activating mutation of the CaSR gene. (2) CKD stage 3 due to nephrocalcinosis.

Clinical Follow-up

The patient was prescribed calcium acetate, 667 mg, 3 times daily with meals; magnesium oxide, 400 mg, 3 times daily; hydrochlorothiazide, 25 mg, twice daily; a sodium-restricted diet; and liberalized water intake to maintain urine flow >2 L daily. Calcitriol therapy was not resumed. Follow-up laboratory data are listed in Table 1.

DISCUSSION

Hyperphosphatemia and hypocalcemia with an inappropriately low PTH level are hallmarks of hypoparathyroidism. Although the patient had moderately decreased kidney function, hyperphosphatemia and hypocalcemia were disproportionate to the decrease in glomerular filtration rate, and hypercalciuria is distinctly abnormal for any CKD population. These features were the clues that steered the consultant from dismissing hyperphosphatemia as simply due to CKD. Confirmation of inappropriately low PTH levels in conjunction with a suggestive family history led to genetic testing that established a molecular diagnosis of autosomal dominant hypoparathyroidism due to an activating mutation of the CaSR. The history of nephrolithiasis and the finding of nephrocalcinosis in the setting of hypoparathyroidism could be indicative of excessive use of calcium and calcitriol supplementation and highlight both the physiologic contribution of the kidney to the pathogenesis of hypoparathyroidism and one of the major obstacles to its effective management.

Normal Phosphate Homeostasis

Gut—Phosphate is absorbed throughout the small intestine through paracellular transport and 1,25-dihydroxyvitamin D–dependent active transport through the sodium-dependent phosphate transporter 2b (NPT2b; encoded by the *SLC34A2* gene).^{2,3} It is estimated that vitamin D–dependent absorption is of secondary importance,⁴ accounting for only up to 20% of total phosphate absorption under conditions of normal phosphate intake.⁵ This concept is supported by studies that demonstrate that inactivating mutations of NPT2b do not have an abnormal phosphate homeostasis phenotype.⁶ In contrast, passive absorption appears to be nonsaturable, such that greater phosphate intake leads to greater net absorption. Although absorption or “bioavailability” of dietary phosphate varies by source (animal vs plant sources vs inorganic food additives), it is estimated that approximately 66%–75% of net intake is absorbed.⁷ Given the wide variability in dietary phosphate intake and relative lack of regulation of its absorption in the gut, the kidney is ultimately responsible for regulating phosphate balance.

Bone—In steady states of bone turnover, flux of phosphate into and out of bone is balanced. Phosphate efflux from bone is stimulated by PTH-mediated bone resorption, which mobilizes both phosphate and calcium into the extracellular fluid. Although FGF-23 is secreted by osteocytes, its direct effects on bone are unclear.

Kidney—Phosphate is freely filtered by the glomerulus and ~90% is reabsorbed by the proximal tubule (ie, fractional excretion is ~10%). Proximal tubular phosphate reabsorption is mediated by transport through apical NPT2a and NPT2c (encoded by *SLC34A1* and *SLC34A3*, respectively), inactivating mutations of which cause phosphate wasting and hypophosphatemic rickets in both animal models and humans.^{8,9} These transporters are regulated by PTH, FGF-23, and perhaps unknown hormones secreted by the gut.¹⁰ The tremendous renal reserve for phosphate excretion explains why most patients with even advanced stages of CKD nevertheless can maintain normal serum phosphate levels. As CKD progresses, modest increases in serum phosphate levels within the normal range increase the

filtered load of phosphate, and at the same time, the fractional excretion of filtered phosphate increases from 10% to >50%.^{11,12} Only after these compensations are exhausted does overt hyperphosphatemia occur, typically in CKD stages 4–5.

Hormonal regulators—PTH and FGF-23 stimulate endocytosis and decrease NPT2a and NPT2c expression in the apical membrane of the proximal tubule.¹³ The result is increased urinary phosphate excretion. Besides PTH and FGF-23, soluble klotho (the cleavage product of the transmembrane FGF-23 coreceptor) is a phosphaturic hormone,¹⁴ and animal studies suggest that a gut-kidney axis also stimulates renal phosphate excretion.¹⁵ Interestingly, both PTH and FGF-23 are needed to regulate serum phosphate, as shown by the presence of hyperphosphatemia in hypoparathyroidism, in which FGF-23 alone cannot normalize serum phosphate levels,^{16,17} and states of FGF-23 deficiency, in which PTH alone cannot normalize serum phosphate levels.^{18,19} It is possible that the phosphaturic hormones have synergistic effects on NPT expression in the proximal tubule. Alternatively, primary deficiencies in PTH or FGF-23 likely induce inappropriately low levels of the other due to their respective effects on 1,25-dihydroxyvitamin D. Treatment of primary hypoparathyroidism with calcitriol leads to an acute increase in FGF-23 and reduced serum phosphate levels,¹⁷ consistent with relative FGF-23 deficiency in untreated hypoparathyroidism that may be mediated by calcitriol deficiency. In addition, because higher serum calcium levels appear to be a secondary stimulus of FGF-23 expression,²⁰ hypocalcemia may also contribute to inappropriately low FGF-23 levels in primary hypoparathyroidism, and rescue of hypocalcemia by restoring gut calcium absorption may augment the increase in FGF-23 levels that accompanies 1,25-dihydroxyvitamin D administration. The observation that calcium infusion in hypoparathyroidism increases phosphate excretion and lowers serum phosphate level supports this possibility.²¹

The primary stimulus for PTH synthesis and secretion is reduced extracellular ionized calcium concentrations sensed by the CaSR. Binding of calcium to the extracellular domain of the CaSR in the parathyroid glands inhibits PTH synthesis and secretion and occurs continuously.²² Secondary stimuli for PTH secretion include hyperphosphatemia,²³ deficiency of 1,25-dihydroxyvitamin D, or impaired vitamin D signaling due to mutations in the vitamin D receptor.^{24,25}

The stimuli and regulation of FGF-23 expression and secretion are less well understood. In a classic negative endocrine feedback loop, calcitriol stimulates FGF-23 while FGF-23 downregulates calcitriol production.²⁶ FGF-23 inhibits PTH secretion²⁷ and PTH stimulates FGF-23, directly and through increases in 1,25-dihydroxyvitamin D level.^{28,29} High dietary phosphate intake and decreased kidney function stimulate FGF-23 production, but the molecular mechanisms are unknown.^{12,30,31} Fundamentally, this requires understanding of how phosphate is sensed, which is elusive.

Phosphate homeostasis can also be maintained even in the context of CKD. Beginning early in the course of CKD, FGF-23 levels begin to increase.³² As glomerular filtration rate decreases, progressive elevation of FGF-23 levels lowers 1,25-dihydroxyvitamin D levels by inhibiting renal 1 α -hydroxylase and stimulating catabolic 24-hydroxylase.³³ The resulting calcitriol deficiency stimulates PTH, leading to secondary hyperparathyroidism.³³ The

combination of increased FGF-23 and PTH levels along with decreased 1,25-dihydroxyvitamin D levels helps maintain serum phosphate levels within the normal range despite the reduction in glomerular filtration rate.

Causes of Hyperphosphatemia and Approach to Diagnosis

The main causes of hyperphosphatemia can be classified as pseudohyperphosphatemia, acute phosphate load, decreased filtered load, and abnormal tubular handling (Box 1). Currently, a PTH-based diagnostic approach should be used to evaluate hyperphosphatemia that is not due to kidney failure (Fig 1A). Because future availability of FGF-23 testing will enhance this approach, we also present expected levels of FGF-23 in the various clinical settings (Fig 1B).

Pseudohyperphosphatemia—A laboratory artifact occasionally encountered in patients with hyperglobulinemia, hyperlipidemia, and hyperbilirubinemia, pseudohyperphosphatemia is caused by colorimetric interference with the assay.³⁴ The present patient had no disorder to suggest pseudohyperphosphatemia, and the rest of the biochemical picture confirms actual hyperphosphatemia.

Acute phosphate load—Delivery of a large load of exogenous or endogenous phosphate over a short time can overwhelm the kidney's capacity to excrete phosphate. Patients with pre-existing CKD or concomitant acute kidney injury are more susceptible. Ingestion of phosphate-containing laxatives in preparation for colonoscopy is the leading cause of acute exogenous phosphate toxicity³⁵; several deaths have been reported.³⁶ Vitamin D intoxication can also cause exogenous phosphate toxicity due to excessive gastrointestinal phosphate absorption. Concomitant hypercalcemia can impede compensatory increases in renal phosphate excretion by inhibiting PTH secretion and inducing renal vasoconstriction, which decreases the filtered load of phosphate. Endogenous phosphate toxicity results from severe cellular necrosis due to tumor lysis syndrome, rhabdomyolysis, and massive hemolysis. Lactic acidosis and insulin deficiency can also lead to hyperphosphatemia through impaired cellular uptake of phosphate. The present patient showed no evidence of any of these conditions.

Decreased filtered load—Despite progressively increasing PTH and FGF-23 levels, the ability to maintain neutral phosphate balance in CKD eventually is overwhelmed by critical reductions in the filtered load of phosphate. Kidney failure is the most common cause of hyperphosphatemia, and no further diagnostic evaluation usually is necessary in patients with end-stage renal disease. Although the present patient had CKD, hyperphosphatemia of this magnitude can be attributed to CKD alone only in stages 4 or 5. Moderate hyperphosphatemia in stage 3 suggested a primary defect in tubular handling of phosphate.

Abnormal tubular phosphate handling—Deficiency of FGF-23 or PTH or resistance to their actions in the proximal tubule leads to hyperphosphatemia with inappropriately low fractional excretion of phosphate. Mutations that result in deficiency of biologically active FGF-23 or resistance to its actions due to mutations in *klotho* cause the rare autosomal recessive disorder familial tumoral calcinosis (Table 2).^{19,37} Lack of FGF-23 activity results

in hyperphosphatemia and elevated 1,25-dihydroxyvitamin D levels.³⁸ Although serum calcium concentration typically is normal, increased intestinal calcium absorption mediated by 1,25-dihydroxyvitamin D in concert with hyperphosphatemia cause massive calcium and phosphate deposition, for which the disease is named.³⁹ Hypocalcemia and low 1,25-dihydroxyvitamin D levels exclude inactivating FGF-23 or klotho mutations and eliminate the possibility of tumoral calcinosis in this case.

Hypoparathyroidism can be due to destruction or surgical resection of parathyroid tissue, functional impairment of PTH secretion, and hereditary diseases (Box 2).⁴⁰ Although incompletely understood, it has been suggested that hypomagnesemia results in defective cyclic adenosine monophosphate generation in the parathyroid glands and PTH target organs,⁴¹ resulting in both impaired secretion and action of PTH, whereas hypermagnesemia, through its calcimimetic effect on the CaSR, can also impair PTH secretion. Among the hereditary disorders, mutations have been reported in numerous genes involved in parathyroid gland development, PTH production, secretion, and end-organ signaling (Table 2).⁴² Pseudohypoparathyroidisms (types Ia and Ib) are hereditary forms of hypocalcemia in which PTH levels are high, but maternally inherited mutations in the gene encoding the alpha subunit of the stimulatory G-protein cause resistance to PTH actions specifically in the proximal tubule, which leads to hyperphosphatemia.⁴³ Hypocalcemia usually is modest because PTH sensitivity is intact in the distal nephron, which enhances calcium reabsorption, and in bone, which increases bone resorption, increasing serum calcium levels. Low PTH levels in the setting of hyperphosphatemia and hypocalcemia in this patient are consistent with hypoparathyroidism and exclude pseudohypoparathyroidism. The combination of hypercalciuria together with the family history suggestive of autosomal dominant inheritance suggests a heterozygous activating mutation of the CaSR gene.

Autosomal Dominant Hypoparathyroidism

More than 50 activating mutations of the CaSR gene have been described since the first report in 1994.⁴⁴ These mutations result in autosomal dominant hypoparathyroidism, in which functional hypoparathyroidism occurs as a result of a left-shifted PTH-calcium sensing curve. Due to these CaSR mutations, the parathyroid glands constitutively “sense” hypercalcemia and PTH secretion is suppressed. Constitutive activation of the CaSR in the thick ascending limb of the nephron results in inappropriate hypercalciuria in the setting of hypocalcemia.⁴⁵ Hypercalciuria increases the risk of nephrolithiasis, and nephrocalcinosis occurs in ~12% of patients.⁴⁶ Risks of nephrolithiasis and nephrocalcinosis can be exacerbated by efforts to normalize serum calcium levels with calcium and calcitriol supplementation, as the present patient likely experienced.

Hypocalcemia usually is not as severe in autosomal dominant hypoparathyroidism as in other causes of primary hypoparathyroidism, and it is often asymptomatic. As a result, the median age of diagnosis varies widely from the neonatal period to the sixth decade.⁴⁷ Incidentally detected hypocalcemia or hyperphosphatemia is frequently the presenting finding in new probands, and screening of family members of affected individuals accounts for many other diagnoses.

The goal of therapy should be to increase the serum calcium concentrations sufficiently to ameliorate symptomatic hypocalcemia without normalizing calcium levels because this worsens hypercalciuria and enhances the risk of nephrolithiasis and nephrocalcinosis to as high as 75% of treated patients.^{46,48,49} Replacement therapy with recombinant PTH is another strategy that has been used successfully in case reports of individuals with autosomal dominant hypoparathyroidism and in larger series of patients with hypoparathyroidism due to other causes.^{50–52} However, hypercalciuria may respond poorly to PTH administration, and the need for twice-daily injections is a practical limitation. Thiazide diuretics in combination with salt restriction are adjunctive treatments that can reduce hypercalciuria by augmenting distal calcium reabsorption through the transient receptor potential cation channel subfamily V member 5 (TRPV5).⁵³ A low-phosphate diet can be considered.

Because this patient had no symptoms of hypocalcemia, administration of calcitriol was withheld. A low dose of calcium acetate was administered at meals to provide a small amount of calcium supplementation and reduce phosphate absorption. Thiazides, salt restriction, and liberalized fluid intake were prescribed to reduce the risk of recurrent nephrolithiasis and progression of nephrocalcinosis. Magnesium supplements were prescribed to offset hypermagnes-uria-induced hypomagnesemia, which is common in autosomal dominant hypoparathyroidism,⁴⁹ and, by inducing PTH resistance, can magnify the effect of PTH deficiency.

In conclusion, serum phosphate concentration is regulated by a complex and integrated system of hormones, receptors, and transporters (see Box 3 for main teaching points). A detailed understanding of the pathophysiology of phosphate homeostasis is essential for accurately diagnosing the cause of hyperphosphatemia. Currently, a PTH-based diagnostic approach should be used, but in the future, FGF-23 testing will likely enhance diagnosis and management.

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Box 1**Causes of Hyperphosphatemia****Pseudohyperphosphatemia**

- Hyperglobulinemia
- Hyperlipidemia
- Hyperbilirubinemia

Acute phosphate load

- Exogenous
 - Phosphate-containing laxatives
 - Vitamin D toxicity
- Endogenous
 - Tumor lysis syndrome
 - Rhabdomyolysis
 - Hemolysis
 - Lactic acidosis
 - Diabetic ketoacidosis

Decreased filtered load of phosphate

- Kidney failure

Abnormal tubular phosphate handling

- Hypoparathyroidism
- Pseudohypoparathyroidism
- Familial tumoral calcinosis

Box 2**Causes of Hypoparathyroidism****Destruction or removal of parathyroid tissue**

- Postsurgical
- Autoimmune
- Metastatic infiltration
- Heavy metal deposition

Functional impairment of PTH secretion

- Activating mutation in the calcium-sensing receptor
- Hypomagnesemia
- Hypermagnesemia

Genetic disorders of parathyroid gland development and PTH biosynthesis

Abbreviation: PTH, parathyroid hormone.

Box 3**Teaching Points**

- PTH, FGF-23, and 1,25(OH)₂D are the main hormonal regulators of serum phosphate concentration.
- Hyperphosphatemia disproportionate to the decrease in GFR should prompt evaluation of an underlying cause other than chronic kidney disease.
- A PTH-based approach should be used in the initial evaluation of hyperphosphatemia. In the future, FGF-23 testing could be integrated.
- Autosomal dominant hypoparathyroidism should be considered in cases of primary hypoparathyroidism, especially when the family history is suggestive.
- To minimize the risk of nephrocalcinosis in patients with autosomal dominant hypoparathyroidism, calcium and calcitriol should be administered judiciously to attenuate symptoms, but not to fully normalize serum calcium level.

Abbreviations: 1,25(OH)₂D, 1,25-dihydroxyvitamin D; FGF-23; fibroblast growth factor 23; GFR, glomerular filtration rate; PTH, parathyroid hormone.

Figure 1. Diagnostic approach to hyperphosphatemia. (A) Parathyroid hormone (PTH)-based diagnostic algorithm; (B) Expected levels of fibroblast growth factor 23 (FGF-23) in different conditions. *Pseudohyperphosphatemia due to multiple myeloma may be associated with hypercalcemia. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table 1**Laboratory Data**

Serum tests	Reference Range	Initial Data	Follow-up
Sodium (mEq/L)	135–145	140	139
Potassium (mEq/L)	3.4–4.8	4.1	3.6
Bicarbonate (mEq/L)	23–32	25	27
Creatinine (mg/dL)	0.8–1.3	1.5	1.5
eGFR (mL/min/1.73 m ²)	>60	41	41
Total calcium (mg/dL)	8.4–10.2	7.6	8.1
Ionized calcium (mEq/L)	2.24–2.64	1.94	2.06
Magnesium (mEq/L)	1.5–2.3	1.1	1.8
Phosphate (mg/dL)	2.5–4.5	6.3	5.1
PTH, intact (pg/mL)	11–80	11	15
25(OH)D (ng/mL)	30–60	27	25
1,25(OH) ₂ D (pg/mL)	25–66	16	20
Urinary tests			
Urinary calcium excretion (mg/d)	<200	315	180
Urinary phosphate excretion (mg/d)	600–1,200	825	710
Urinary sodium excretion (mmol/d)	50–150	255	165

Note: eGFR estimated using the 4-variable Modification of Diet in Renal Disease Study equation. Conversion factors for units: serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; eGFR in mL/min/1.73 m² to mL/s/1.73 m², $\times 0.01667$; serum calcium in mg/dL to mmol/L, $\times 0.2495$; ionized calcium and serum magnesium in mEq/L to mmol/L, $\times 0.5$; serum phosphate in mg/dL to mmol/L, $\times 0.3229$; 25(OH)D in ng/mL to nmol/L, $\times 2.496$; 1,25(OH)₂D in pg/mL to pmol/L, $\times 2.6$. No conversion necessary for sodium, potassium, and bicarbonate in mEq/L and mmol/L and PTH in pg/mL and ng/L.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

Table 2**Leading Genetic Causes of Hyperphosphatemia in Humans**

Mutation	Function	Inheritance	Accompanying Characteristics
<u>Decreased FGF-23 Activity → Familial Tumoral Calcinosis</u>			
FGF-23; (–)	Phosphaturia; inhibition of 1,25(OH) ₂ D production	Autosomal recessive	Low intact but high carboxy-terminal FGF-23; high 1,25(OH) ₂ D; ectopic calcification
GALNT3; (–)	Post-translational glycosylation of FGF-23; increases FGF-23 stability	Autosomal recessive	Low intact but high carboxy-terminal FGF-23; high 1,25(OH) ₂ D; ectopic calcification
Klotho; (–)	FGF-23 co-receptor	Unknown	High intact FGF-23, carboxy-terminal FGF-23, 1,25(OH) ₂ D; ectopic calcification
<u>Decreased PTH → Hypoparathyroidism</u>			
PTH; (–)	Phosphaturic hormone and regulator of serum calcium	Variable	Low PTH, serum calcium; may be part of a broader genetic syndrome
GCMB; (–)	Transcription factor required for parathyroid gland development	Autosomal dominant	Low PTH; low serum calcium
CaSR; (+)	Regulation of PTH release and urinary calcium reabsorption	Autosomal dominant	Low PTH, serum calcium, and magnesium; hypercalciuria; nephrolithiasis; nephrocalcinosis
<u>Resistance to PTH Action → Pseudohypoparathyroidism</u>			
GNAS; (–)	Encodes the stimulatory G-protein alpha subunit (G _s -α)	Maternally inherited	High PTH, low serum calcium; may also manifest hypothyroidism, hypogonadism

Abbreviations: (+), gain of function; (–), loss of function; CaSR, calcium-sensing receptor; FGF-23; fibroblast growth factor 23; GALNT3, *N*-acetylgalactosaminyltransferase 3; GCMB, glial cells missing homolog b; PTH, parathyroid hormone; GNAS, guanine nucleotide binding protein, alpha stimulating.