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Pseudohypoparathyroidism

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PATHOPHYSIOLOGY

On binding of parathyroid hormone (PTH) to its receptor, the heptahelical PTH/PTHrP receptor (PTH1R), leads to dissociation of G α (encoded by *GNAS*), the alpha-subunit of the heterotrimeric stimulatory G protein from the $\beta\gamma$ -subunits, with subsequent activation by G α of adenylyl cyclase and synthesis of the intracellular messenger cyclic AMP (cAMP) from ATP. Protein kinase A (PKA) is a primary target of cAMP, and binding of cAMP to regulatory subunits (eg, R1A encoded by *PRKARIA*) unlocks the catalytic subunits, which unleashes a cascade of events that affect various cellular functions, including cell growth and differentiation, gene transcription, and protein expression. For example, PKA-dependent phosphorylation of intracellular enzymes either increases or decreases their activity, and

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phosphorylation of the transcription factor CREB (cAMP response element-binding protein) allows it to enter the cell nucleus where it regulates gene transcription. Among the many enzymes that are phosphorylated are phosphodiesterases (PDEs) such as PDE4D, which metabolize cAMP thereby terminating cAMP-dependent signaling events. Several additional cAMP targets have been identified, such as cyclic nucleotide-gated cation channels and the exchange proteins 1 and 2 (Epac 1 and 2) that are activated by cAMP.^{1–3}

Renal resistance to PTH leads to impaired formation of 1,25(OH)₂D, the fully active form of vitamin D, and reduces expression of sodium-dependent phosphate transporters in the renal tubules, thereby leading to hypocalcemia and hyperphosphatemia, with elevated serum PTH levels. PTH resistance can result from impaired cAMP generation, from accelerated cAMP degradation, or from impaired cAMP-dependent PKA activation. So far, most identified cases of PTH resistance are due to impaired generation of cAMP, and the defects are in the G α protein that couples the PTH1R to adenylyl cyclase rather than in the PTH1R itself. Because this post-receptor signal transduction pathway is used by many different G-protein-coupled receptors (GPCRs), it is not unusual to see reduced responsiveness to numerous other hormones, including thyroid-stimulating hormone (TSH), PTHrP (PTH-related peptide, a ligand that activates the PTH1R in chondrocytes thereby delaying their differentiation), growth hormone releasing hormone (GHRH), gonadotropins, catecholamines, and calcitonin, whose receptors couple to G α . Remarkably, even though the genetic defect that affects G α is present in all cells, hormonal resistance can vary with age and can affect tissues differently.^{4–8}

PSEUDOHYPOPARATHYROIDISM FROM 1942 TO THE TWENTY-FIRST CENTURY

In 1942, Fuller Albright and colleagues⁹ introduced the term pseudohypoparathyroidism (PHP) to describe PTH resistance in 3 patients with biochemical hypoparathyroidism (ie, hypocalcemia and hyperphosphatemia) and a constellation of unusual features that included short stature, obesity, round faces, brachydactyly, and heterotopic ossification (ie, Albright hereditary osteodystrophy [AHO]) who showed no change in their urinary phosphorous excretion after administration of parathyroid extract. A decade later, Albright and his colleagues¹⁰ identified a variant of PHP, subsequently namely pseudo-PHP (PPHP), in a patient with AHO who had normal serum levels of calcium and phosphorus and showed an appropriate phosphaturic response to parathyroid extract. Since then, several related phenotypes have been described that resulted in the discovery of additional underlying disease mechanisms and/or genes, which provided novel insights into major biological functions like cAMP signaling, epigenetics, development, and cell differentiation, and thereby helped further refine the meaning of the term “pseudohypoparathyroidism.”

In the 1960s, Aurbach and colleagues^{11,12} discovered that kidney-derived and bone-derived tissues increase cAMP formation in response to parathyroid extract. They revealed that patients with PHP, diagnosed on the basis of hypocalcemia, hyperphosphatemia, and features of AHO, failed to increase urinary excretion of cAMP after administration of PTH, thereby linking the absent phosphaturic response to PTH to failure to generate cAMP in the

kidney.¹³ More than 20 years later, the introduction of sensitive immunometric PTH assays readily allowed establishing the diagnosis of PTH resistance in the setting of hypocalcemia and hyperphosphatemia.¹⁴

In 1980, the critical role of *Gsα* deficiency in the pathophysiology of PHP was independently demonstrated by Levine as well as Bourne and their respective collaborators. Both groups showed through the use of in vitro assays in which extracts from human erythrocyte membranes could reconstitute hormone-responsive adenylyl cyclase activity that patients with PHP with AHO have an approximately 50% reduction in *Gsα* bioactivity.^{15,16} By contrast, patients with PHP without obvious AHO features had normal or only mildly impaired *Gsα* bioactivity. This led to a revised classification for PHP in which patients with PHP with AHO and reduced *Gsα* bioactivity were said to have PHP1A. Patients without AHO and largely normal *Gsα* bioactivity were said to have PHP1B.

Ten years later, the first mutations in *GNAS*, the gene encoding *Gsα*, were identified in PHP1A and PPHP, which stimulated a series of discoveries leading to a better understanding of this complex and heterogeneous group of diseases.^{17,18} Particularly important was the observation that PHP1A occurs only in children of women affected by PHP1A or PPHP, whereas men with either condition have children affected by only PPHP.^{19–22} This unusual mode of inheritance was confirmed in mouse models of PHP1A, that furthermore revealed first evidence for the tissue-specific reduction in paternal *Gsα* expression, namely an almost complete disappearance of *Gsα* protein in the renal cortex of animals with ablation of either *Gnas* exon 1 or 2 on the maternal allele.^{23,24} In the early 2000s, Hayward and colleagues^{25,26} discovered additional coding regions upstream of the *GNAS* exons encoding *Gsα* and demonstrated that the promoters of these exons undergo parent-specific methylation, namely methylation on the maternal allele for exons A/B, AS, and XL, methylation on the paternal allele for exon NESP.

Because patients affected by PHP1B typically show no evidence for AHO and normal *Gsα* activity, this PHP variant was initially thought to be caused by mutations in the *PTH1R*. However, after cloning the *PTH1R* in 1991,²⁷ several groups excluded mutations in this gene and its messenger RNA.^{28–31} A few years later, it was demonstrated that PHP1B is associated with methylation defects at the *GNAS* A/B:TSS-DMR and frequently other differentially methylated regions (DMRs) within this complex locus.³² The subsequent analyses of several large families in which numerous members are affected by PHP1B showed a dominant mode of inheritance and genetic studies revealed linkage to a region on chromosome 20q13.3 that comprises the *GNAS* locus; furthermore, PTH-resistant hypocalcemia occurred only when the disease-associated haplotype was inherited from a woman. Subsequent studies confirmed linkage to this chromosomal region in additional PHP1B families, but excluded most portions of the *GNAS* locus.³³ A loss of methylation restricted to the *GNAS* A/B:TSS-DMR was identified in the patients affected by this autosomal dominant (AD-PHP1B) form of the disease and a 3-kb deletion was eventually found 220 kb telomeric of the exon A/B that is located within the genomic region of the *STX16* gene; this deletion is the most frequent cause of AD-PHP1B.³⁴ Several other imprinting control regions were characterized through similar or related experimental

approaches.^{35–37} However, most PHP1B cases are sporadic and the underlying genetic defect has not yet been identified.

In recent years, it has become apparent that some AHO features, albeit less pronounced in most cases, can be encountered also in patients affected by PHP1B.^{38–40} Furthermore, additional genes were identified as other causes of AHO-like abnormalities that occur in the absence or presence of PTH resistance.^{41–46} These important advances in defining the molecular landscape of the different PHP and AHO variants, as well as the insights gained from different animal models raises the question whether a novel nomenclature is needed to more precisely define the clinical features of these related disorders. A European consortium therefore proposed a classification that is based on the underlying molecular diagnosis (see 8“classifications”),⁴⁷ with a particular emphasis on PTH- and PTHrP-dependent signaling events. This led a group of 35 experts to produce the first consensus for the diagnosis and management of PHP and related disorders, which is a major advance to the field that will help guide health care professionals and patients.⁴⁸

PSEUDOHYPOPARATHYROIDISM AND DIFFERENT CLASSIFICATION SYSTEMS

AHO features with or without hormonal resistance (particularly PTH, TSH, and GHRH resistance), and the presence of reduced or normal G_{α} activity, measured by in vitro assays using patient-derived cells, is the basis of the first classification that was established in the early 1980s. According to this classification, cAMP response to exogenously administered PTH differentiates PHP1, in which blunted cAMP and phosphaturic responses are observed, from PHP2, in which the increase in urinary cAMP excretion is conserved but the phosphaturic response is deficient.¹¹ Because patients with PHP2 do not have other features of PHP, it is likely that in many cases these patients have undiagnosed vitamin D deficiency. In addition, PHP1A refers to the combination of AHO, hormonal resistances, and low G_{α} activity, whereas PHP1C refers to the combination of AHO and hormonal resistances, yet normal G_{α} activity. PHP1B refers to hormonal resistance and normal G_{α} activity, typically in the absence of obvious AHO features, and PPHP refers to AHO features and reduced G_{α} activity, in the absence of hormonal resistance.^{13,49,50} Table 1A summarizes the first widely used, well-known classification, which is based on clinical and biochemical characteristics that can be readily assessed. On the other hand, this classification has several limitations that have been pointed out over the years, particularly the absence of disease-specific genetic mutations and the lack of inclusion of disorders that resemble AHO variants, for example, progressive osseous heteroplasia (POH), or that are caused by mutations in the PTH1R/ G_{α} /cAMP pathway, for example, different forms of acrodysostosis caused by mutations in *PTHLH*, *PRKARIA*, *PDE4D*, *PDE3A*, and possibly other genes. Recently, several reviews including that of Haldeman-Englert and colleagues,⁶ took advantage of the genetic and epigenetic discoveries, and proposed a modern overview of the spectrum of disorders of the *GNAS* inactivation (Table 1B).

In 2016, another classification was proposed by a European consortium through a methodological approach (Table 1C). This classification encompasses disorders that share a

common mechanism responsible for clinical features, that is, «inactivating PTH/PTHrP signaling disorder» (iPPSD). Clinical and biochemical features that show minimal or no overlap with other conditions were defined as major criteria for the diagnosis of iPPSD, that is, PTH-resistance, subcutaneous ossifications, and brachydactyly type E, when associated with other features. The underlying genetic mutation has been incorporated into the classification through numbering; each gene with the disease-causing mutation is given a number, thus allowing patients to be assigned to a single genetically defined entity. However, this novel classification requires further validation, designation of the parental allele carrying the mutation, and the implication that impaired signaling at the PTH/PTHrP receptor is the “*sine qua non*” for the different forms of iPPSD can be misunderstood, as it excludes disease aspects that result from impaired cAMP-mediated signaling downstream of other Gs α -coupled receptors.⁴⁷ This latest classification (as well as the others) should be improved further, possibly by using another term that focuses on abnormal cAMP generation, metabolism, or action.

MAIN FEATURES LEADING TO THE DIAGNOSIS OF PSEUDOHYPOPARATHYROIDISM

We detail herein the main features leading to the diagnosis of PHP or triggering additional clinical, biochemical, and molecular investigations. Additional, less specific symptoms are also present in patients with pseudohypoparathyroidism. They are defined in Table 2 and in the descriptions of the different diseases that follow.

Parathyroid Hormone Resistance

Resistance to PTH, the central hallmark of all forms of PHP, is defined by the association of hypocalcemia, hyperphosphatemia, and elevated serum PTH levels in the absence of vitamin D deficiency, abnormal magnesium levels, and renal insufficiency.⁴⁸ In the proper context, a patient may be suspected to have PHP, when very young, on the basis of hyperphosphatemia and elevated PTH levels, which usually precedes hypocalcemia.^{6,51,52} As in all forms of hypoparathyroidism, hyperphosphatemia can lead to an elevated calcium-phosphorus product that induces ectopic calcifications (to be distinguished from heterotopic ossification) in certain tissues, notably the basal ganglia or ocular lens.⁶

Ectopic Ossifications

Ectopic ossification is a developmental defect that results from Gs α deficiency in mesenchymal stem cells, and is unrelated to serum levels of calcium or phosphorus. The Gs α deficiency leads to de novo differentiation of osteoblasts in extraskeletal connective tissues that produce islands of ectopic membranous bone, most commonly in the dermis and subcutaneous fat. They may present as small and asymptomatic nodules or as large, coalescent plaques of bone that evolve deeply into muscles and around joints. Subcutaneous ossifications preferentially affect the periarticular areas of the hands and feet and the feet plantar region⁵³ (Fig. 1). There is no evidence that environmental factors such as trauma or inflammation affect their progression. Some lesions occasionally extrude a chalky material.^{6,48,53} Ectopic ossifications have been reported only so far in patients who have PHP1A or

PPHP due to inactivating mutations involving *GNAS* exon 1 to 13 and are not observed in patients with mutations in *PRKAR1A*, *PDE4D*, *PTHLH*, or *PDE3A*.

Brachydactyly

Shortening of the metacarpals and metatarsals is the most common skeletal feature associated with PHP1A and PPHP, although some patients with PHP1B may also manifest this osteodystrophy.^{38–40} Typically, brachydactyly involves the fourth and the fifth metacarpals/tarsals, that is, brachydactyly type E, and the distal phalanx of the thumb, that is, brachydactyly type D. Sometimes, brachydactyly E may be absent, yet there is always a short thumb and/or cone-shaped epiphyses.^{54,55} Brachydactyly is the result of accelerated closure of growth plates, and is due to impaired PTHrP signaling in chondrocytes resulting from *Gsa* deficiency. This process also occurs in the long bones of the skeleton, and accounts in part for the short stature that is typical of PHP1A and PPHP. In some patients, for example, acrodysostosis, all bones are affected and short.^{54,56,57} In patients with *GNAS* inactivation, brachydactyly is not present at birth, and develops over time and is usually obvious by puberty. In patients with acrodysostosis, the shortening of the bones in the hands and feet is usually observed early in infancy.^{41,43}

DIAGNOSIS OF PSEUDOHYPOPARATHYROIDISM

The diagnoses of PHP and AHO are based on the association of clinical and biochemical features that may vary depending on the age of the patient and on the family history. An infusion of PTH is rarely required to make a diagnosis.

Patients with a Coding Mutation on the Maternal *GNAS* Allele/PHP1A-1C/iPPSD2

These patients are born with moderate intrauterine growth retardation⁵⁸ yet develop early-onset obesity⁵⁹ (Fig. 2). An elevated TSH is often detected by neonatal screening and may be an initial feature of the disease,^{8,51,60–63} which may be misdiagnosed as congenital hypothyroidism associated with a small thyroid gland.⁶⁴ Thirty percent to 80% of these patients may have subtle subcutaneous ossifications as early as in infancy that are not as severe as in POH.^{65,66} PTH resistance, the hallmark of this disease, is usually not present at birth; it develops over time and hypocalcemia is present in most patients by the age of 7 to 8 years.^{51,52,67} Interestingly, because brachydactyly and short stature represent the effect of premature cessation of long bone growth, these features also develop over time, and children are often normal statured during the first 5 to 7 years of life.⁵⁹ Growth hormone deficiency, due to impaired responsiveness of pituitary somatotropes to GHRH, also contributes to short stature.^{68–71} These patients also have an increased risk of asthma, as well as sleep apnea, that is not solely explained by their obesity.⁷²

Mild to moderate cognitive impairment is common in these patients, with a high degree of variability even within families. It is important to note that several psychiatric manifestations have been reported in these patients, which has been attributed to long-standing hypocalcemia.^{73,74} Some patients may have structural central nervous system (CNS) findings, such as macrocephaly,^{6,9} spinal stenosis, Chiari 1 malformation, and craniosynostosis, that may lead to neurologic abnormalities^{75–77} (Fig. 3). The average final

height of men and women with PHP1A is 158.1 ± 6.7 cm and 146.3 ± 8.0 cm, respectively.⁵⁹ As patients age, their mean body mass index tends to improve, although many patients remain obese in adulthood, especially women.^{59,78} Resistance to other hormones has been described,^{5,8} in particular to gonadotropins^{22,79} and calcitonin.⁸⁰ Very few data are available on the gonadal function and fertility of these individuals.

Patients with a Coding Mutation on the Paternal GNAS Allele/PPHP-POH-Osteoma Cutis/iPPSD2

Patients with osteoma cutis, a variant of PPHP, manifest mild subcutaneous ossifications as the only feature of AHO. By contrast, patients with POH and PPHP are born with severe growth retardation.^{58,59} In PPHP, prenatal growth retardation may be the only sign at birth; diagnosis may be delayed by several years. In newborns or infants, subcutaneous ossifications are highly suggestive of POH and osteoma cutis due to an inactivating mutation involving the paternal *GNAS* exons encoding Gs α .^{53,81,82} Patients with PPHP present with an AHO phenotype and, in most cases, heterotopic ossifications. Patients with POH present with severe ossifications and mild or no other features of AHO. Osteoma cutis may present as an isolated plaque of ossification without any other clinical or biochemical features.⁵³ Mild elevations in PTH and TSH levels have been reported in occasional patients with PPHP.⁸³

Patients with a GNAS Methylation Disorder/PHP1B/iPPSD3

The preeminent feature of PHP1B is resistance to PTH in proximal renal tubular cells. As in PHP1A, this biochemical phenotype develops progressively after birth^{6,60,84} and leads to the diagnosis on average by age of 13 years; note that many patients are diagnosed only during adulthood. Long-standing undiagnosed or insufficiently treated PTH resistance in patients with PHP1B is associated with increased bone resorption. In children, this may lead to bone pain, bone deformities, and “rickets”-like changes on radiographs.^{84,85} In addition, children, as well as adults, may develop brown tumors and tertiary hyperparathyroidism.⁸⁶ Mild resistance to TSH is often present and characterized by TSH levels slightly above the upper level of normal (average 5.3 ± 4.7 mUI); free T4 levels are usually reported as normal.⁴⁸ Patients with PHP1B have significantly increased birth weights and/or lengths implying that maternally derived *GNAS* transcripts have an important role in fetal growth.^{59,87} Possibly because of the defective Gs α signaling at the α MSH receptor in the CNS, these patients can show a dramatic weight gain in their first years of life, which is often not recognized by physicians.⁵⁹ The final height is similar to that of the reference population, that is, 160.4 ± 7.4 cm and 172.7 ± 8.4 cm for women and men with the autosomal form of PHP1B, and 160.7 ± 8.4 cm and 172.0 ± 6.2 cm for women and men with the sporadic form of PHP1B, respectively.⁵⁹ Most patients with PHP1B appear to have normal psychomotor development, gonadal function, and fertility.

Patients with Acrodysostosis/iPPSD4 and 5

The bone dysplasia is usually the first recognized sign in patients with acrodysostosis, in some cases as soon as the first months of life. In most patients, all bones of the hand and feet are short. Statural growth is impaired both prenatally and after birth. When acrodysostosis is caused by a *PRKARIA* mutation, patients present with elevated levels of PTH and TSH, yet

calcium and free T4 circulating levels remain within the normal range and do not appear to vary throughout life.^{41,56,88,89} Some patients with *PDE4D* mutations also have evidence for PTH and TSH resistance, can have cognitive difficulties, and CNS complications, such as Chiari malformation.^{42,43,56,90,91} Patients with *PDE3A* mutations have brachydactyly type E plus hypertension.

MOLECULAR DIAGNOSIS

The diagnosis of PHP is based on clinical characteristics and endocrine findings, but, whenever possible, should be confirmed through molecular genetic testing. The strategy for the molecular diagnosis of PHP has evolved considerably in the past decade thanks to the discovery of mutations in different genes involved in the Gsα/cAMP/PKA signaling pathway and to the implementation of new genomic techniques.

Analysis of the *GNAS* Locus in Patients with Distinctive Phenotypes

Patients affected with the specific phenotypes should undergo genetic testing targeted to the *GNAS* gene/locus.

Confirmatory sequencing of the *GNAS* locus should be performed in patients with suspected PHP1A, PPHP, POH, and osteoma cutis. Note that *GNAS* exon 1 is GC-rich and may be difficult to analyze through techniques involving DNA amplification by polymerase chain reaction (PCR).^{17,22,38,58,92–97} Furthermore, microdeletions removing one or several *GNAS* exons may not be detected by Sanger or Next-Generation Sequencing, thus requiring techniques quantifying both parental alleles, such as multiplex ligation amplification probe (MLPA).⁹⁸

Methylation analysis at the *GNAS* A/B:TSS-DMR should be performed in patients who present with PTH resistance with no or few signs of AHO, that is, PHP1B/iPPSD3, or in patients with PHP1A who do not have a mutation in those *GNAS* exons encoding Gsα.^{34,38,99–102} Different techniques are available to screen for methylation defects including pyrosequencing or methyl-sensitive MLPA (MS-MLPA). Once the epigenetic defect has been characterized at the *GNAS* A/B:TSS-DMR, it is of major importance to identify the genetic defect responsible for the disease.¹⁰³ Approximately 20% of the patients present with an inherited form of the disorder that is, in most cases, associated with a recurrent deletion removing 3 kb of the *STX16* gene located upstream of *GNAS*.³⁴ In rare patients, the deletion is located elsewhere within the *GNAS* locus.^{34–37,104–107} Approximately 10% of the patients present with epigenetic defects that involve all *GNAS* DMRs that are caused by a cytogenetic defect known as paternal uniparental disomy of chromosome 20q (patUPD20).^{108–112} Therefore, in sporadic patients with PHP1B/iPPSD3 that display a broad *GNAS* methylation defect, experimental approaches to search for patUPD20, for example, single-nucleotide polymorphism array or microsatellite analysis, are recommended. Finally, approximately 70% of the patients with PHP1B/iPPSD3 are characterized by a methylation defect involving at least one *GNAS* DMR, in addition to the *GNAS* A/B:TSS-DMR, which establishes the diagnosis of sporadic PHP1B.

Exome Sequencing in Patients with Features of Pseudohypoparathyroidism

Patients who present with PTH resistance and/or features of AHO, especially in the absence of subcutaneous ossifications, may be preferentially investigated through targeted sequence analysis of different genes, for example, *GNAS*, *PRKAR1A*, *PTHLH*, *PDE4D*, and *PDE3A*. Patients with PHP for whom no molecular cause has been identified through these diagnostic approaches may benefit from exome and/ or whole-genome sequencing.^{8,56,96}

Genetic Counseling

Because of the variety of genes and molecular mechanisms involved in PHP, genetic counseling should be performed by physicians and/or geneticists trained for these rare disorders. Mutations in *PRKAR1A*, *PTHLH*, *PDE4D*, and *PDE3D* show an autosomal dominant mode of inheritance, that is, an approximately 50% risk of recurrence. In contrast, the phenotype associated with an inactivating defect in *GNAS* depends on the parent-of-origin. Maternally inherited mutations involving *GNAS* exons 1 to 13 lead to PHP1A/1C, whereas these mutations when paternally inherited may lead to PPHP, POH, or osteoma cutis. The transmission of the 3-kb *STX16* deletion through the maternal lineage always leads to PTH resistance and thus the autosomal dominant form of PHP1B, whereas paternal transmission of such a mutation has no pathologic consequences. Patients who are affected with patUPD20q do not transmit their molecular defect, as imprints are erased and reset in the gametes. The mode of inheritance in patients with sporadic PHP1B with broad methylation defects at the *GNAS* locus remains unknown; the risk of recurrence is unknown, but it seems low.

MANAGEMENT

Once diagnosed, PTH resistance should be treated with activated forms of vitamin D, for example, calcitriol or alfacalcidol, to increase the serum calcium levels and to thereby reduce PTH levels. The authors recommend targeting a serum calcium level that is in the low-normal range and against normalizing the serum PTH concentration, to avoid the risk of hypercalcemia and/or hypercalciuria. PTH levels should be maintained at the upper limit or slightly above the reference range (eg, 50–150 pg/mL), as the distal renal nephron remains responsive to PTH and can reabsorb calcium, thereby reducing the risk of hypercalciuria. The vitamin D analogs may be started in infants when PTH rises (eg, 100–150 pg/mL), before hypocalcemia develops. The calcium intake should meet age-appropriate guidelines through regular diet or supplements. Severe hyperphosphatemia can be treated with oral phosphate binders other than CaCO₃, if needed. Because cholecalciferol therapy helps increase calcium absorption in hypocalcemic patients,¹¹³ we suggest maintaining serum levels of 25(OH) vitamin D within the normal range. Adequate management of PTH resistance to reduce the calcium-phosphate product to less than 55 may reduce the development or worsening of calcifications in the lens and brain, but will of course have no effect on heterotopic ossification (see previously). The treatment of PTH resistance and functional hypoparathyroidism requires regular monitoring of serum levels of calcium, phosphorus, PTH, monitoring of renal urinary excretion of calcium (<4 mg/kg per day in children) and renal function. Most patients with PHP1A are not at risk of developing renal calcifications¹¹⁴ unless overtreated, thus increasing the risk of developing hypercalciuria.¹¹⁵

Patients with hypothyroidism due to TSH resistance should receive oral thyroxine and undergo regular assessment of their thyroid function. Patients with PHP and short stature or decreased growth velocity should be evaluated for growth hormone (GH) deficiency. Although we lack long-term data to formally recommend GH therapy in patients with PHP and short stature, short-term results and small series have provided encouraging results for patients.^{68,116} Dietary and lifestyle measures should be implemented at the time of diagnosis, irrespective of the body mass index, to prevent the development of obesity and metabolic complications. Weight control can be very challenging, as obesity is the result in part of decreased resting energy expenditure, and patients may not respond to standard approaches to caloric restriction. At present, there is no specific therapy for heterotopic ossifications. Small ossifications usually do not progress and do not require treatment. Ossifications that cause pain and/or irritations may be surgically removed, unless a large skin surface area is involved.^{6,66} Nonsteroidal anti-inflammatory drugs, thiosulfate, or bisphosphonates have been sporadically reported for the treatment of extensive ossifications.^{66,117} Large studies are, however, necessary to assess the efficacy of these drugs. Regular limb mobilization and physiotherapy are necessary when ossifications surround joints.⁴⁸ Future innovative therapies for patients with PHP may include phosphodiesterase inhibitors (eg, theophylline) aimed at increasing intracellular cAMP levels, and melanocortin receptor agonist (eg, setmelanotide).¹¹⁸

SUMMARY

PHP refers to rare clinical and endocrine manifestations that require additional investigations and molecular genetic testing to identify a defect in the Gs α /cAMP/PKA signaling pathway. Ectopic ossifications, TSH resistance, GH deficiency, and early-onset obesity are the most common associated features. Recognition of the causative genetic or epigenetic defect is of particular importance for predicting the natural history of the disorder as well as disease inheritance, and thus affording appropriate medical and genetic counseling to families. The signs and symptoms evolve throughout life and affect many organs; therefore, coordinated and multidisciplinary management is recommended for adult and pediatric patients.

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KEY POINTS

- Impaired parathyroid hormone (PTH)-dependent signaling at the PTH/PTHrP receptor is the principal feature of pseudohypoparathyroidism.
- Subcutaneous ossifications, brachydactyly, thyroid-stimulating hormone resistance, short stature, and early-onset obesity are common associated features of pseudohypoparathyroidism.
- Molecular genetic and/or epigenetic testing is advised.
- PTH resistance and secondary hyperparathyroidism should be managed to prevent hypocalcemia and increased bone resorption, respectively.
- Care is multidisciplinary for children and adults.

Fig. 1.

Subcutaneous ossifications in patients with PHP1A or POH. All patients presented carry a loss-of-function mutation at the coding sequence of the *GNAS* gene. (A–C) Different features of subcutaneous ossifications in infants; note the red/purple color of the lesions. (D–F) Subcutaneous ossifications in children and adolescents. Small lesions become more pale. (G, H) Organized painful ossification below the heel; surgical excision was performed and the ossification did not recur. (I) Severe extended ossification of the foot and ankle, one part is extruding white material. (J) Painful ossification surrounding the metatarsal joint of the second toe.

Fig. 2.

Growth and weight charts of a boy who was referred at the age of 12 months because of an excessive weight gain. Elevated TSH and PTH at the time of referral led to genetic analyses that identified a *GNAS* mutation on exon 7. (A) growth and weight charts. (B) Body mass index chart.

Fig. 3.

Cranial circumference chart (A) and craniosynostosis (B) of a young girl with a maternally inherited *GNAS* deletion removing *GNAS* exons 1 and 2, and a severe PHP1A phenotype. The computed tomography scan was done at the time of the first surgery. Note the fusion of the coronal and sagittal sutures, and the cupped aspect of the skull.

Table 1

Overview of the current classifications for pseudohypoparathyroidism

A: Classification Based on the cAMP Response to PTH and Gsa Functional Activity

	PHP1A	PHP1C	PPHP	PHP1B	PHP2
Clinical features	AHO	AHO	AHO		AHO
Additional features	Early-onset obesity Asthma Sleep apnea	Early-onset obesity		Early-onset obesity Lack of pubertal growth spurt	
Hormone resistance	Resistance to • PTH • TSH • Gonadotropins • Calcitonin	Resistance to • PTH • TSH		Resistance to • PTH • TSH (mild) • Calcitonin	Resistance to • PTH • TSH
In vitro activity of Gsa	≈ 50% of controls	Similar to controls	≈ 50% of controls	Similar or slightly below controls	Similar to controls
Molecular GNAS alteration	Mutation in the coding sequence of <i>GNAS</i> (maternal allele)	Mutation in the coding sequence of <i>GNAS</i> (maternal allele) (exon 13 preferentially)	Mutation in the coding sequence of <i>GNAS</i> (paternal allele)	Abnormal methylation at the <i>GNAS</i> A/B:TSS-DMR ^a	

B: GNAS Inactivation⁶

	GNAS Maternal Allele					GNAS Paternal Allele		
	PHP1B							
	PHP1A	PHP1C	AD-PHP1B	Spor-PHP1B	patUPD20q	PPHP	POH	<i>Osteoma cutis</i>
Clinical features	AHO	AHO	Macrosonia	Macrosonia	Macrosonia	AHO IUGR Subcutaneous ossifications frequent	IUGR Subcutaneous ossifications	Subcutaneous ossifications
Hormonal features	Resistance to • PTH • TSH • Gonadotropins • Calcitonin	Resistance to • PTH • TSH • Gonadotropins • Calcitonin	Resistance to • PTH • TSH (mild) Gonadotropins Calcitonin	Resistance to • PTH • TSH (mild)	Resistance to • PTH • TSH (mild)	AHO IUGR Subcutaneous ossifications frequent	IUGR Subcutaneous ossifications	Subcutaneous ossifications

Gsa functional activity	≈ 50% of controls	Similar to controls	Similar or slightly below controls	≈ 50% of controls	?
	Mutation in the coding sequence of Abnormal <i>GNAS</i> (maternal allele)	Abnormal methylation at the <i>GNAS A/B</i> :TSS-DMR And 3-kb deletion at the <i>STX16</i> gene	Abnormal methylation at the <i>GNAS A/B</i> :TSS-DMR and at least at another <i>GNAS</i> DMR	Abnormal methylation at all <i>GNAS</i> DMRs Pat disomy of chromosome 20q	Mutation in the coding sequence of <i>GNAS</i> (maternal allele)

C: Inactivating PTH/PTHrP Signaling Disorders⁴⁷

iPPSD	Molecular Cause	Main Features
iPPSD1	Mutation in the coding sequence of <i>PTH1R</i>	PTH resistance and/or brachydactyly
iPPSD2	Mutation in the coding sequence of <i>GNAS</i>	PTH resistance and/or subcutaneous ossifications and/or brachydactyly
iPPSD3	Abnormal methylation at the <i>GNAS A/B</i> :TSS-DMR ^a	PTH resistance
iPPSD4	Mutation in the coding sequence of <i>PRKAR1A</i>	PTH resistance and/or brachydactyly
iPPSD5	Mutation in the coding sequence of <i>PDE4D</i>	Brachydactyly
iPPSD6	Mutation in the coding sequence of <i>PDE3D</i>	Brachydactyly +/- hypertension

Abbreviations: AD-PHP1B, PHP type 1B with autosomal dominant inheritance; AHO, Albright hereditary osteodystrophy; BMI, body mass index; cAMP, cyclic AMP; DMR, differentially methylated region; GH, growth hormone; iPPSD, inactivating PTH/PTHrP signaling disorder; IUGR, intrauterine growth retardation; pat, paternal; patUPD20, paternal disomy of chromosome 20; PHP, pseudohypoparathyroidism; POH, progressive osseous heteroplasia; PPHP, pseudopseudohypoparathyroidism; PTH, parathyroid hormone; PTH1R, PTH receptor type 1; Spor-PHP1B, sporadic PHP type 1B; Mat: maternal; TSH, thyroid-stimulating hormone.

^aPatients with the autosomal dominant form of PHP1B display an abnormal methylation restricted to the *GNAS A/B*:TSS-DMR. In most cases, this loss of methylation is due to a recurrent deletion of about 3-kb in the genomic region of the *STX16* gene, 220-kb upstream of *GNAS*. In sporadic cases, the abnormal methylation at the *GNAS A/B*:TSS-DMR is associated with a loss of methylation involving at least another *GNAS* DMR. In patUPD20q patients, the methylation is abnormal at all *GNAS* DMRs, including the *GNAS A/B*:TSS-DMR.

Table 2

Clinical and biochemical features associated with the diagnosis of pseudohypoparathyroidism apart from PTH resistance, brachydactyly, and subcutaneous ossifications

Specific Features	Description	Mechanism	References
Impaired fetal growth	Mild IUGR in mat <i>GNAS</i> mutations Significant IUGR in pat <i>GNAS</i> mutations Increased birth weight and or length in mat <i>GNAS</i> LOI Significant IUGR in <i>PRKARIA</i> and <i>PDE4D</i> mutations	Gsa and XLas (and downstream signaling) contributes to fetal growth	59,87,119
Short stature	Short stature, z-score ≈ -2.5 in mat and pat <i>GNAS</i> mutations Lack of pubertal growth spurt in mat and pat <i>GNAS</i> mutations, and mat <i>GNAS</i> LOI	Gsa is crucial for the PTHrP signaling in the chondrocytes, especially during puberty	59,78
Obesity	Early-onset obesity in mat <i>GNAS</i> inactivation (mutations and LOI) Adult patients with a BMI >25 kg/m ² $\approx 70\%$ of those with a mat <i>GNAS</i> mutation $\approx 55\%$ of those with a mat <i>GNAS</i> LOI	Gsa is crucial for the melanocortin signaling in the periventricular nucleus of the hypothalamus that regulates satiety. In addition, Gsa deficiency contributes to a low energy expenditure, decreased lipolysis and GHRH resistance	78,59,120,121
Metabolic syndrome	Decreased insulin sensitivity in children and adults with mat <i>GNAS</i> mutations	Gsa deficiency and obesity	122,123
Sleep apnea	Increased frequency in $\approx 45\%$ of those with a mat <i>GNAS</i> mutation Likely increased in patients with <i>PRKARIA</i> and <i>PDE4D</i> mutations as well	Not related to obesity, maybe to the mid-face hypoplasia	72
Cognitive impairment	$\approx 70\%$ of those with a mat <i>GNAS</i> mutation In small series: a subset of patients with <i>PRKARIA</i> mutations and most patients with <i>PDE4D</i> mutations	cAMP is necessary for the neuronal development	43,56,73,74
Asthma	Increased prevalence in Patients with a mat or pat <i>GNAS</i> mutation Patients with a mat <i>GNAS</i> LOI Patients with acrodysostosis		72,120,124
Dental symptoms	All descriptions in patients with mat <i>GNAS</i> mutations: enamel defects, blunted and shortened roots; hypodontia and oligodontia; failure of tooth eruption and tooth ankyloses	The defective signaling downstream of PTH1R in the tooth germ and cells may be involved	125
Cranial, skeletal, and neurologic anomalies	Craniosynostosis and Chiari 1 malformation may exist in patients with mat <i>GNAS</i> mutations and patients with acrodysostosis Carpal tunnel syndrome is as frequent as $\approx 70\%$ of adults with a mat <i>GNAS</i> mutation Spinal stenosis has been described in case reports of patients with mat <i>GNAS</i> mutations and patients with acrodysostosis Sensorineural hearing loss in patients with mat <i>GNAS</i> mutations and patients with acrodysostosis		43,56,76,126
TSH resistance	Is present since infancy in Patients with a mat <i>GNAS</i> mutation (average TSH is $\approx 14 \pm 10$ mUI/L); some patients may have overt hypothyroidism at birth ≈ 30 –100 patients with a mat <i>GNAS</i> LOI (average TSH is ≈ 5 mUI/L) Patients with a mutation in <i>PRKARIA</i>	Excessive TSH response to TRH Partial resistance to TSH in the thyroid gland	48
Calcitonin resistance	Is present in Patients with a mat <i>GNAS</i> mutation Patients with a mat <i>GNAS</i> LOI Patients with a mutation in <i>PRKARIA</i>		48
Gonadotropin resistance	Delayed puberty, oligo- and amenorrhea in girls; cryptorchidism in boys with mat <i>GNAS</i> mutations Variable reports on elevated levels of FSH/ LH. Prolactin deficiency in patients with a mat <i>GNAS</i> mutation		22,79
GHRH resistance	GH deficiency: $\approx 50\%$ – 80% of children with a mat <i>GNAS</i> mutation	Defective Gsa signaling in the pituitary where Gsa is imprinted	69,70,92,127

Abbreviations: BMI, body mass index; cAMP, cyclic AMP; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, GH releasing hormone; IUGR, intrauterine growth retardation; LH, luteinizing hormone; LOI, Loss of imprinting; mat, maternal; pat, paternal; PTH1R, PTH receptor type 1; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.