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## Abstract

This chapter describes the spectrum of problems in children in which there is resistance to parathyroid hormone. This is described by the term pseudohypoparathyroidism. The authors describe the clinical presentation of all of the various parathyroid hormone resistant syndromes and their associated general endocrine abnormalities and skeletal changes. The known genetic abnormalities are highlighted in each of these disorders. The chapter concludes with a detailed presentation of the clinical management of all these problems.

## Keywords

Renal phosphate transporters—NaPi2c, NaPi2a • PTH or parathormone • Hypocalcemia • Hyperphosphatemia • Receptor PTHR1, PTH/PTHrp • G receptor coupled • Chondrocytes • Pseudohypoparathyroidism • Blomstrand chondrodysplasia • Alpha stimulatory subunit of G protein—Gsa • Heterotrimers • Nephrogenic cyclic AMP—cAMP • PHP1a, PHP1b, PHP1c • Parental imprinting • DMR • Bone dysplasia • Brachymetacarpia • Brachymetatarsia • Chondrogenesis • GHRH resistance • IGF1 • Heterotopic ossification • Fuller Albright osteodystrophy • 1 Alpha hydroxylase • Calcitriol • 1,25 Dihydroxyvitamin D • TSH resistance • LH • ACTH • Loss of function mutation • Pseudopseudohypoparathyroidism • Progressive osseous heteroplasia • Phenotypes • GNAS • Alfacalcidol • Hypercalciuria

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## Abbreviations

GNAS	Guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide
NaPi2c	Sodium phosphate cotransporter type 2a
NaPi2a	Sodium phosphate cotransporter type 2c
PTHR1	PTH receptor type 1
PTHrP	Parathyroid hormone-like hormone
NESP	Neurosecretory protein
AS	Antisense
GHRH	Growth hormone releasing hormone
IGF1	Insulin-like growth factor 1
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
ACTH	Adrenocorticotrophic hormone
STX16	Syntaxin 16

## Introduction

Parathormone or PTH is a 84-amino-acid peptide maintaining the blood calcium level between 2.25 and 2.65 mM. Besides its crucial role in calcium homeostasis, PTH controls the urinary excretion of phosphate through the repression of the expression of the renal phosphate transporters (NaPi2c and NaPi2a) at the apical border of the tubular cell. As a consequence, PTH secretion or action deficiency results in hypocalcemia, hyperphosphatemia, and increased tubular reabsorption of phosphates. However, defects of PTH secretion are revealed by low levels of PTH, whereas PTH resistance due to a deficient action of the PTH is associated with high levels of PTH. PTH action on target tissues (bone and kidney) requires the binding to its receptor (PTHrP or PTH/PTHrP receptor), a G-protein-coupled receptor (GPCR). PTHrP- or PTH-related peptide is an alternative ligand for PTHR1 that is necessary for chondrocyte differentiation.

Failure in PTH action through its receptor is termed pseudohypoparathyroidism (PHP) because of the association of hypocalcemia and

hyperphosphatemia reminiscent of hypoparathyroidism, but in this case the PTH levels are elevated.

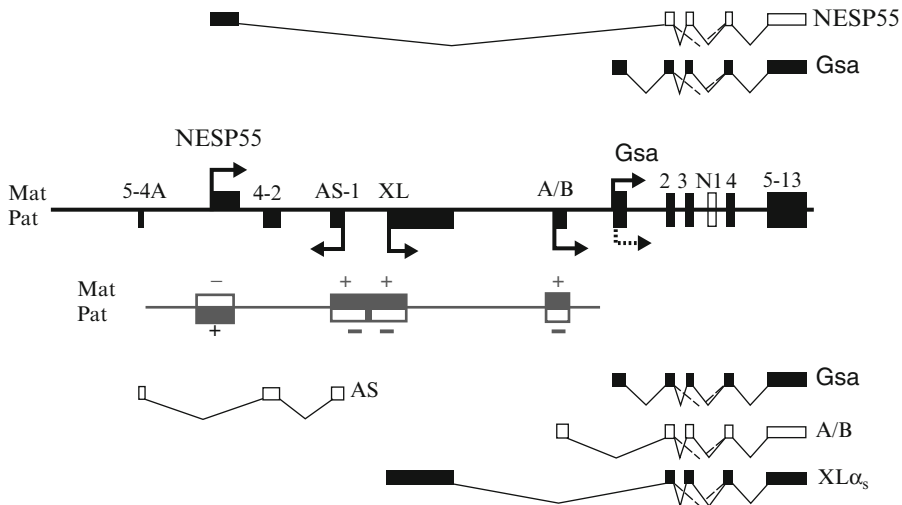
Several causes of PHP have been now identified, all of them being consequences of a deficient signaling of the PTHR1:

- Loss of function of the PTHR1. Blomstrand chondrodysplasia is a recessive autosomal rare disease due to a mutation on both alleles of the PTHR1 [1].
- Deficient expression or function of the alpha stimulatory subunit of the G protein (or Gsa) that is necessary for the signaling of PTHR1. G proteins are heterotrimers (alpha, beta, and gamma), which, after ligand-binding, induce the production of intracellular cAMP through the activation of adenylate cyclase (AC). In vivo, absent or deficient Gsa prevents the response to the injection of exogenous PTH, which, in physiological conditions, increases nephrogenic cAMP and decreases phosphate tubular reabsorption. Such PHP are classified as PHP type I.
- A defect downstream of the cascade PTHR1/Gsa/AC. Those PHP are classified as type II as the injection of exogenous PTH induces an increase in nephrogenic cAMP, although with no phosphaturic response.

This chapter focuses on the description of PHP type I, the most common and recently deciphered form of PHP. Most of them are due to genetic or epigenetic defects at the *GNAS* locus encoding Gsa.

## Parental Imprinting at the *GNAS* Locus

Parental imprinting refers to mechanisms that lead to the repression of gene expression from one parental allele. Genes subjected to parental imprinting are usually clustered in regions rich in CpG dinucleotides and contain imprinting control elements in differentially methylated regions (DMRs). In most loci, the parent-specific expressed transcripts are associated with a pattern of non- or low-methylated DNA, whereas the nonexpressed transcripts are associated with a pattern of methylated DNA [1].



**Fig. 17.1** Schematic drawing of the *GNAS* locus. The *GNAS* locus is not scaled. The four DMRs mentioned in this chapter are represented below the genomic line by gray boxes (+ or methylated) or white boxes (- or unmethylated) on the paternal (Pat) or maternal (Mat) allele.

Exons are indicated as black rectangles and allelic origin of transcription as broken arrows on the paternal (Pat) or maternal (Mat) allele. Transcripts arising from the locus are depicted above (maternal) or below (paternal) the genomic line

*GNAS* is an imprinted locus that produces several transcripts comprising *Gsa*, the alpha stimulatory subunit of the G protein, *XL*, *A/B* (also referred as 1A), *NESP*, and the antisense transcript *AS*. Due to differential methylation of their promoters, most transcripts of this locus originate from one parental allele only. *XL*, *A/B*, and *AS* are transcribed from the paternal allele; *NESP* is transcribed from the maternal allele only [2, 3]. The promoter of *Gsa* is not differentially methylated and therefore, *Gsa* expression arises from both alleles in most tissues (Fig. 17.1). However, due to a yet incompletely understood imprinting mechanism, *Gsa* is expressed from the maternal allele only in several tissues including the renal proximal tubule, the thyroid, the pituitary, and the gonads [4–6]. For a detailed review on genomic imprinting at the *GNAS* locus, see [2].

## PHP Type I

As mentioned above, the biochemical properties of an acute injection of PTH in vivo have delineated the main PHP subtypes (I and II) and pinpointed *Gsa* as the main candidate-gene for

the PHP type I. Based on clinical and in vitro assays (G protein activity measured in red blood cells or in Cyc cells), PHP type I has been subdivided into type Ia (Albright osteodystrophy and diminished G protein activity), type Ib (absence of Albright osteodystrophy and normal G protein activity), and type Ic (Albright osteodystrophy and normal G protein activity) [3–6]. Molecular genetics has shown that those three subtypes overlap and suggested that a new classification based on the molecular mechanism of the disease may be more appropriate (Table 17.1).

## PHP-Ia

PHP type Ia is a rare autosomal dominant disease due to a defect in the expression or function of *Gsa*. The maternal inheritance of the disease is due to the allele-specific expression of *Gsa* in certain tissues. Clinical features depend on the mono- or biallelic transcription of *Gsa* in tissues (maternal-specific expression in renal proximal tubules, thyroid or gonads; biallelic expression in lymphocytes, fibroblasts, adipocytes, and bone).

**Table 17.1** Classifications of pseudohypoparathyroidism type I

Clinical classification		Molecular classification					Syndrome of severe pre- and postnatal growth retardation		
Clinical features	PHP-1a	PHP-1b	PHP-1c	pPHP	PHP-1a	PHP-1b	pPHP	POH	
Albright osteodystrophy	Albright osteodystrophy	Albright osteodystrophy	Albright osteodystrophy	Albright osteodystrophy	Albright osteodystrophy	Some features of the Albright osteodystrophy may be present	Albright osteodystrophy <sup>a</sup>	Albright osteodystrophy <sup>a</sup> and heterotopic ossifications, small for gestational age	Severe intrauterine growth retardation, feeding difficulties, and severe postnatal growth retardation
Hormonal resistances	PTH, TSH, calcitonin, epinephrin, gonadotropins, GHRH resistances	PTH resistance	PTH, TSH, calcitonin, epinephrin, gonadotropins, GHRH resistances	PTH, TSH, calcitonin, epinephrin, gonadotropins, GHRH resistances	PTH, TSH, calcitonin, epinephrin, gonadotropins, GHRH resistances	PTH resistance, mild TSH, and calcitonin resistances <sup>b</sup>	PTH resistance, mild TSH, and calcitonin resistances <sup>b</sup>	PTH resistance, mild TSH, and calcitonin resistances <sup>b</sup>	–
Biological activity of the G protein, in vitro	Low	Normal	Normal	Low	Low or normal	Normal	Low or normal	Low or normal	Normal
Molecular analysis	Heterozygous loss of function maternal mutation in the coding sequence of the GNAS gene (exons 1–13) in about 70–80% of the patients	Loss of methylation at the A/B promoter of GNAS	Heterozygous loss of function maternal mutation in the coding sequence of the GNAS gene (exons 1–13)	Heterozygous loss of function paternal mutation in the coding sequence of the GNAS gene (exons 1–13)	Heterozygous loss of function maternal mutation in the coding sequence of the GNAS gene (exons 1–13)	Loss of methylation at the A/B promoter of GNAS	Heterozygous loss of function paternal mutation in the coding sequence of the GNAS gene (exons 1–13)	Heterozygous loss of function paternal mutation in the coding sequence of the GNAS gene (exons 1–13)	Paternal deletion of the GNAS locus removing the XL exon

<sup>a</sup>Mild features of Albright osteodystrophy, see text

<sup>b</sup>In our experience

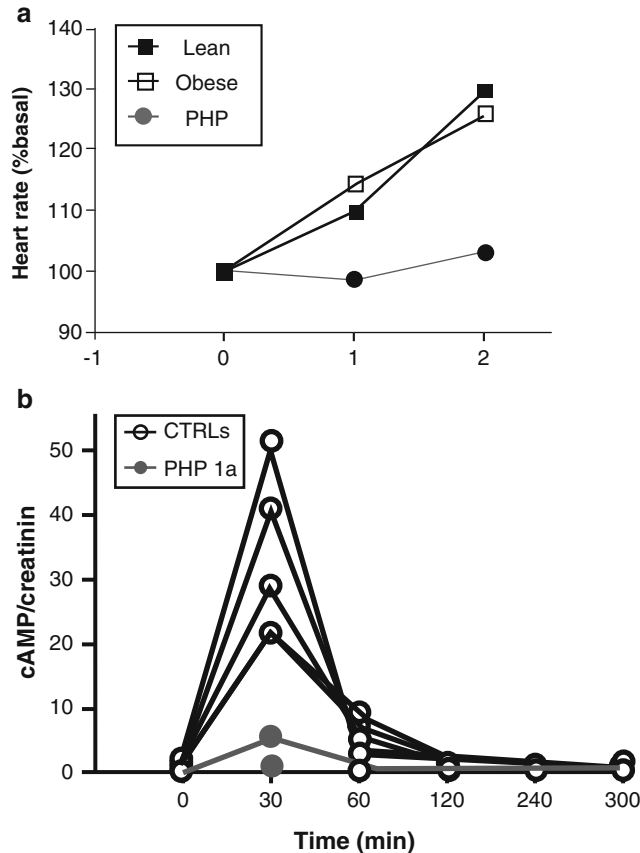


**Fig. 17.2** Progressive development of the brachymetacarpia and brachydactyly in a girl (*upper panels*) and a boy (*lower panels*) affected with PHP-Ia

In addition to the resistance to hormones that signal through GPCRs, patients affected with PHP-Ia present with a collection of features, first described by Fuller Albright in 1942, the Albright hereditary osteodystrophy.

- Bone dysplasia comprises a brachymetacarpia (mainly fourth and fifth metacarpals), brachydactyly (Fig. 17.2) and/or brachymetatarsia (present in all patients albeit at variable degrees), narrowed lumbar shaft, and underdeveloped femoral necks. Absent at birth, the bone dysplasia develops overtime, especially at puberty and likely results from the deficient action of the PTHrP during chondrogenesis. In fact, loss of function mutations of the *PTHLH* (the gene coding PTHrP) are associated with
- Adult patients affected with PHP-Ia have short final heights as shown by height z-score ( $-2.5 \pm 0.3$  and  $-3.0 \pm 0.9$  in Long's and our series of patients, respectively). Most children with PHP-Ia have normal stature until they undergo premature closure of the epiphyses which occurs mainly between 10 and 15 years of age. Short stature results from both the deficient chondrogenesis and the GHRH resistance assessed by the insufficient secretion of growth hormone in response to stimulation

similar bone shape abnormalities. The bone density of the patients is roughly normal, yet they are prone to rheumatologic complications such as femoral slipped epiphysis or osteoarthritis [7, 8].



**Fig. 17.3** (a) The epinephrine resistance is shown by the absence of increase in the heart rate during the IV infusion of epinephrine in six patients affected with PHP-1a compared to lean and obese controls. (b) The resistance

to PTH is shown by the absence of increase in urinary cAMP after IV infusion of recombinant PTH in two patients affected with PHP-1a (gray) compared to controls (CTRLs)

and the low normal IGF1 levels in about 70% of the patients [9]. Finally, the gonadotropin resistance, by limiting the sex steroid production during adolescence, may also participate in the height deficit.

- Obesity is one of the main features of the disease. In our series, 42% of the patients (children and adults) had a body mass index (BMI) over 2 SD compared to the age-reference. The mean z-score BMI of 40 patients reported by Long and colleagues was  $2.3 \pm 0.2$  SD, including two adults with a BMI over 40 kg/m<sup>2</sup> thereby affected by severe obesity [10]. Two contributing factors have been identified as favoring obesity in PHP-1a. One is the resistance to epinephrine, a lipolysis stimulating hormone that acts through GPCRs (Fig. 17.3) [11], and

the second is the potent antiadipogenic effect of Gsa in vitro [12].

- Heterotopic ossifications (*osteoma cutis*) in children, inadequately called heterotopic calcifications, compose a specific feature of Gsa loss of function. They are usually superficial (dermal or subcutaneous fat), made of endochondral bone, and may progress unforeseeably superficially or within deeper tissues [13]. In contrast with progressive osseous heteroplasia (see below), heterotopic ossification in patients affected with PHP-1a may appear after a trauma or at friction zones. Consequences of these ossifications depend on their localization, pain, limited movements [13], etc.
- Developmental delay and cognitive dysfunction have been reported repeatedly in textbooks

since the first description by Fuller Albright in 1942. In 2008, Mouallem and colleagues have shown that approximately 70% of the patients affected with PHP-Ia exhibit a moderate-to-severe cognitive impairment (i.e., that 30% do not have any impairment). Prolonged hypocalcemia or hypothyroidism due to PTH and TSH resistances, respectively, may be partly involved [14].

In our experience, PHP-Ia is diagnosed early (6 years and a half on average) during the investigation of symptomatic hypocalcemia (48%), heterotopic ossifications (9.5%), growth retardation (9.5%), familial screening (14%), hypothyroidism (9.5%), or developmental delay (9.5%).

The resistance to PTH is defined by the association of low calcium level ( $2.05 \pm 0.27$  mM), elevated phosphate level ( $1.93 \pm 0.45$  mM), elevated circulating intact PTH ( $333 \pm 178$  pg/ml), and undetectable urinary calcium excretion. Absent at birth, the PTH resistance gradually develops during the first months or years of life [15, 16]. Phosphate and PTH levels increase first, followed by a decrease in calcemia due to the defect in the PTH-dependant 1 alpha hydroxylation of vitamin D. In the renal proximal tubule, the defect in PTH signaling induces (1) the lack of 1 alpha hydroxylase transcription and 1,25 (OH)<sub>2</sub> vitamin D production, and (2) an increased expression of the phosphate transporters, therefore an increase in tubular phosphate reabsorption. In the distal tubule, the calcium reabsorption depends also on the PTH-driven intracellular cAMP production. However, likely due to the biallelic expression of *Gsa* in the distal tubule, urinary calcium reabsorption seems close to normal in patients with PHP-Ia (personal data) and may be involved in the long-term tolerance of the PTH resistance in patients before they develop hypocalcemia. Events requiring increasing amounts of calcium like vitamin D deficiency or pubertal growth spurt may worsen the hypocalcemia and reveal the disease. In fact, low vitamin D is often present at the time of diagnosis. Hyperphosphatemia, Albright osteodystrophy, and TSH resistance allow the differential diagnosis with secondary hyperparathyroidism due to vitamin D deficiency. In rare cases, the

examination of the renal response to the infusion of PTH (or Ellsworth-Howard test) is required and shows the absence of nephrogenic cAMP production and of increase in phosphaturia (Fig. 17.3).

The resistance to TSH is found in most, if not all, patients affected and is, in our experience, a contributive element for the diagnosis of PHP-Ia [17]. TSH resistance is characterized by elevated TSH (15.1 mUI/L on average in our series, 4.9 mUI/L in Balavoine's), low normal free T4 ( $11.1 \pm 2.5$  pmol/L), and small or normal thyroid volume. Usually present at birth, the TSH resistance is sometimes revealed through the neonatal screening program. Jean-Louis Wemeau's group has shown in 2008 and 2001 that the patients affected with PHP-Ia also display resistances to TRH and calcitonin [18, 19] with no clinical symptoms.

Gonadotropins signal through GPCRs and their actions are likely modified in patients with *Gsa* loss of function. In fact, cryptorchidism, even bilateral, is frequent in boys; menarche may be delayed and elevated FSH levels (150–200% of the upper normal range in our experience), yet normal LH levels, have been measured in affected girls [20, 21].

ACTH resistance has not been found in patients, may be because *Gsa* does not seem to be imprinted in human adrenals [22]. GHRH and catecholamine resistances have previously been mentioned.

The diagnosis of PHP-Ia relies on the identification of a loss of function mutation on the maternal allele of the coding sequence of *GNAS* (exons 1–13). All types of mutations can be found such as deletion, insertion, amino-acid substitution or stop codon; three hot-spots, not exclusive, are located in exons 6, 7, and 13, respectively. Note that the alternatively spliced exon 3 may also be mutated [23]. We will mention here only mutations associated with specific phenotypes:

- The A366S mutation was identified in a patient affected with PHP-Ia and testotoxicosis [24].
- Although mutations in the first exon of *Gsa* do not modify the sequence nor the function of XLAs, the alternative transcript of *Gsa* able to stimulate the cAMP production, the

phenotype of mutated patients do not appear different from those harboring mutations in exons 2–13 [25].

- Mutations located at the 3' end of the exon 13 modify the domain of interaction between Gsa and the GPCRs. However, those mutations do not affect the GTPase activity nor the interaction with the AC, two characteristics assayed when measuring the G protein biological activity in vitro. Therefore, those mutations are characterized by an in vitro biological activity of the G protein close to controls [26, 27].
- A deletion of isoleucine at position 382 of Gsa was found in two brothers exhibiting isolated PTH resistance and improperly diagnosed with PHP-Ib. Later on, the functional characterization of the mutation was performed in vitro and showed the deficient coupling of the mutated Gsa to the PTHR1 [26].
- Finally, large deletions of the *GNAS* locus may be inaccessible to current molecular biology techniques and misinterpreted as methylation changes, i.e., PHP-1b [28].

In our center, the measure of the biological activity of the G protein is not required for the diagnosis of PHP-Ia; however, it may be necessary for a better understanding of the genotype–phenotype relationship. Note that this in vitro assay has to be performed after correction of vitamin D deficiency which artificially decreases the Gsa biological activity.

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### **Pseudopseudohypoparathyroidism or pPHP or Isolated Albright Osteodystrophy**

Patients affected with pPHP have been first identified within relatives of PHP-Ia patients. They present with Albright osteodystrophy and no hormonal resistances, and harbor the exact same loss of function mutation of Gsa than their relatives albeit on the paternal allele. Very few studies have attempted to delineate their phenotypes. However, recent observations have shown that patients affected with pPHP are not obese (average BMI of  $0.1 \pm 0.5$ , significantly inferior to that in PHP-Ia ( $p=0.02$ ) [10]) and do not have

cognitive impairment [14]. Nonetheless, they exhibit short final height and heterotopic ossifications sometimes more severe than their PHP-Ia counterparts [29]. The search for a mutation in the Gsa coding sequence in sporadic patients with short stature, brachydactyly, and obesity has proven to be frequently unsuccessful.

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### **Progressive Osseous Heteroplasia or POH**

POH is a rare disorder of osteogenesis characterized by a single characteristic manifestation (progressive heterotopic ossification) that can vary in its degree of severity. POH appears during infancy with heterotopic bone in the derma and subcutaneous fat. Bone plaques eventually fuse and progress deeper into fascia, skeletal muscle, tendons, and ligaments, leading to ankylosis and preventing the natural limb growth. In some patients, Kaplan and colleagues noted features of Albright osteodystrophy and subsequently identified *GNAS* as the causing-disease gene [29, 30]. Mutations in the coding sequence of Gsa found in patients affected with POH are also found in patients with PHP-Ia or pPHP, although they are exclusively located on the paternal allele and are mostly severely affecting the protein function [31]. We believe that pPHP and POH are both extremes of a common disease.

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### **PHP-Ib**

PHP-Ib is a rare disease due to the defective signaling through Gsa in selected tissues like the renal proximal tubule or the thyroid. Because of an abnormal methylation at the maternal A/B promoter of *GNAS*, the Gsa expression is limited in those tissues resulting in hormonal resistances.

The mean age at diagnosis is about 13 years of age, mostly because of hypocalcemic symptoms. In our experience, patients diagnosed after the age of 20 represent at least 20% of our cohort.

The PTH resistance is the main symptom of the disease (for a long time considered as the single one). This is likely because of the absence



of physical features allowing an earlier diagnosis in PHP-Ia. Patients affected with PHP-Ib usually show a very low calcium level at the time of diagnosis ( $1.6 \pm 0.3$  mM), high phosphate level ( $2.2 \pm 0.2$  mM) due to an increased tubular reabsorption of phosphates, elevated intact PTH levels ( $530 \pm 304$  pg/ml), undetectable urinary calcium excretion, and, in most patients, vitamin D deficiency that triggered the symptoms [4, 32]. Like in PHP-Ia, the PTH resistance develops overtime [16]. In contrast to PHP-Ia, in which haploinsufficiency ensures end-organ resistance in all tissues, patients affected with PHP-Ib maintain a biallelic expression of *Gsa* in most tissues (lymphocytes and bone). Consequently, their bone responds adequately to the elevated PTH levels through an increased bone resorption and demineralization resembling severe primary hyperparathyroidism [33, 34].

It is now widely accepted that PTH resistance is not the sole manifestation of PHP-Ib. In fact, resistances to several hormones signaling through GPCRs have been found in patients affected with PHP-Ib. The TSH resistance is not always present in patients affected with PHP-Ib, and usually mild (in our 35 patients, the mean TSH was  $4.6 \pm 1.0$  mUI/L, minimum 2.5, and maximum 10.0 mUI/L; in Liu's report TSH ranged between 2.4 and 9.5 mUI/L; in Levine's report TSH level was 4.5 mUI/L) [35, 36]. Despite high TSH, we could not detect any symptoms of hypothyroidism and free T4 levels were within the normal range. As in PHP-Ia, we found elevated calcitonin levels in eight out of ten patients investigated. Mantovani et al.'s group failed to identify neither gonadotropin nor GHRH resistance in those patients [37].

It is noteworthy that several features of Albright osteodystrophy might be present, rarely all of them in a single patient. Some patients present with a typical brachymetacarpus [38] or slender heterotopic ossifications [39]. In our series of patients, the BMI, especially in girls, was significantly higher than that of the general population ( $1.0 \pm 0.4$  SD,  $p = 0.019$ ), yet the final height was normal. In fact, Mantovani et al.'s group had shown that patients affected with PHP-Ib are frequent among the samples sent for

PTH resistance and AHO yet having no mutation in the *GNAS* coding sequence [40].

In patients affected with an isolated PTH resistance or with PTH resistance and few associated features (TSH resistance or mild AHO), we would first look for methylation changes at the *GNAS* promoters. Patients affected with PHP-Ib typically show a loss of cytosine methylation of the maternal A/B promoter (often referred in molecular biology articles as the A/B differentially methylated region or DMR) [41]. The A/B DMR is located just upstream of the *Gsa* promoter and first exon and controls the tissue-specific expression of *Gsa*. Consequently, a loss of methylation at A/B leads to a suppression of *Gsa* expression in the renal proximal tubule and the thyroid, hence, PTH and TSH resistance, respectively.

Several subtypes of PHP-Ib have now been recognized:

- The autosomal dominant form of PHP-Ib or AD-PHP-Ib. It represents most of the familial form of PHP-Ib, and about 15% of the patients affected with PHP-Ib. These patients show a loss of methylation restricted to the maternal A/B DMR (the methylation at the rest of the *GNAS* locus is preserved). Most of the patients, except one family worldwide, carry an identical maternal deletion of 3,6-kb at the neighboring *STX16* gene, 220-kb upstream of *GNAS* [16, 42]. This deletion likely removes a genomic element that is necessary for the proper methylation at the A/B DMR of *GNAS*. The phenotype of AD-PHP-Ib is associated with the maternal transmission of the deletion, whereas no phenotype, including no methylation abnormality, is associated with the paternal transmission of the disease (healthy carriers).
- In three families affected with AD-PHP-Ib, Murat Bastepe and HaraldJueppner's group has identified deletions removing the exons 3 and 4 of the antisense transcript of *GNAS*. The patients differed from the most frequent AD-PHP-Ib patients because they harbored methylation changes spanning the entire maternal *GNAS* locus (loss of methylation at A/B, AS, and XL DMRs, gain of methylation at the NESP DMR). As mentioned previously, we

believe that those deletions removed a genomic sequence that is required for the methylation over the whole *GNAS* locus [43, 44].

- The sporadic form of PHP-Ib is the by far the most frequent. The patients do not have any affected siblings. In those patients, the methylation defect is not restricted to A/B (it always includes a loss of methylation at A/B) but spreads to the other DMRs of *GNAS* comprising AS, XL, and NESP. The cause of these methylation changes is still unknown. Researchers failed to identify deletions in *STX16* or in AS in those patients [40, 41, 45].

There is no major difference in the phenotypes of patients affected with the familial or the sporadic form of PHP-Ib [32]. Therefore, the diagnosis of PHP-Ib relies on (1) the identification through molecular biology of the loss of methylation at the A/B DMR of *GNAS* and (2) its characterization through the search for the common deletion at *STX16* and the analysis of the methylation at the entire *GNAS* locus.

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## Treatment

The objectives of the treatment of the PTH resistance could be defined as (1) maintain calcemia within the low normal range (2.0–2.5 mM), (2) prevent hypercalciuria, (3) prevent the bone resorption due to elevated PTH levels (lower PTH below 150 pg/ml). In children, the key treatment is the 1 alpha hydroxylated vitamin D (calcitriol twice a day or alfacalcidol once a day). The dose does not depend on the weight; most patients have 1–2 µg/day of alfacalcidol or 0.5–1 µg of calcitriol. Highest doses may be needed during periods of high growth velocity (infancy and puberty). The treatment with calcitriol or alfacalcidol permits to recover a normal calcium level and lowers the PTH levels to the normal or upper normal range. Usually, phosphate levels remain slightly elevated as they do not depend on 1,25 (OH)<sub>2</sub> vitamin D, but on PTH signaling alone. As mentioned before, the ability of the distal tubule to maintain, at least in part, the urinary calcium reabsorption prevents excessive excretion of calcium in the urine; in contrast to patients affected

with hypoparathyroidism, the treatment with alfacalcidol or calcitriol in patients with PTH resistance rarely leads to hypercalciuria.

Calcium supplements, 500–1,000 mg daily according to age, are recommended during the first year following the diagnosis of PTH resistance.

The TSH resistance is usually treated in patients affected with PHP-Ia by oral thyroxin according to the weight. Except during pregnancy, patients affected with PHP-Ib do not require a treatment for their TSH resistance.

Off-label use of growth hormone has been done in patients affected with PHP-Ia and short stature with variable results. Unfortunately, clinical trials are lacking to prove the efficacy of the drug [46].

The treatment of the heterotopic ossifications is one of the most important challenges of this disease. Small and non-problematic ossifications should remain untouched as they easily recur after surgery. Orthopedic measures or surgery may be necessary to maintain the mobility of the joints. Several treatments like nonsteroidal anti-inflammatory drugs or bisphosphonates have been reported in case reports yet are not considered as fully effective [47].

At birth, the molecular diagnosis for the newborn may be done on cord blood [16]. Because of the absent PTH resistance during the first months of life, affected newborn babies do not risk hypocalcemia. However, TSH resistance may be present at birth, especially in PHP-Ia. Therefore, a blood test is recommended for those babies at day 3 of life, and a treatment with thyroxin should be started in newborns with elevated TSH even before the result of the molecular biology analysis.

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## Conclusion

PHP type I is a rare disease that has been characterized at the clinical, genetic, and epigenetic level in the last 20 years. We propose that the classification of the PHP subtypes should now include the molecular biology analysis as it has been shown that the different phenotypes overlap significantly. The treatment of the hormonal resistance in PHP, whatever the subtype, is fairly easy; we feel,

however, that a specific therapy is needed for at least three specific features of the disease: heterotopic ossifications, obesity, and short stature.

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