Recommendations for diagnosis and treatment of pseudohypoparathyroidism and related disorders: an updated practical tool for physicians and patients

Running title: Updated practical tool: diagnosis and treatment of pseudohypoparathyroidism-related disorders

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Abstract

Patients affected by pseudohypoparathyroidism (PHP) or related disorders are characterized by physical findings that may include brachydactyly, short stature, a stocky build, early-onset obesity, ectopic ossifications, neurodevelopmental deficits, as well as hormonal resistance most prominently to parathyroid hormone (PTH). In addition to these alterations, patients may develop other hormonal resistances, leading to overt or subclinical hypothyroidism, hypogonadism and growth hormone (GH) deficiency, impaired growth without measurable evidence for hormonal abnormalities, type 2 diabetes and skeletal issues with potentially severe limitation of mobility.

PHP and related disorders are primarily clinical diagnoses. Given the variability of the clinical, radiological and biochemical presentation, establishment of the molecular diagnosis is of critical importance for patients. It facilitates management, including prevention of complications, screening and treatment of endocrine deficits, supportive measures, and appropriate genetic counselling.

Based on the first international consensus statement for these disorders, this article provides an updated and ready-to-use tool to help physicians and patients outlining relevant interventions and their timing.

A life-long coordinated and multidisciplinary approach is recommended, starting as far as possible in early infancy, and continuing throughout adulthood with an appropriate and timely transition from paediatric to adult care.

Keywords: Acrodysostosis, Bone disorders, Brachydactyly, Calcium and Phosphate metabolism, Consensus, Diagnosis, Management, Ossification, Parathyroid hormone, Pseudohypoparathyroidism, Treatment

Introduction

Much progress has been made since 1942 when Albright and colleagues described pseudohypoparathyroidism (PHP) as a novel disorder of hormone resistance, in which hypocalcaemia and hyperphosphataemia were due to decreased responsiveness to parathyroid hormone (PTH). Patients also manifested an unusual appearance characterized by short stature, brachydactyly, obesity with a round face, and heterotopic ossifications. This was known as Albright hereditary osteodystrophy (AHO)[1]. Initially, reports focused on clinical aspects, leading to the identification of a constellation of disorders associated with a similar spectrum of physical characteristics, neurocognitive and endocrine abnormalities, which included the different subtypes of PHP (i.e., PHP1A, PHP1B, PPHP, POH).

Today the term pseudohypoparathyroidism (OMIM #103580 for PHP type 1A (PHP1A), #603233 for PHP type 1B (PHP1B) and #612462 for PHP type 1C (PHP1C)) describes disorders that share biochemical characteristics of hypoparathyroidism, i.e. hypocalcaemia and hyperphosphataemia, as a result of proximal tubular resistance to PTH. Some patients present with resistance to other hormones (such as thyroid-stimulating hormone (TSH), and/or gonadotropins, growth-hormone-releasing hormone and calcitonin).

Patients with PHP1A, and rare PHP1B cases, manifest physical features of AHO due to defects in chondrocyte and osteoblast differentiation, early closure of growth plates, brachydactyly, short stature and development of ectopic ossifications. AHO typically develops during late childhood. Years after the description of PHP, Albright and coworkers described patients with some physical features of AHO despite appropriate PTH responsiveness. Albright originally termed this condition pseudopseudohypoparathyroidism (PPHP; OMIM #612463). We know today that progressive osseous heteroplasia (POH; OMIM #166350) or *osteoma cutis* belong to the same disease entity, with variable extent of the heterotopic ossifications and brachydactyly. On the other side, PTH resistance in absence of AHO phenotype is the main characteristic of most PHP1B patients[2]. Recent studies have further defined the phenotype of these related disorders including other associated features such as impaired intrauterine growth in PPHP[3], and early-onset obesity[4], frequent respiratory and ENT complications [5], delayed verbal[6] and non-verbal[7] milestones and cognitive impairment[7], mainly in PHP1A.

Since the 1990s, PHP1A and PPHP are known to be caused by heterozygous Gsα inactivating pathogenic variants[8,9]. It was subsequently shown that the disease phenotype associated to the variant depends on the alterations' maternal (PHP1A) or paternal (PPHP)[10] / POH[11] inheritance. The molecular mechanism leading to PHP1B was discovered in 2003. Patients affected with PHP1B present with methylation defects at the *GNAS* locus[12] (see "Molecular

diagnosis" section below). The term of PHP type 1C was initially used for patients displaying a PHP1A phenotype yet a biochemical normal Gsα activity; as for now, the denomination should now be abandoned and patients referred to as PHP1A, as they carry maternally inherited inactivating pathogenic Gsα variants.

New biochemical and molecular techniques have uncovered that disorders similar to PHP, such as acrodysostosis (OMIM #101800)[13,14], are due to different defects within various genes involved in the stimulatory G-protein-coupled receptor signaling pathway[15] (e.g. *GNAS*[2,16,17], *PRKAR1A*[14], *PDE4D*[13,18] or *PDE3A*[19]). Today, molecular analyses can identify *de novo* or inherited genetic or epigenetic alterations in around 80-90% of patients with PHP or related disorders[20,21] (Figure 1).

Since publication of the original Consensus Statement for PHP and related disorders[22], new relevant findings have been published. Therefore, with the aim of disseminating and updating the international consensus statement, the three main investigators (AL, GM and GPdN) together with 34 of the 37 experts collaborated on this shortened and updated paper.

Literature search was updated from December 18th, 2016 to 31st December, 2019 using the same key terms as in the previous version, leading to a total of over 1000 articles.

The addition of the recently published evidence did not modify the content of the previously published recommendations but further strengthened the underlying background and experts' opinions and prompted us to develop a more concise and practical tool designed to help health care professionals involved in the management of patients with PHP and patients and their families.

Clinical diagnosis and management

PHP and the afore-mentioned disorders share a common defect in the cAMP signaling pathway downstream of the PTH/PTHrP receptor. Despite this unifying molecular umbrella, presentation and disease severity can vary considerably between affected individuals, even amongst patients carrying the same genetic alteration, highlighting the important clinical and molecular overlap of these diseases. Newborns and young infants usually present with unspecific features such as being born small for gestational age (SGA)[23], early onset obesity[3] or transient hypothyroidism. In the absence of familial history or typical symptoms such as ectopic ossifications, diagnosis may be delayed for years due to lack of recognition of the syndrome and associated features. Later in life, growth failure, brachydactyly, obesity, and/or hypocalcaemia leading to neuromuscular symptoms or even seizures often lead to investigations and identification of the underlying cause.

Therefore, diagnosis of PHP and related disorders should be based on clinical and biochemical characteristics, and, in some cases, family history.

The following major features should be present in order to diagnose a patient with PHP or related disorder: PTH resistance and/or ectopic ossifications, and/or early-onset (before 2 years of age) obesity associated with TSH resistance, and/or AHO. In addition, other features can be considered as supporting the diagnosis of PHP and related disorders: unexplained primary hypothyroidism, hypercalcitoninaemia, hypogonadism, growth hormone deficiency, cognitive impairment, hearing impairment, craniosynostosis and neurosurgical features, tooth ankylosis, oligodontia, cataract and/or CNS calcifications, sleep apnoea, ear infections, asthma, and restricted fetal growth (Figure 2).

Once a clinical suspicion exists, molecular analyses are critically important for genetic counselling and in some cases for diagnosis, particularly when there is significant overlap in clinical features (e.g. PHP1A versus acrodysostosis). Nowadays, the genetic or epigenetic diagnosis relies on the most likely identified causes of the disease at the time of analysis according to the algorithm (Figure 3). The use of genetic and epigenetic analyses to diagnose patients with PHP and related disorders has reduced the need for administration of exogenous PTH or assessment of Gsα bioactivity.

Altogether, a correct diagnosis will guide appropriate management including prevention of complications, lifestyle adjustments, screening and treatment of endocrine deficits and appropriate genetic counselling.

Sufficient prospective clinical trials and outcomes data in PHP and related disorders is lacking. Thus, management guidelines are mainly based on experts' consensus. We have summarized in this document (see below) and in table 1, the principal multi-disciplinary interventions that should take place during the follow-up of these patients.

Resistance to PTH

PTH resistance is the hallmark of PHP, found in 45-80%[24] of the patients, particularly in those with PHP1A and 1B. It is defined ~~as~~ by the association of hypocalcaemia, hyperphosphataemia and elevated serum levels of PTH in the absence of vitamin D deficiency, abnormal magnesium levels and/or renal insufficiency[22]. PTH resistance is usually absent at birth and develops over time[25]; in addition, the diagnosis maybe difficult in the absence of one or several biochemical features, e.g. hypocalcaemia; or hyperphosphataemia[13,18,22,26–28]. Typically, in children, symptoms appear during periods of rapid growth, most likely because of increased calcium and

vitamin D requirements[29]. The screening and follow-up of PTH resistance should include measurement of PTH, 25-OH-vitamin D, calcium and phosphate every 3 to 6 months in children and at least yearly in adults. Monitoring should be more frequent in symptomatic individuals and during acute phases of growth, intercurrent illness, pregnancy and breastfeeding, when dosage requirements for active vitamin D metabolites or analogues might change. Patients and/or their family should be taught to recognize clinical signs of hypocalcaemia and hypercalcaemia[22].

Management of severe symptomatic hypocalcaemia does not differ from that of hypoparathyroidism[30]. However, treatment using activated forms of vitamin D combined with (in most cases) oral calcium supplementation should target levels of calcium and phosphorus within the normal range, whilst avoiding hypercalciuria; PTH levels should be within mid-normal to up to two-times the upper limit of normal as higher levels of PTH might have adverse effects on skeletal mineralization or on the growth plate and evolve towards tertiary hyperparathyroidism[31–34]. Whatever the level of serum calcium, treatment with active vitamin D analogues should be considered when PTH levels reach more than twice the upper level of normal. Calcium supplements should also be considered, depending on the calcium dietary intake. Normal levels of 25-OH-vitamin D should be maintained for all patients with appropriate supplementation[22].

Patients with PHP and related disorders rarely develop hypercalciuria and/or nephrocalcinosis because of the preserved PTH sensitivity of the distal renal convoluted tubules[29,35,36]. However, episodes of nephrolithiasis have been seldomly observed (unpublished observations) in patients with PHP1A and PHP1B, particularly after completion of pubertal growth. Monitoring of urine calcium levels is recommended at regular intervals during treatment, as well as appropriate renal imaging in patients with persistent hypercalciuria on repeated measurements[22,30].

Chronic hypocalcaemia with hyperphosphataemia can result in an elevated calcium x phosphate product, which can lead to ectopic calcification (not to be confused with the ectopic *ossification* of AHO that occurs independently of serum levels of calcium and phosphate). Intracranial calcifications of the basal ganglia resemble those occurring in Fahr syndrome due to pathogenic variants in the *SLC20A2* gene; note that patients with PHP may often have additional calcification of the cerebral white matter[37]. So far, brain calcifications have not been described in patients with PPHP, POH or those with an alteration in the *PRKAR1A* or *PDE4D* genes[13,14,38–41]. Ectopic depositions of calcium and phosphorus may occur in the eyes, leading to posterior subcapsular cataract or corneal opacities[41–45]. Brain CT scan is indicated only in the case of

neurological manifestations, whilst systematic and regular ophthalmologic examination is recommended to diagnose or manage cataracts.

Finally, pseudohypoparathyroidism is often associated with dental and oral features such as failure of tooth eruption, impaction of primary molars, hypodontia, enamel hypoplasia, malocclusion, gingival hyperplasia, gingivitis with spontaneous bleeding and pain[46–49]. Regular 6-12 monthly dental reviews are recommended, at least during childhood[22,50].

Ectopic ossification

Ectopic ossifications are found in 100% and 80–100% of patients with POH and PPHP/AHO respectively, in 30–70% of PHP1A patients, and very sporadically in those with PHP1B, while they have never been reported in patients with acrodysostosis[27,51]. Ectopic ossifications should be therefore considered as a specific consequence of *GNAS* molecular alterations, especially when located on the paternal allele[52]; Gsα deficiency in mesenchymal stem cells favors *de novo* formation of extra-skeletal islands of ectopic bone in dermis and subcutaneous fat[53,54].

In contrast to what has been described in *Gnas* knockout mouse models of AHO[55], and unlike *fibrodysplasia ossificans progressiva* (FOP), there is no scientific evidence that inflammation or traumatic events contribute to ectopic bone formation in *GNAS*-related conditions[56,57]. Notwithstanding, ectopic bone formation often develops, in *GNAS* related disorders, in locations subjected to high pressure loads, such as the heel[58].

POH is defined by ossifications located in and extending towards connective tissues, muscles, tendons and ligaments[11,52,57]. In contrast, ectopic bone formation remains superficial in *osteoma cutis*, PHP1A, PPHP or AHO.

Ectopic ossifications are uncommon in the general population, and the presence of these lesions should trigger a clinical and biochemical work up to search for signs of AHO, PTH and TSH resistance, or FOP. Skin biopsy is not necessary in obvious cases and contraindicated in case of suspicion of FOP.

Due to the rarity of these conditions, limited information is available about prognosis, and so far no effective treatments exist for the management or prevention of ectopic ossifications.

Cutaneous bony plaques should be investigated by careful clinical examination at each visit, especially in patients with pathogenic or probably pathogenic variants on the *GNAS* paternal allele (POH and PPHP). Patients and families should be instructed about self-examination. Location and size of the ossifications, involvement of joints and impairment of movement and bone growth, and evolution during puberty or rapid growth should be documented at each visit.

Imaging of ossifications should be performed using CT or MRI only in the case of painful or symptomatic lesions, if joint or organ function is being jeopardized, or when considering surgical excision.

Physical therapy and meticulous skin care are critical for the prevention of complications due to ectopic ossifications. Due to a high risk of recurrence, surgical excision should be limited to well-delimitated, superficial lesions causing pain and/or movement impairment [11,22,57]. In ossifications involving joints, immobilization, e.g. through casts, should be avoided to prevent ankyloses. No evidence supports the use of non-steroidal anti-inflammatory drugs, bisphosphonates or steroids in primary or peri-surgical treatment of asymptomatic ectopic ossifications[22].

Brachydactyly

Brachydactyly is not specific to PHP and related disorders. Affected patients display brachydactyly type E[59], with a high degree of variability in frequency and severity. Brachydactyly is found in the majority of patients with PHP1A and PPHP (70-80%), in few with PHP1B (15-33%), and in all patients with acrodysostosis[22] (Figure 2).

Brachydactyly develops over time and might not be present or visible in early life, except in patients with acrodysostosis[14,60]. The clinical and radiological examination of the hands and feet is important from early childhood onwards to establish the diagnosis. It may impair fine motor skills, such as handwriting[61]. In some patients occupational therapy and/or appropriate orthopedic devices may be indicated, e.g. special shoes and orthopedic insoles[22].

Additional bone features have been described such as carpal tunnel syndrome[61], Madelung deformity[62], spinal stenosis[63], acro-osteolysis, phalangeal cone-shaped epiphyses, and craniosynostosis[64]. Depending on the functional consequences, these skeletal manifestations may require a specific multidisciplinary evaluation and orthopedic corrective surgery[22].

Management of growth and GH deficiency

The majority of PHP1A and PPHP patients display adult short stature, 2.5 SD below mean in average, despite having normal length/height during childhood[3]. Short stature is even more pronounced in acrodysostosis, with final height being on average -3.5 SD (-8.8 to -0.5 SD)[22]. Noticeably, most patients with a paternal *GNAS* pathogenic variant ~~mutation~~ (that is, patients with PPHP or POH) and patients with acrodysostosis show a restricted foetal growth and are thus born small for gestational age (SGA)[22]. Intrauterine growth restriction, advanced bone maturation, impaired pubertal growth spurt, and, in PHP1A, growth hormone-releasing

hormone (GHRH) resistance and consequently GH deficiency, can contribute to the premature cessation of growth and short stature in adulthood[3,22]. Careful and regular monitoring of growth, skeletal maturation and GH secretion is therefore advised in all affected children, starting around the age of 3-6 years. Patients born SGA who do not demonstrate appropriate catch-up growth or patients showing GH deficiency should be rapidly considered for treatment with rhGH[22]. As of today, there is insufficient evidence to establish efficacy and safety of pubertal blockers to increase final height in these patients[65]. In contrast to PHP1A and PPHP patients, and despite an enhanced growth velocity during infancy, PHP1B patients display adult heights similar to that of the general population[3,66].

Obesity

Patients with PHP1A or PHP1B develop early-onset obesity, usually within the first 2 years of life; this may be the first and only symptom in many patients until diagnosis is established during adolescence or adulthood[3,4,67,68]. Several mechanisms may contribute to excessive acquisition and maintenance of fat mass, including a defect in the Gsα-dependent melanocortin signaling pathway (possibly responsible for the patients' hyperphagic trait[68,69]), decreased resting energy expenditure compared with obese controls[70,68,71], low sympathetic nervous system activity, decreased lipolysis[72], and growth hormone-releasing hormone resistance in the pituitary[73,74]. Overall, we now know that obesity or overweight are associated with all types of PHP and related disorders[22] with the exception of POH, PPHP and *osteoma cutis*[3,52,57,75,76]. Once diagnosis is made, BMI and eating behavior should be regularly monitored. Patients, parents and families should be provided with psychological support and educational programs, as early as possible, even in the presence of a normal BMI as a preventive strategy, also taking into account the low resting energy expenditure of these patients[3].

Sleep apnea, well-known complication of obesity, is reported to be more frequent in patients affected with PHP1A[77,78], and may also be present in acrodysostosis[40]. Phenotypically, these patients present with round faces, a flattened nasal bridge and/or maxillary hypoplasia[26,50] which combined with obesity mechanically contributes to the development of sleep and respiratory disturbances[70,77]. All patients with PHP and related disorders should therefore be screened for restless sleep, snoring, inattentiveness and daytime somnolence and, if present, polysomnography is recommended.

Metabolic syndrome

Decreased insulin sensitivity and type 2 diabetes are present in a large proportion of adult PHP1A patients and may not be solely related to obesity[79]. Post-prandial hyperglycemia is common in children with PHP1A and PHP1B [71]. Lipid profile is not profoundly affected in PHP1A patients[69,80]. Hypertension was reported in one study of PHP[81] yet the incidence of cardiovascular diseases is not increased in cohort studies conducted in Denmark[41,80]. Other studies have failed to find an increased risk of hypertension compared to matched controls [69,71,79]. Overall, we propose to include regular monitoring of blood pressure, lipid profile and glucose metabolism parameters within the regular multidisciplinary follow-up of patients affected with PHP and related disorders.

Cognitive features

Cognitive impairment has been reported in 40-70% of patients with PHP1A, in 0-10% of patients with PPHP or POH, is rarely observed in patients with PHP1B and has a variable prevalence in patients with acrodysostosis[22]. Cognitive performance studies have been undertaken only in PHP1A and showed reduced scores in comparison to peers[6,37,82,83], with an average IQ of 85.9 and a reduction of 21.5 IQ points below an unaffected sibling[7]. Patients with PHP1A were found to have impaired executive function, delayed adaptive behavior skills and increased rates of attention deficit hyperactivity disorder (ADHD)[7]. One retrospective review of developmental milestones showed a greater delay in language compared with gross motor skills, with ~~and~~ a tendency to improve during late childhood[6]. Neurological and neuropsychiatric manifestations can be linked to the function ~~In addition to the role~~ of Gsα in brain development[84], and other organic CNS alterations, including Chiari 1 malformation[85–87] or prolonged periods of hypocalcaemia[83,87] found in some patients. Patients with PHP and related disorders should be referred to a neuropsychologist for neurocognitive and/or behavioral assessment at diagnosis or at pre-school age, especially in patients with PHP1A and acrodysostosis due to *PDE4D* pathogenic variants ~~mutations~~. Most patients will require specialized educational assistance[7].

TSH resistance

TSH resistance is not as severe as PTH resistance due to partial Gsα imprinting in the thyroid tissue[88–90]. Most patients with PHP1A[51,74] present elevated serum levels of TSH, a small thyroid gland and normal or only mildly depressed serum levels of thyroid hormone. Elevated levels of TSH due to TSH resistance are often present at birth; some patients may be diagnosed through the neonatal screening[22]. In contrast, PHP1B patients display TSH levels at the upper end of normal or mildly elevated[22]. TSH resistance is present in patients with acrodysostosis

due to pathogenic variants at *PRKAR1A* but not in those at *PDE4D*[26,27]. Despite a prompt diagnosis of hypothyroidism after birth and initiation of treatment, this does not seem to prevent motor or cognitive delay[82].

In children and adults, investigation, monitoring and treatment objectives do not differ from other aetiologies of hypothyroidism/subclinical hypothyroidism, including hypothyroidism related to TSH resistance[22,91].

Alterations in gonadal function

Gonadal function and puberty

Resistance to gonadotrophins is more subtle than resistance to other hormones such as PTH and TSH. This suggests that PHP1A patients display only partial resistance to gonadotropins[22,92]. Clinically, patients may present with menstrual irregularities in girls[92], cryptorchidism in boys ([93] and experts' experience), and blunted or absent pubertal growth spurt in adolescents[3] with PHP1A. PHP1B and PPHP patients seem to have normal gonadal function[94], while variable resistance to gonadotropins has been described in patients with acrodysostosis and pathogenic variants in the *PRKAR1A* gene[26].

In children with PHP or related disorders, Tanner staging of sexual maturation and testicular descent and location should be regularly assessed. As skeletal maturation is typically advanced in these children, bone age should be radiographically determined. Conversely, biochemical assessment of gonadal status is not recommended unless clinically indicated. Cryptorchidism and/or hypogonadism, when present, should be corrected and managed according to standard recommendations[22].

Fertility and pregnancy

Assisted and spontaneous pregnancies have been reported in women with PHP and related disorders[22,92,95]. Men with PHP1A have also fathered children. For disease transmission risks, see "Molecular diagnosis" section.

In case of hypocalcaemia and/or hypothyroidism, pregnant women with PHP and related disorders should be monitored following the international guidelines for any pregnancy associated with these disturbances. Vaginal delivery may be contra-indicated due to reduced pelvic size and decreased range of motion of the hips due to local ossifications[22]. The newborn should be evaluated for the presence of skin ossifications, levels of TSH, calcium and phosphorus. Breastfeeding is not contraindicated, but close follow-up and clinical monitoring of the baby is advised[22].

Menopause and osteoporosis

Although patients with PHP do have several potential risk factors for bone fragility, they do not generally demonstrate evidence for decreased bone density and/or increased fracture risk[41,96,97]; in this context, routine DXA measurements is not indicated[22]. On the other hand, further investigation is required should a diagnosis of osteoporosis be suspected, for instance after sustaining a low trauma fracture, or in the case of skeleton unloading (e.g. joint ankyloses secondary to aberrant ossification). Patients should then be screened for potential secondary causes of bone loss such as vitamin D deficiency, hypogonadism or growth hormone deficiency, and all efforts should be made to correct these before treating the osteoporosis if still required according to national and international standard recommendations.

Other hormone resistances

Elevated calcitonin levels, most likely due to calcitonin resistance, have been reported in PHP1A[98,99], PHP1B and acrodysostosis patients with PRKAR1A pathogenic variants[14]. They may be used to support the diagnosis of PHP and related disorders. Additional resistance to hormones that mediate their actions through Gsα-coupled receptors have also been previously reported, although, the clinical relevance of these abnormalities remains to be established[100]. Screening of additional hormone resistances, and calcitonin measurement, is not recommended in patients with PHP and related disorders, except for diagnostic purposes[22].

Molecular diagnosis

The main subtypes of PHP and related disorders are caused by *de novo* or autosomal dominant inherited inactivating genetic pathogenic variants within the genes of the PTH/PTHrP signalling pathway[15] or by epigenetic alterations at *GNAS* locus. *GNAS* locus presents four distinct differentially methylated regions (DMRs) (see supplementary figure 1): the paternally methylated *GNAS-NESP*:TSS-DMR and three maternally methylated *GNAS-AS1:*TSS-DMR, *GNAS-XL:*Ex1-DMR and *GNAS A/B:*TSS-DMR.

PHP1A is caused by inactivating pathogenic variants on the maternal allele of the *GNAS* gene, including both single nucleotide and copy number variants [8,9,22]. When the pathogenic variants are on the paternal allele, the outcome is mainly PPHP, but can also include *osteoma cutis* or POH[11,22]. Single nucleotide variants can be easily detected by sequence analysis whereas genomic rearrangements can be detected by quantitative methods[101]. Determination of the affected allele in *de novo* cases is becoming relevant, as a few PPHP patients may also develop hormone resistance[102]. Genetic counselling is critical for PHP and

related disorders; patients with *GNAS* genetic variants have a 50% chance of transmitting the molecular defect. Depending on parental sex, their offspring will develop PPHP, *osteoma cutis*, or POH (when the transmitting patient is male) or PHP1A (when the transmitting patient is female).

Loss of methylation at *GNAS A/B*:TSS-DMR is detected in all patients with PHP1B[22,103]. When it is the only affected DMR (15–20% of PHP1B cases)[21], it is most often the consequence of an alteration in the maternal allele of *cis*-acting control elements within *STX16*[12]. Other maternally inherited deletions and duplications have also been identified in some rare familial cases, affecting either an isolated *GNAS A/B:*TSS-DMR or all four DMRs[22]. This clinical form is classified as AD-PHP1B, due to its autosomal dominant mode of inheritance when maternally inherited (i.e., paternally inherited deletions are not associated with methylation defects)[12].

On the other hand, sporadic PHP1B is often associated with methylation defects at two or more DMRs, in addition to *GNAS A/B*:TSS-DMR, with no identified underlying genetic mechanism[104]. In around 8-10%[21,105] of these sporadic cases, the methylation anomalies are caused by paternal uniparental disomy of the chromosomal region comprising *GNAS* (UPD(20q)pat)[22,106]. In these patients, recurrence and transmission risks are expected to be similar to that of the general population.

Although *GNAS* methylation defects can be detected through the use of several methods, a methylation sensitive-MLPA (MS-MLPA) kit from MRC-Holland (MS-MLPA ME031 GNAS) enables the detection simultaneously of methylation defects at the different GNAS-DMRs as well as *STX16* and *NESP/AS* deletions and deletions encompassing *GNAS*[107].
Paternal uniparental isodisomy can be analyzed either by microsatellite (STR) typing or SNP array.

In brief, in individuals with a suspected diagnosis of PHP, molecular diagnosis must include DNA sequence, methylation and CNVs analyses at the *GNAS* locus following the proposed algorithm described in Figure 3.

Acrodysostosis can be caused by heterozygous point pathogenic variants in *PRKAR1A* or *PDE4D*[13,14,18], so they can be easily detected by sequencing. They mostly occur *de novo*[22], so the recurrence risk is similar to that of the general population. As it presents an autosomal

dominant way of inheritance, patients have a 50% of chance of passing on the molecular defect and the disease to their children.

Conclusions

Patients with PHP and related disorders may display a highly heterogeneous and progressive clinical picture over their life span from infancy to adulthood, which renders a life-long multidisciplinary approach mandatory. Each of the many clinical aspects and potential complications of the disease should be managed by health care professionals with expertise in these disorders, preferably when possible at referral centers. In addition, the different and complex genetic and epigenetic defects underlying these disorders also require a specialized approach in order to establish a correct molecular diagnosis, which is often difficult and time-consuming for both patients and their families, but that might in turn help clinicians to look for specific clinical manifestations with consequent appropriate management.

Following up on the recent publication of the first international consensus statement on these disorders, this article provides an updated concise and ready-to-use tool for physicians and patients with Table 1 summarizing the main interventions as well as their timing.

Given the lack of strong evidence-based data, particularly for the management of these patients, there is an urgent need to implement registries with large cohorts of patients, to better understand the natural history of PHP and related disorders, to identify the intersections as well as the specificities of these clinically heterogeneous but closely related diseases and, last but not least, to enable the development of novel disease-specific therapies.

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Author contributions

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REFERENCES

1 Albright F, Burnett CH, Smith PH, Parson W. Pseudohypoparathyroidism - an example of "Seabright-Bantam syndrome." Endocrinology. 1942;30:922–32.

2 Mantovani G, Spada A, Elli FM. Pseudohypoparathyroidism and Gsα-cAMP-linked disorders: current view and open issues. Nat Rev Endocrinol. 2016 Jun;12(6):347–56.

3 Hanna P, Grybek V, Perez de Nanclares G, Tran LC, de Sanctis L, Elli F, et al. Genetic and Epigenetic Defects at the GNAS Locus Lead to Distinct Patterns of Skeletal Growth but Similar Early-Onset Obesity. J Bone Miner Res Off J Am Soc Bone Miner Res. 2018 Aug;33(8):1480–8.

4 Grüters-Kieslich A, Reyes M, Sharma A, Demirci C, DeClue TJ, Lankes E, et al. Early-Onset Obesity: Unrecognized First Evidence for GNAS Mutations and Methylation Changes. J Clin Endocrinol Metab. 2017 01;102(8):2670–7.

5 Shoemaker AH, Jüppner H. Nonclassic features of pseudohypoparathyroidism type 1A. Curr Opin Endocrinol Diabetes Obes. 2017 Feb;24(1):33–8.

6 Miyakawa Y, Takasawa K, Matsubara Y, Ihara K, Ohtsu Y, Kamasaki H, et al. Language delay and developmental catch-up would be a clinical feature of pseudohypoparathyroidism type 1A during childhood. Endocr J. 2019 Mar;66(3):215–21.

7 Perez KM, Lee EB, Kahanda S, Duis J, Reyes M, Jüppner H, et al. Cognitive and behavioral phenotype of children with pseudohypoparathyroidism type 1A. Am J Med Genet A. 2018;176(2):283–9.

8 Weinstein LS, Gejman PV, Friedman E, Kadowaki T, Collins RM, Gershon ES, et al. Mutations of the Gs alpha-subunit gene in Albright hereditary osteodystrophy detected by denaturing gradient gel electrophoresis. Proc Natl Acad Sci U S A. 1990 Nov;87(21):8287–90.

9 Patten JL, Johns DR, Valle D, Eil C, Gruppuso PA, Steele G, et al. Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy. N Engl J Med. 1990 May;322(20):1412–9.

10 Davies SJ, Hughes HE. Imprinting in Albright's hereditary osteodystrophy. J Med Genet. 1993 Feb;30(2):101–3.

11 Shore EM, Ahn J, Jan de Beur S, Li M, Xu M, Gardner RJM, et al. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. N Engl J Med. 2002 Jan;346(2):99–106.

12 Bastepe M, Fröhlich LF, Hendy GN, Indridason OS, Josse RG, Koshiyama H, et al. Autosomal dominant pseudohypoparathyroidism type Ib is associated with a heterozygous microdeletion that likely disrupts a putative imprinting control element of GNAS. J Clin Invest. 2003 Oct;112(8):1255–63.

13 Michot C, Le Goff C, Goldenberg A, Abhyankar A, Klein C, Kinning E, et al. Exome sequencing identifies PDE4D mutations as another cause of acrodysostosis. Am J Hum Genet. 2012 Apr;90(4):740–5.

14 Linglart A, Menguy C, Couvineau A, Auzan C, Gunes Y, Cancel M, et al. Recurrent PRKAR1A mutation in acrodysostosis with hormone resistance. N Engl J Med. 2011 Jun;364(23):2218–26.

15 Thiele S, Mantovani G, Barlier A, Boldrin V, Bordogna P, De Sanctis L, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network. Eur J Endocrinol. 2016 Dec;175(6):P1–17.

16 Mantovani G. Clinical review: Pseudohypoparathyroidism: diagnosis and treatment. J Clin Endocrinol Metab. 2011 Oct;96(10):3020–30.

17 Turan S, Bastepe M. GNAS Spectrum of Disorders. Curr Osteoporos Rep. 2015 Jun;13(3):146–58.

18 Lee H, Graham Jr. JM, Rimoin DL, Lachman RS, Krejci P, Tompson SW, et al. Exome Sequencing Identifies PDE4D Mutations in Acrodysostosis. Am J Hum Genet. 2012 Apr;90(4):746–51.

19 Boda H, Uchida H, Takaiso N, Ouchi Y, Fujita N, Kuno A, et al. A PDE3A mutation in familial hypertension and brachydactyly syndrome. J Hum Genet. 2016 Apr;61(8):701–3.

20 Elli FM, deSanctis L, Ceoloni B, Barbieri AM, Bordogna P, Beck-Peccoz P, et al. Pseudohypoparathyroidism type Ia and pseudo-pseudohypoparathyroidism: the growing spectrum of GNAS inactivating mutations. Hum Mutat. 2013 Mar;34(3):411–6.

21 Elli FM, Linglart A, Garin I, de Sanctis L, Bordogna P, Grybek V, et al. The Prevalence of GNAS Deficiency-Related Diseases in a Large Cohort of Patients Characterized by the EuroPHP Network. J Clin Endocrinol Metab. 2016 Oct;101(10):3657–68.

22 Mantovani G, Bastepe M, Monk D, de Sanctis L, Thiele S, Usardi A, et al. Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement. Nat Rev Endocrinol. 2018 Aug;14(8):476–500.

23 Thiele S, Werner R, Grötzinger J, Brix B, Staedt P, Struve D, et al. A positive genotype-phenotype correlation in a large cohort of patients with Pseudohypoparathyroidism Type Ia and Pseudo-pseudohypoparathyroidism and 33 newly identified mutations in the GNAS gene. Mol Genet Genomic Med. 2015 Mar;3(2):111–20.

24 Shoback DM, Bilezikian JP, Costa AG, Dempster D, Dralle H, Khan AA, et al. Presentation of Hypoparathyroidism: Etiologies and Clinical Features. J Clin Endocrinol Metab. 2016 Jun;101(6):2300–12.

25 Gelfand IM, Eugster EA, DiMeglio LA. Presentation and clinical progression of pseudohypoparathyroidism with multi-hormone resistance and Albright hereditary osteodystrophy: a case series. J Pediatr. 2006 Dec;149(6):877–80.

26 Linglart A, Fryssira H, Hiort O, Holterhus P-M, Perez de Nanclares G, Argente J, et al. PRKAR1A and PDE4D Mutations Cause Acrodysostosis but Two Distinct Syndromes with or without GPCR-Signaling Hormone Resistance. J Clin Endocrinol Metab. 2012 Ottobre;97(12):E2328–38.

27 Elli FM, Bordogna P, de Sanctis L, Giachero F, Verrua E, Segni M, et al. Screening of PRKAR1A and PDE4D in a Large Italian Series of Patients Clinically Diagnosed with Albright

Hereditary Osteodystrophy and/or Pseudohypoparathyroidism. J Bone Miner Res. 2016 Jan;31:1215–24.

28 Lindstrand A, Grigelioniene G, Nilsson D, Pettersson M, Hofmeister W, Anderlid B-M, et al. Different mutations in PDE4D associated with developmental disorders with mirror phenotypes. J Med Genet. 2014 Jan;51(1):45–54.

29 Linglart A, Maupetit-Méhouas S, Silve C. GNAS -Related Loss-of-Function Disorders and the Role of Imprinting. Horm Res Pædiatrics. 2013;79(3):119–29.

30 Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, et al. European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015 Aug;173(2):G1-20.

31 Murray TM, Rao LG, Wong MM, Waddell JP, McBroom R, Tam CS, et al. Pseudohypoparathyroidism with osteitis fibrosa cystica: direct demonstration of skeletal responsiveness to parathyroid hormone in cells cultured from bone. J Bone Miner Res. 1993 Jan;8(1):83–91.

32 Kidd GS, Schaaf M, Adler RA, Lassman MN, Wray HL. Skeletal responsiveness in pseudohypoparathyroidism. A spectrum of clinical disease. Am J Med. 1980 May;68(5):772–81.

33 Sbrocchi AM, Rauch F, Lawson ML, Hadjiyannakis S, Lawrence S, Bastepe M, et al. Osteosclerosis in two brothers with autosomal dominant pseudohypoparathyroidism type 1b: bone histomorphometric analysis. Eur J Endocrinol. 2011 Feb;164(2):295–301.

34 Neary NM, El-Maouche D, Hopkins R, Libutti SK, Moses AM, Weinstein LS. Development and Treatment of Tertiary Hyperparathyroidism in Patients with Pseudohypoparathyroidism Type 1B. J Clin Endocrinol Metab. 2012 Sep;97(9):3025–30.

35 Hansen DW, Nebesio TD, DiMeglio LA, Eugster EA, Imel EA. Prevalence of Nephrocalcinosis in Pseudohypoparathyroidism: Is Screening Necessary? J Pediatr. 2018;199:263–6.

36 Chen Y-J, Shu S-G, Chi C-S. Pseudohypoparathyroidism: report of seven cases. Acta Paediatr Taiwanica Taiwan Er Ke Yi Xue Hui Za Zhi. 2005 Dec;46(6):374–80.

37 Bhadada SK, Bhansali A, Upreti V, Subbiah S, Khandelwal N. Spectrum of neurological manifestations of idiopathic hypoparathyroidism and pseudohypoparathyroidism. Neurol India. 2011 Aug;59(4):586–9.

38 Kadilli I, Colicchio S, Guglielmo R, Vollono C, Della Marca G, Janiri L. Clinical insights by the presence of bipolar disorder in pseudohypoparathyroidism type 1A. Gen Hosp Psychiatry. 2015 Oct;37(5):497.e3-5.

39 Lemos MC, Thakker RV. GNAS mutations in Pseudohypoparathyroidism type 1a and related disorders. Hum Mutat. 2015 Jan;36(1):11–9.

40 Lynch DC, Dyment DA, Huang L, Nikkel SM, Lacombe D, Campeau PM, et al. Identification of Novel Mutations Confirms PDE4D as a Major Gene Causing Acrodysostosis. Hum Mutat. 2013 Gennaio;34(1):97–102.

41 Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Pseudohypoparathyroidism - epidemiology, mortality and risk of complications. Clin Endocrinol (Oxf). 2016 Jun;84(6):904–11.

42 Grajewski RS, Koch KR, Koch H-R, Ciotu IM, Cursiefen C, Heindl LM. Cataract in pseudohypoparathyroidism. J Cataract Refract Surg. 2016 Jul;42(7):1094–6.

43 Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, et al. Epidemiology and Diagnosis of Hypoparathyroidism. J Clin Endocrinol Metab. 2016 Jun;101(6):2284–99.

44 Sunder RA, Singh M. Pseudohypoparathyroidism: a series of three cases and an unusual presentation of ocular tetany. Anaesthesia. 2006 Apr;61(4):394–8.

45 Maheshwari R, Rani RP, Prasad RN, Reddy KTS, Reddy AP. Visual disturbances as a presenting feature of pseudohypoparathyroidism. Indian J Endocrinol Metab. 2013 Oct;17(Suppl 1):S219-220.

46 Reis MTA, Matias DT, Faria MEJ de, Martin RM. Failure of tooth eruption and brachydactyly in pseudohypoparathyroidism are not related to plasma parathyroid hormone-related protein levels. Bone. 2016 Apr;85:138–41.

47 Ritchie GM. Dental manifestations of pseudohypoparathyroidism. Arch Dis Child. 1965 Oct;40(213):565–72.

48 Hejlesen J, Underbjerg L, Gjørup H, Bloch-Zupan A, Sikjaer T, Rejnmark L, et al. Dental Findings in Patients With Non-surgical Hypoparathyroidism and Pseudohypoparathyroidism: A Systematic Review. Front Physiol. 2018;9:701.

49 Le Norcy E, Reggio-Paquet C, de Kerdanet M, Mignot B, Rothenbuhler A, Chaussain C, et al. Dental and craniofacial features associated with GNAS loss of function mutations. Eur J Orthod. 2019 Nov;cjz084.

50 Schlund M, Depeyre A, Kohler F, Nicot R, Ferri J. Cranio-Maxillofacial and Dental Findings in Albright's Hereditary Osteodystrophy and Pseudohypoparathyroidism. Cleft Palate-Craniofacial J Off Publ Am Cleft Palate-Craniofacial Assoc. 2019 Jul;56(6):831–6.

51 Salemi P, Skalamera Olson JM, Dickson LE, Germain-Lee EL. Ossifications in Albright Hereditary Osteodystrophy: Role of Genotype, Inheritance, Sex, Age, Hormonal Status, and BMI. J Clin Endocrinol Metab. 2018 01;103(1):158–68.

52 Adegbite NS, Xu M, Kaplan FS, Shore EM, Pignolo RJ. Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification. Am J Med Genet A. 2008 Jul;146A(14):1788–96.

53 Pignolo RJ, Xu M, Russell E, Richardson A, Kaplan J, Billings PC, et al. Heterozygous inactivation of Gnas in adipose-derived mesenchymal progenitor cells enhances osteoblast differentiation and promotes heterotopic ossification. J Bone Miner Res. 2011 Nov;26(11):2647–55.

54 Regard JB, Malhotra D, Gvozdenovic-Jeremic J, Josey M, Chen M, Weinstein LS, et al. Activation of Hedgehog signaling by loss of GNAS causes heterotopic ossification. Nat Med. 2013 Nov;19(11):1505–12.

55 Huso DL, Edie S, Levine MA, Schwindinger W, Wang Y, Jüppner H, et al. Heterotopic ossifications in a mouse model of albright hereditary osteodystrophy. PloS One. 2011;6(6):e21755.

56 Convente MR, Wang H, Pignolo RJ, Kaplan FS, Shore EM. The immunological contribution to heterotopic ossification disorders. Curr Osteoporos Rep. 2015 Apr;13(2):116–24.

57 Pignolo RJ, Ramaswamy G, Fong JT, Shore EM, Kaplan FS. Progressive osseous heteroplasia: diagnosis, treatment, and prognosis. Appl Clin Genet. 2015;8:37–48.

58 Schrander DE, Welting TJ, Caron MMJ, Schrander JJP, van Rhijn LW, Körver-Keularts I, et al. Endochondral ossification in a case of progressive osseous heteroplasia in a young female child. J Pediatr Orthop Part B. 2014 Sep;23(5):477–84.

59 de Sanctis L, Vai S, Andreo MR, Romagnolo D, Silvestro L, de Sanctis C. Brachydactyly in 14 genetically characterized pseudohypoparathyroidism type Ia patients. J Clin Endocrinol Metab. 2004 Apr;89(4):1650–5.

60 Virágh K, Tőke J, Sallai A, Jakab Z, Rácz K, Tóth M. Gradual development of brachydactyly in pseudohypoparathyroidism. J Clin Endocrinol Metab. 2014 Jun;99(6):1945–6.

61 Joseph AW, Shoemaker AH, Germain-Lee EL. Increased prevalence of carpal tunnel syndrome in albright hereditary osteodystrophy. J Clin Endocrinol Metab. 2011 Jul;96(7):2065–73.

62 Sanchez J, Perera E, Jan de Beur S, Ding C, Dang A, Berkovitz GD, et al. Madelung-like deformity in pseudohypoparathyroidism type 1b. J Clin Endocrinol Metab. 2011 Sep;96(9):E1507-1511.

63 Okada K, Iida K, Sakusabe N, Saitoh H, Abe E, Sato K. Pseudohypoparathyroidism-associated spinal stenosis. Spine. 1994 May;19(10):1186–9.

64 García García E, Rivero Garvía M, Alonso Luengo O. Craniosynostosis as the first manifestation of an Albright's osteodystrophy associated with pseudohypoparathyroidism type 1A. Med Clin (Barc). 2017 22;149(4):184–5.

65 Mantovani G, Ferrante E, Giavoli C, Linglart A, Cappa M, Cisternino M, et al. Recombinant human GH replacement therapy in children with pseudohypoparathyroidism type Ia: first study on the effect on growth. J Clin Endocrinol Metab. 2010 Nov;95(11):5011–7.

66 Kinoshita K, Minagawa M, Anzai M, Sato Y, Kazukawa I, Shimohashi K, et al. Characteristic Height Growth Pattern in Patients with Pseudohypoparathyroidism: Comparison between Type 1a and Type 1b. Clin Pediatr Endocrinol. 2007;16(1):31–6.

67 Long DN, McGuire S, Levine MA, Weinstein LS, Germain-Lee EL. Body mass index differences in pseudohypoparathyroidism type 1a versus pseudopseudohypoparathyroidism may implicate paternal imprinting of Galpha(s) in the development of human obesity. J Clin Endocrinol Metab. 2007 Mar;92(3):1073–9.

68 Wang L, Shoemaker AH. Eating behaviors in obese children with pseudohypoparathyroidism type 1a: a cross-sectional study. Int J Pediatr Endocrinol. 2014;2014(1):21.

69 Perez KM, Curley KL, Slaughter JC, Shoemaker AH. Glucose homeostasis and energy balance in children with pseudohypoparathyroidism. J Clin Endocrinol Metab. 2018 Aug;103(11):4265–74.

70 Roizen JD, Danzig J, Groleau V, McCormack S, Casella A, Harrington J, et al. Resting Energy Expenditure Is Decreased in Pseudohypoparathyroidism Type 1A. J Clin Endocrinol Metab. 2016 Mar;101(3):880–8.

71 Shoemaker AH, Lomenick JP, Saville BR, Wang W, Buchowski MS, Cone RD. Energy expenditure in obese children with pseudohypoparathyroidism type 1a. Int J Obes 2005. 2013 Aug;37(8):1147–53.

72 Carel JC, Le Stunff C, Condamine L, Mallet E, Chaussain JL, Adnot P, et al. Resistance to the lipolytic action of epinephrine: a new feature of protein Gs deficiency. J Clin Endocrinol Metab. 1999 Nov;84(11):4127–31.

73 Mantovani G, Maghnie M, Weber G, De Menis E, Brunelli V, Cappa M, et al. Growth hormone-releasing hormone resistance in pseudohypoparathyroidism type ia: new evidence for imprinting of the Gs alpha gene. J Clin Endocrinol Metab. 2003 Sep;88(9):4070–4.

74 Germain-Lee EL, Groman J, Crane JL, Jan de Beur SM, Levine MA. Growth hormone deficiency in pseudohypoparathyroidism type 1a: another manifestation of multihormone resistance. J Clin Endocrinol Metab. 2003 Sep;88(9):4059–69.

75 Liu J, Russell E, Zhang D, Kaplan FS, Pignolo RJ, Shore EM. Paternally inherited gsα mutation impairs adipogenesis and potentiates a lean phenotype in vivo. Stem Cells Dayt Ohio. 2012 Jul;30(7):1477–85.

76 Germain-Lee EL. Management of pseudohypoparathyroidism. Curr Opin Pediatr. 2019 Aug;31(4):537–49.

77 Landreth H, Malow BA, Shoemaker AH. Increased Prevalence of Sleep Apnea in Children with Pseudohypoparathyroidism Type 1a. Horm Res Pædiatrics. 2015;84(1):1–5.

78 Curley KL, Kahanda S, Perez KM, Malow BA, Shoemaker AH. Obstructive Sleep Apnea and Otolaryngologic Manifestations in Children with Pseudohypoparathyroidism. Horm Res Paediatr. 2018;89(3):178–83.

79 Muniyappa R, Warren MA, Zhao X, Aney SC, Courville AB, Chen KY, et al. Reduced insulin sensitivity in adults with pseudohypoparathyroidism type 1a. J Clin Endocrinol Metab. 2013 Nov;98(11):E1796-1801.

80 Underbjerg L, Sikjaer T, Rejnmark L. Cardiovascular findings in patients with nonsurgical hypoparathyroidism and pseudohypoparathyroidism: A cohort study. Clin Endocrinol (Oxf). 2019 Apr;90(4):592–600.

81 Brickman AS, Stern N, Sowers JR. Hypertension in pseudohypoparathyroidism type I. Am J Med. 1988 Dec;85(6):785–92.

82 Mouallem M, Shaharabany M, Weintrob N, Shalitin S, Nagelberg N, Shapira H, et al. Cognitive impairment is prevalent in pseudohypoparathyroidism type Ia, but not in

pseudopseudohypoparathyroidism: possible cerebral imprinting of Gsalpha. Clin Endocrinol (Oxf). 2008 Feb;68(2):233–9.

83 Farfel Z, Friedman E. Mental deficiency in pseudohypoparathyroidism type I is associated with Ns-protein deficiency. Ann Intern Med. 1986 Aug;105(2):197–9.

84 Chen M, Wang J, Dickerson KE, Kelleher J, Xie T, Gupta D, et al. Central nervous system imprinting of the G protein G(s)alpha and its role in metabolic regulation. Cell Metab. 2009 Jun;9(6):548–55.

85 Martínez-Lage JF, Guillén-Navarro E, López-Guerrero AL, Almagro MJ, Cuartero-Pérez B, de la Rosa P. Chiari type 1 anomaly in pseudohypoparathyroidism type Ia: pathogenetic hypothesis. Childs Nerv Syst. 2011 Dec;27(12):2035–9.

86 Kashani P, Roy M, Gillis L, Ajani O, Samaan MC. The Association of Pseudohypoparathyroidism Type Ia with Chiari Malformation Type I: A Coincidence or a Common Link? Case Rep Med. 2016;2016:7645938.

87 Visconti P, Posar A, Scaduto MC, Russo A, Tamburrino F, Mazzanti L. Neuropsychiatric phenotype in a child with pseudohypoparathyroidism. J Pediatr Neurosci. 2016 Sep;11(3):267–70.

88 Germain-Lee EL, Ding CL, Deng Z, Crane JL, Saji M, Ringel MD, et al. Paternal imprinting of Galpha(s) in the human thyroid as the basis of TSH resistance in pseudohypoparathyroidism type 1a. Biochem Biophys Res Commun. 2002 Aug;296(1):67–72.

89 Mantovani G, Ballare E, Giammona E, Beck-Peccoz P, Spada A. The gsalpha gene: predominant maternal origin of transcription in human thyroid gland and gonads. J Clin Endocrinol Metab. 2002 Oct;87(10):4736–40.

90 Liu J, Erlichman B, Weinstein LS. The stimulatory G protein alpha-subunit Gs alpha is imprinted in human thyroid glands: implications for thyroid function in pseudohypoparathyroidism types 1A and 1B. J Clin Endocrinol Metab. 2003 Sep;88(9):4336–41.

91 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J. 2014 Jun;3(2):76–94.

92 Namnoum AB, Merriam GR, Moses AM, Levine MA. Reproductive dysfunction in women with Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 1998 Mar;83(3):824–9.

93 Linglart A, Carel JC, Garabédian M, Lé T, Mallet E, Kottler ML. GNAS1 lesions in pseudohypoparathyroidism Ia and Ic: genotype phenotype relationship and evidence of the maternal transmission of the hormonal resistance. J Clin Endocrinol Metab. 2002 Jan;87(1):189–97.

94 Mantovani G, Bondioni S, Linglart A, Maghnie M, Cisternino M, Corbetta S, et al. Genetic analysis and evaluation of resistance to thyrotropin and growth hormone-releasing hormone in pseudohypoparathyroidism type Ib. J Clin Endocrinol Metab. 2007 Sep;92(9):3738–42.

95 Takatani R, Molinaro A, Grigelioniene G, Tafaj O, Watanabe T, Reyes M, et al. Analysis of Multiple Families with Single Individuals Affected by Pseudohypoparathyroidism Type Ib (PHP1B) Reveals Only One Novel Maternally Inherited GNAS Deletion. J Bone Miner Res. 2015 Oct;31:796–805.

96 Long DN, Levine MA, Germain-Lee EL. Bone mineral density in pseudohypoparathyroidism type 1a. J Clin Endocrinol Metab. 2010 Sep;95(9):4465–75.

97 Underbjerg L, Malmstroem S, Sikjaer T, Rejnmark L. Bone Status Among Patients With Nonsurgical Hypoparathyroidism, Autosomal Dominant Hypocalcaemia, and Pseudohypoparathyroidism: A Cohort Study. J Bone Miner Res Off J Am Soc Bone Miner Res. 2018 Mar;33(3):467–77.

98 Wägar G, Lehtivuori J, Salvén I, Backman R, Sivula A. Pseudohypoparathyroidism associated with hypercalcitoninaemia. Acta Endocrinol (Copenh). 1980 Jan;93(1):43–8.

99 Vlaeminck-Guillem V, D'herbomez M, Pigny P, Fayard A, Bauters C, Decoulx M, et al. Pseudohypoparathyroidism Ia and hypercalcitoninemia. J Clin Endocrinol Metab. 2001 Jul;86(7):3091–6.

100 Levine MA, Downs RW, Moses AM, Breslau NA, Marx SJ, Lasker RD, et al. Resistance to multiple hormones in patients with pseudohypoparathyroidism. Association with deficient activity of guanine nucleotide regulatory protein. Am J Med. 1983 Apr;74(4):545–56.

101 Garin I, Elli FM, Linglart A, Silve C, de Sanctis L, Bordogna P, et al. Novel microdeletions affecting the GNAS locus in pseudohypoparathyroidism: characterization of the underlying mechanisms. J Clin Endocrinol Metab. 2015 Apr;100(4):E681-687.

102 Turan S, Thiele S, Tafaj O, Brix B, Atay Z, Abali S, et al. Evidence of hormone resistance in a pseudo-pseudohypoparathyroidism patient with a novel paternal mutation in GNAS. Bone. 2015 Feb;71:53–7.

103 Liu J, Litman D, Rosenberg MJ, Yu S, Biesecker LG, Weinstein LS. A GNAS1 imprinting defect in pseudohypoparathyroidism type IB. J Clin Invest. 2000 Nov;106(9):1167–74.

104 Liu J, Nealon JG, Weinstein LS. Distinct patterns of abnormal GNAS imprinting in familial and sporadic pseudohypoparathyroidism type IB. Hum Mol Genet. 2005 Jan;14(1):95–102.

105 Takatani R, Minagawa M, Molinaro A, Reyes M, Kinoshita K, Takatani T, et al. Similar frequency of paternal uniparental disomy involving chromosome 20q (patUPD20q) in Japanese and Caucasian patients affected by sporadic pseudohypoparathyroidism type Ib (sporPHP1B). Bone. 2015 Oct;79:15–20.

106 Bastepe M, Lane AH, Jüppner H. Paternal uniparental isodisomy of chromosome 20q--and the resulting changes in GNAS1 methylation--as a plausible cause of pseudohypoparathyroidism. Am J Hum Genet. 2001 May;68(5):1283–9.

107 Alsum Z, Abu Safieh L, Nygren AOH, Al-Hamed MA, Alkuraya FS. Methylation-specific multiplex-ligation-dependent probe amplification as a rapid molecular diagnostic tool for pseudohypoparathyroidism type 1b. Genet Test Mol Biomark. 2010 Feb;14(1):135–9.

Figure 1

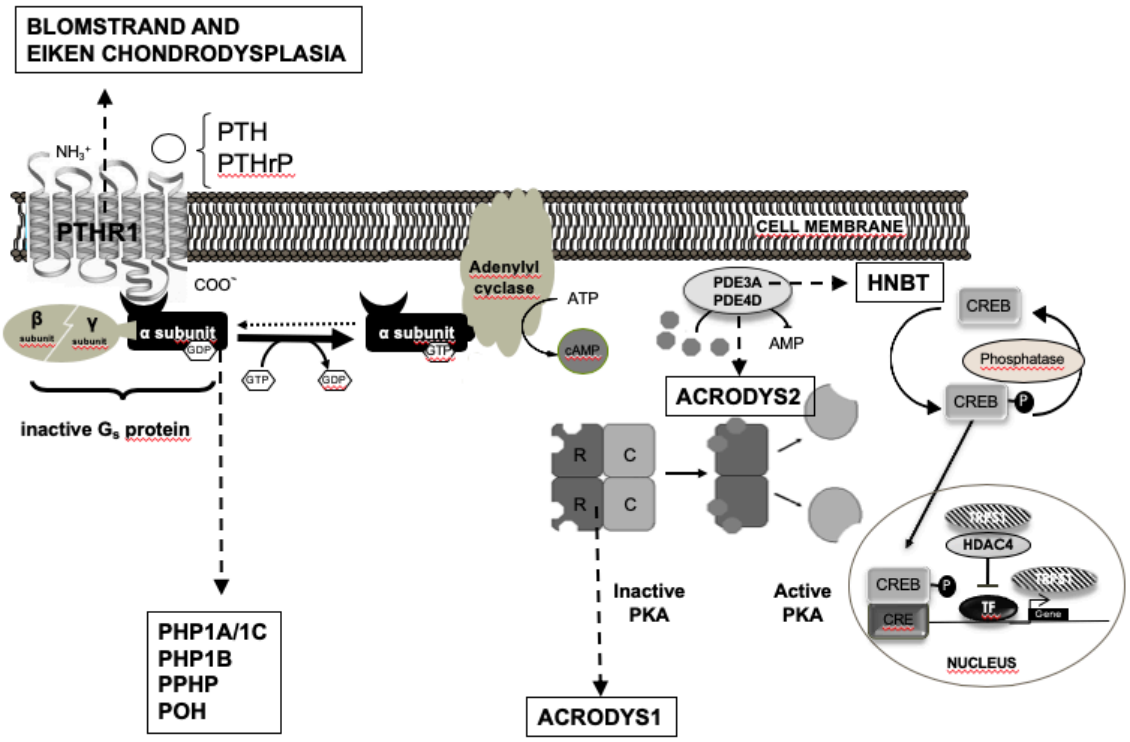


Figure 1: Molecular defects in the PTH–PTHrP signalling pathway in PHP and related disorders. The main clinical features of PHP and related disorders are due to molecular defects within the PTH–PTHrP signalling pathway, with the exception, perhaps, of ectopic ossification. Some of the clinical features result from the impaired signaling of other GPCRs such as TSHR. The diseases caused by alterations at the genes codifying the indicated proteins are shown in bold. Differential diagnoses are indicated in grey. PTHR1: PTH/PTHrP receptor type 1; G protein: trimer α, β, γ; cAMP: grey diamond; PKA: tetramer R (regulatory subunit 1A; dense grey) and C (catalytic subunit; light grey); phosphodiesterases: ovals PDE4D and PDE3A; PHP: pseudohypoparathyroidism; HTNB: autosomal dominant hypertension and brachydactyly type E syndrome; TF: transcription factor.

Figure 2

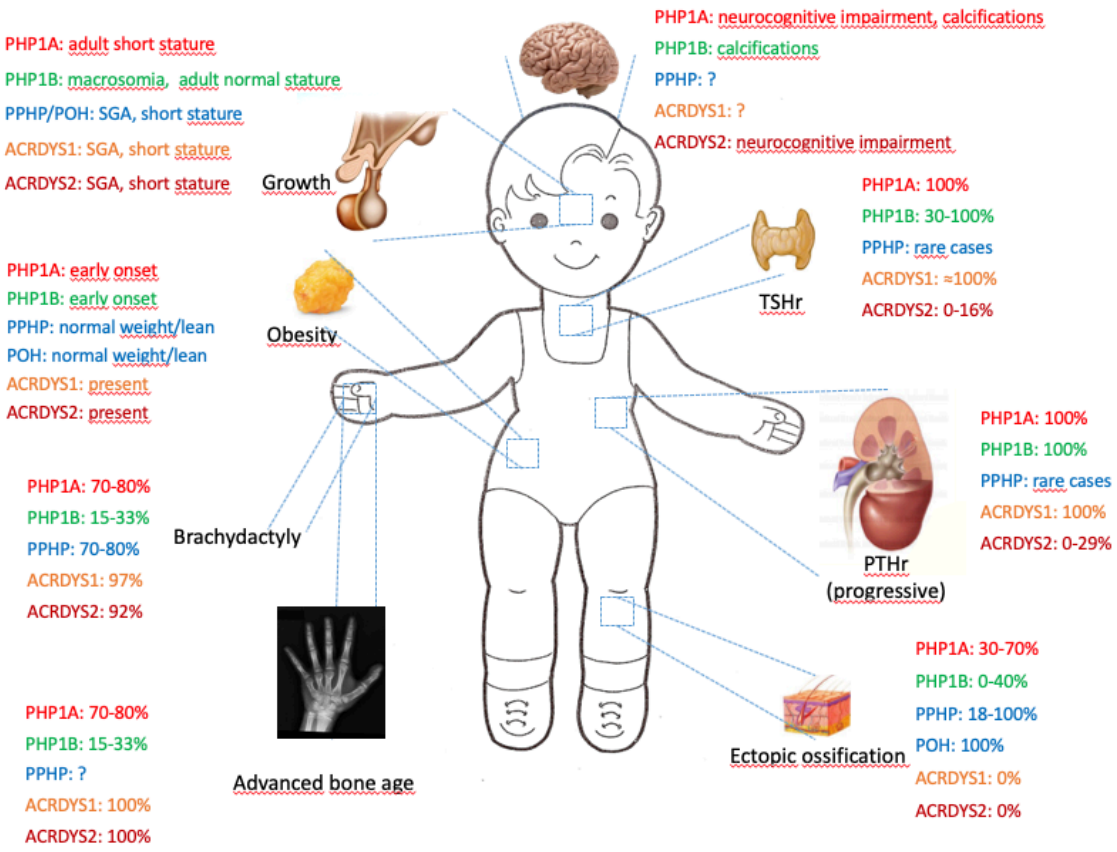


Figure 2: Main clinical features of PHP and related disorders. PHP and related disorders affect many organs unequally. The clinical and biochemical features of the main diseases have been represented with their frequency when known. PHP1A: pseudohypoparathyroidism type 1A due to maternal loss of function variants at the *GNAS* coding sequence, PHP1B: pseudohypoparathyroidism type 1B due to methylation defect at *GNAS* locus; PPHP: pseudopseudohypoparathyroidism due to paternal loss of function genetic variant at the *GNAS* coding sequence; POH: progressive osseous heteroplasia due to paternal loss of function variant at the *GNAS* coding sequence; ACRDYS1: acrodysostosis due to pathogenic variant in *PRKAR1A*; ACRDYS2: acrodysostosis due to alterations in *PDE4D*; SGA: small for gestational age.

Figure 3

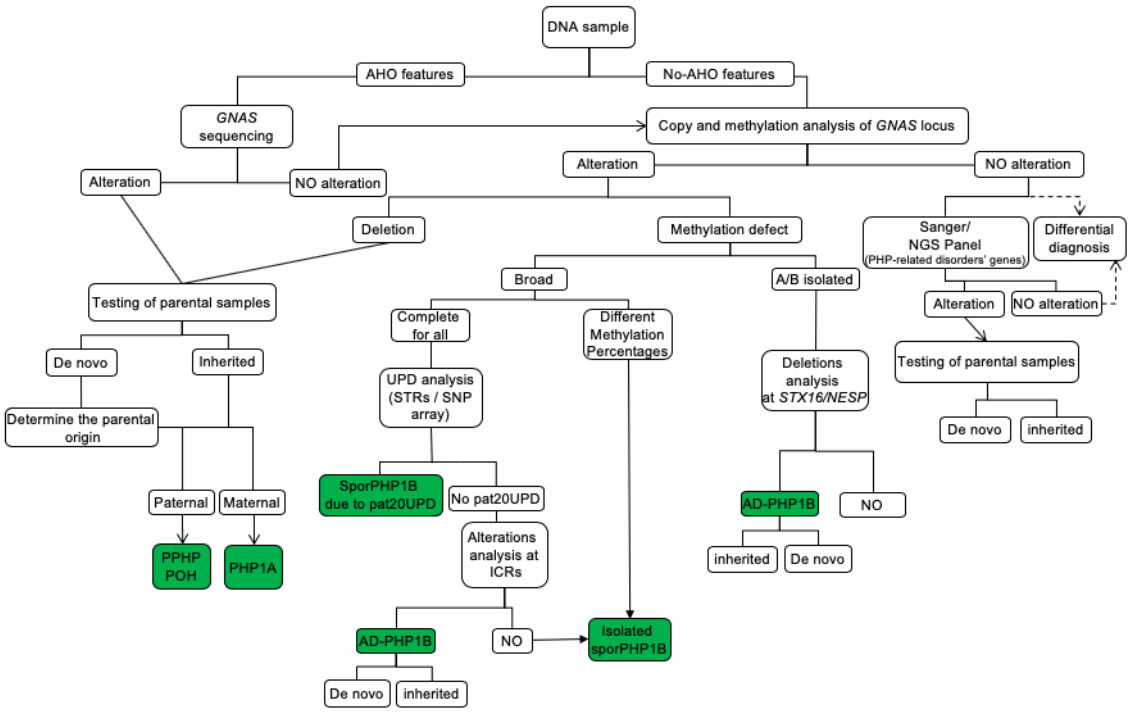
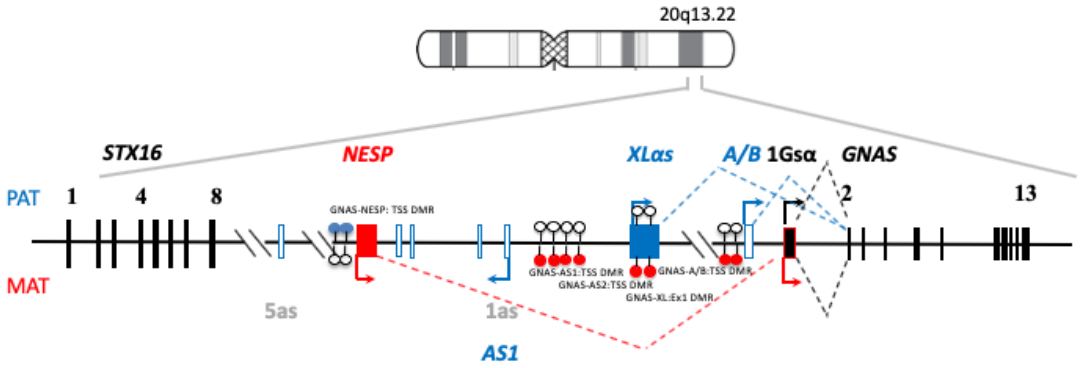


Figure 3: Molecular algorithm for the confirmation of the diagnosis of PHP and related disorders. If patients present with Albright's hereditary osteodystrophy (AHO), genetic alterations at *GNAS* should be studied, including point variants (sequencing) and genomic rearrangements (such as MLPA and aCGH). In the absence of AHO, epigenetic alterations should be analyzed first. According to the results obtained for the methylation status, further tests are needed to reach the final diagnosis: if the methylation defect is restricted to *GNAS A/B*:TSS DMR, STX16 deletions should be screened for, and, if present, the diagnosis of AD-PHP1B is confirmed; if the methylation is modified at the four DMRs, paternal uniparental disomy of chromosome 20 [UPD(20q)pat] should be screened for; in absence of UPD(20q)pat, deletions at NESP should be screened for; if no genetic cause is identified as the cause of the methylation defect, the sporadic form of the disease (spor-PHP1B) is suspected. After exclusion of the *GNAS* locus as the cause of the phenotype, and in patients with AHO, PHP-related genes (that is, at least *PDE4D* and *PRKAR1A*) should be sequenced. RT-PCR: Reverse-Transcription Polymerase Chain Reaction; SNP: Single Nucleotide Polymorphism; NGS: Next-Generation Sequencing; A/B: *GNAS A/B:* TSS-DMR; STRs: Short Tandem Repeats (microsatellites); UPD: uniparental disomy; WES: Whole Exome Sequencing; WGS: Whole Genome Sequencing; ICR: imprinting control region; VUS: variant of unknown significance.



Sup Figure 1: Scheme of the *GNAS* locus. Schematic diagram of the human GNAS cluster with DMRs (lollipops indicate the methylation pattern: in red maternally imprinted and in blue, paternally ones). The arrows show initiation and direction of transcription for maternal (mat)- and paternal (pat)-derived transcripts (in red and blue, respectively). Each box or vertical line represent each exon (empty boxes, when exons give rise to noncoding RNAs). *GNAS* exon 1 (1Gsα) is outlined in red to indicate that *GNAS* is preferentially expressed from maternal allele in some tissues (proximal renal tubules, neonatal brown adipose tissue, thyroid, gonads, paraventricular nucleus of the hypothalamus and pituitary). Discontinue lines represent the alternative splicing of each isoforms derived from *GNAS* cluster (the alternative splicing of 2-13 exons of *GNAS* gene were omitted).