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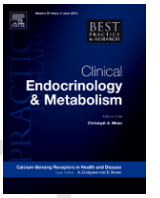

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Multiple hormone resistance and alterations of GPCRs signaling

Mantovani Giovanna MD, PhD*, Elli Francesca Marta MS, PhD[2],

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Endocrinology Unit, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

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Metabolic disorders deriving from the non-responsiveness of target organs to hormones, which manifest clinically similar to the deficiency of a given hormone itself, derive from molecular alterations affecting specific hormone receptors.

Pseudohypoparathyroidism (PHP) and related disorders exemplify an unusual form of hormone resistance as the underlying molecular defect is a partial deficiency of the α subunit of the stimulatory G protein (Gsα), a key regulator of cAMP signaling pathway, or, as more recently described, of downstream effector proteins of the same pathway, such as PKA regulatory subunit 1A (R1A) and phosphodyestarase type 4D (PDE4D). In this group of diseases, resistance to hormones such as PTH, TSH, gonadotropins and GHRH may be variably present, so that the clinical and molecular overlap among these different but related disorders represents a challenge for endocrinologists as to differential diagnosis and genetic counseling.

This review will describe the presenting features of multiple resistance in PHP and related disorders, focusing on both our current understanding and future challenges.

Introduction

Metabolic disorders deriving from the non-responsiveness of target organs to hormones, which manifest clinically similar to the deficiency of a given hormone itself, usually derive from molecular alterations affecting specific hormone receptors. The pleiotropic effect of multiple hormone resistance is a consequence of its different pathophysiology compared to single hormone resistances, as pathologic features arise from the lack of activation of downstream signaling pathways rather than of the receptor itself.

The interaction between agonists (polypeptide hormones monoamines, neurotransmitters, PGs and extracellular Ca^{+}) and their specific GPCRs activates G proteins, a superfamily of heterotrimeric guanine nucleotide binding proteins composed of three functionally distinct subunits (alpha, beta and gamma), which specificity depend on the alpha subunit. Sixteen mammalian α subunits have been described, which vary in range of expression and specificity of receptor-effector coupling, that trigger the activation of effectors, enzymes and ion channels, inducing both short-term effects on hormone secretion, neurotransmission and muscle contraction and long term effects on gene transcription [1–5].

The alpha subunit of the stimulatory G protein (Gsα) is responsible for the cAMP-mediated signaling by activating the enzyme adenylyl cyclase, which stimulates the cAMP formation and the subsequent protein kinase A (PKA) activation. Molecular alterations that deregulate the Gsα/cAMP/PKA pathway mostly affect the signaling of PTH/PTHrp, activated by the PTHR1 receptor, and, with different severity, the signaling of additional hormones, including TSH, epinephrin and calcitonin (Fig. 1).

In the past years, the GPCRs abnormal signal transduction causing resistance to multiple hormones was demonstrated to be secondary to molecular defects affecting the Gsα, a clinical condition named as Pseudohypoparathyroidism (PHP), or other

* Corresponding author. Fax +39 02 50320605.
Email addresses: giovanna.mantovani@unimi.it (M. Giovanna); francesca.elli@unimi.it (E.F. Marta)
[2] Fax +39 02 55033361.

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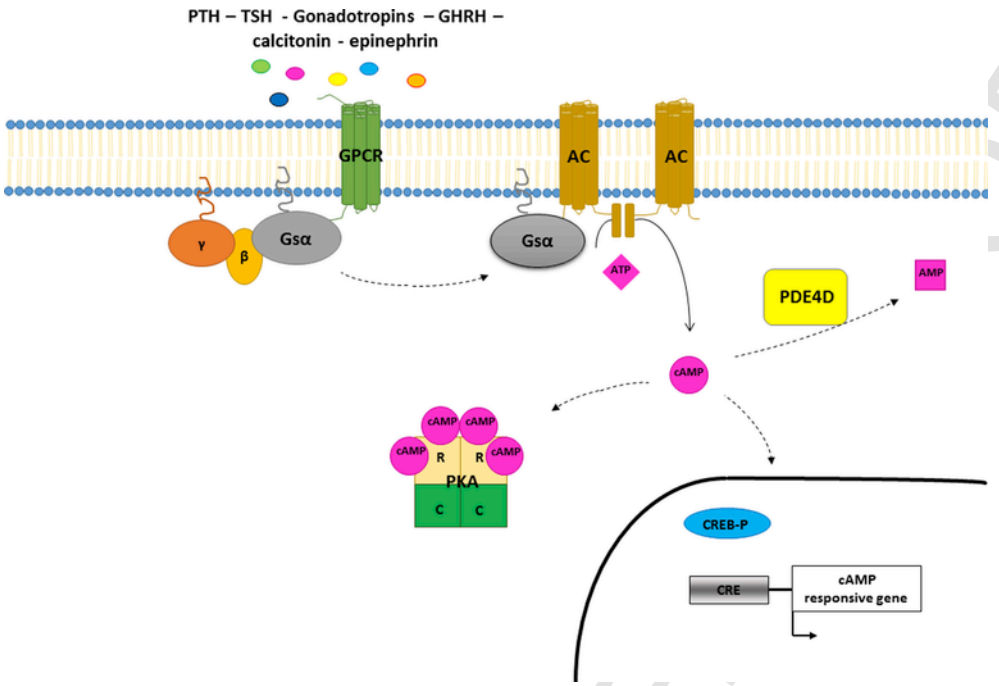

Fig. 1. Schematic representation of the cAMP signalling pathway. After hormone stimulation of the G-protein-coupled receptor (GPCR), the activated α subunit of the stimulatory G protein (Gsα; encoded by *GNAS*) interacts with the adenylate cyclase (AC) promoting cAMP production, that, interacting with the cAMP-dependent protein kinase type 1α regulatory subunits (R; encoded by *PRKAR1A*), determines the activation of the protein kinase A (PKA) catalytic subunit (C). The cAMP-specific 3′,5′-cyclic phosphodiesterase 4D (PDE4D; encoded by *PDE4D*) convert cAMP to AMP to switch off the signal.

downstream molecular effectors, including the Protein Kinase cAMP-Dependent Type 1 Regulatory Subunit Alpha (Prkar1a) and the Phosphodiesterase 4D (Pde4d), that were associated with Acrodysostosis (ACRDYS) [6–11] (Fig. 2).

PHP is the first hormone resistance syndrome ever described, and the term now encompasses a heterogeneous group of rare and impairing metabolic diseases, all characterized by end-organ resistance to the action of different hormones, primarily PTH. Main clinical characteristics are hypocalcemia and hyperphosphoremia associated with elevated PTH levels, frequently encompassing additional heterogeneous features, referred to as Albright's hereditary osteodystrophy (AHO), such as brachydactyly, ectopic ossifications, short stature and mental retardation [8,12,13].

ACRDYS describes a group of rare skeletal disorders characterized by severe brachydactyly, nasal and/or midfacial hypoplasia and variable intellectual/developmental/behavioural disabilities. Frequently observed features are the resistance to multiple hormones that bind to GPCRs (including PTH and TSH), progressive growth failure with short stature, advanced bone age and obesity [14].

The overlap between different but related disorders affecting the cAMP pathway represents a challenge to perform differential diagnosis and genetic counseling, and highlights the need for novel and updated classification models [12,15,16].

Pathophysiology

The first description of patients affected with PHP dates back to 1942, when patients with normal renal function, hypocalcemia, hyperphosphatemia and raised serum PTH levels were reported [17,18]. In contrast with patients affected by primary hypoparathyroidism, PHP patients presented immunologically and biologically active PTH in the parathyroid glands and an unresponsiveness to the calcium-mobilizing or phosphaturic effects of injected PTH [19]. The demonstration that PTH administration in PHP patients failed to determine the expected physiological response and confirmed that the metabolic defect underlying PHP can be accounted for a lack of responsiveness to PTH action, via its GPCR PTHR1, in target tissues [20].

In the renal proximal tubule, PTH resistance determines a defect in the generation of active 1,25 dihydroxyvitamin D3 by the loss of the transcriptional induction of the 25-hydroxyvitamin D 1-α hydrolase gene. Because of the different site of action of the anticalciuric (distal tubules) and the phosphaturic (proximal tubule) effects of PTH, PHP patients preserve normohypocalciuria and renal function but develop hyperphosphatemia, as the defective renal response occurs only in the proximal tubule. PTH/1,25-dihydroxyvitamin D promote calcium ions absorption in the intestine, via the basolateral membrane channel calbindin/TRPV6 and membrane pumps and transporters on the latter membrane. Moreover, PTH enhances bone resorption by osteoclasts and the release of calcium to the circulation, in a osteoblast-mediated manner [21–25].

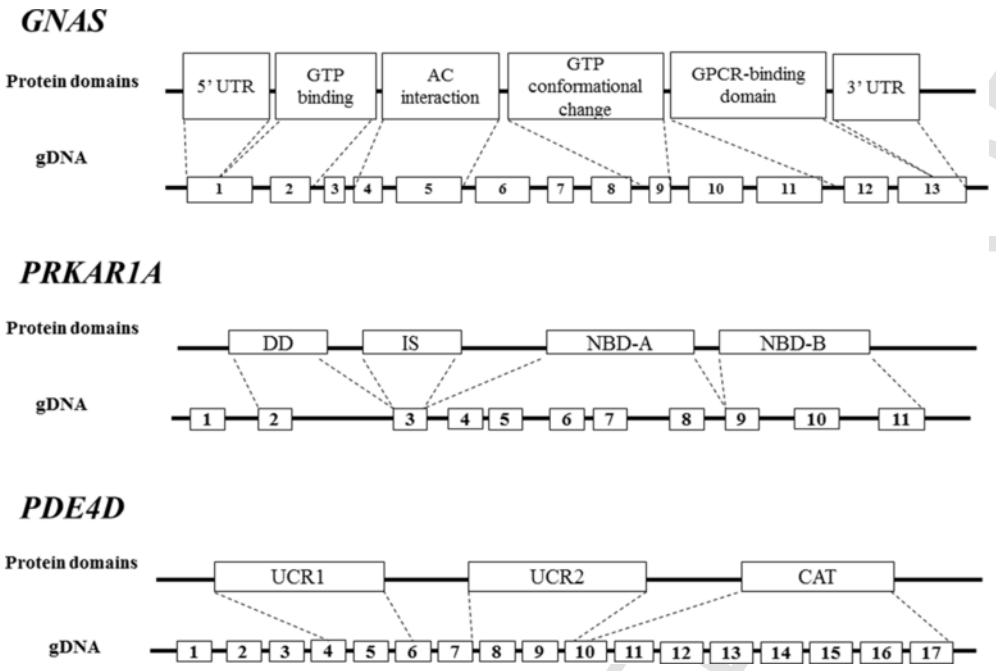

Fig. 2. Schematic illustration of *GNAS*, *PRKAR1A* and *PDE4D* genes. For each gene, the genomic structure (gDNA) and encoded functional domains (protein domains) are shown. UTR, untranslated region; GTP, guanosine triphosphate; AC, adenylate cyclase; GPCR, G protein coupled receptor; DD, dimerization domain; IS, inhibitory site; NBD, nucleotide-binding domain; UCR, upstream conserved region; CAT, catalitic.

The identification of defective Gs activity in erythrocyte membranes from PHP patients showed that the hormone resistance derived from Gs inability to correctly activate the signal transduction cascade, consisting GPCRs and several downstream intracellular effectors, including the Gs, the cAMP-dependent protein kinase A (PKA) and cAMP-specific phosphodiesterases (PDEs) [2,5,6,26,27] (Fig. 1).

The discovery of the associated molecular defect, namely heterozygous loss of function (LoF) mutations in the *GNAS* gene encoding for Gsα, confirmed the Gs pathogenetic role in the PHP phenotype [7,28,29].

Further studies allowed to deeply characterize GNAS locus, a complex imprinted locus mapping to chromosome 20q13.2–13.3, and demonstrated that Gsα expression is subject to tissue-specific imprinting, with a predominant maternal expression in specific human tissues (i.e. proximal renal tubules, pituitary gland, gonads, and thyroid) [30–38].

A paternal-specific imprinting pattern of GNAS differentially methylated regions (DMR) on both alleles was associated with a clinical phenotype characterized by renal resistance to PTH and mild resistance to TSH in the absence of other endocrine or physical abnormalities, thus including PHP also among imprinting disorders [35,39].

Despite the high detection rate of GNAS molecular defects, a subset of patients with a clinical suspect of PHP still lacked a confirming molecular diagnosis, hence additional molecules involved in the cAMP signaling cascade were screened and genetic alterations within *PRKAR1A* (cAMP-dependent protein kinase type I-α regulatory subunit) and *PDE4D* (cAMP-specific phosphodiesterase 4D) were discovered and associated to ACRDYS [40–42] (Fig. 2).

Hormone resistances and clinical presentation

The identification of hormone resistance is based upon the observation of increased hormone levels associated with a reduction in the peripheral response to the hormone itself (Table 1).

Resistance to PTH

The diagnosis of PTH resistance is based on the observation of low or normal calcemia, elevated phosphatemia and elevated serum PTH in the absence of vitamin D deficiency. It can be definitively ascertained using recombinant PTH [1–33], either as an infusion test based on the Ellsworth–Howard test or as a subcutaneous challenge [43].

Usually PTH resistance is absent at birth, but gradually develops during infancy or childhood. Being conserved the anticalciuric action exerted at the level of the distal tubule, patients show normo-hypocalciuria and life-long normal renal function in the absence of kidney stones. This latency of PTH resistance seemed to derive from the temporary physiological biallelic expression of maternal and paternal Gsα alleles renal proximal tubules during early postnatal development. Hyperphosphatemia, if

Table 1
Table summarizing PHP diagnostic criteria.

Biochemical signs
Major laboratory findings:
• PTH resistance: raised serum PTH levels, hypocalcemia and hyperphosphatemia, in the absence of vitamin D deficiency.
Additional laboratory findings:
• TSH resistance: raised serum TSH levels, usually in the absence of anti-thyroid antibodies and in the presence of normal thyroid scan.
• Resistance to gonadotropins: elevated LH and FSH levels, low oestradiol/testosterone levels.
• GHRH resistance: blunted GH response to provocative tests.
Clinical signs
• Findings associated with acute or chronic hypocalcemia: nervous hyper-excitability with paresthesia, cramps, tetany, hyperreflexia, convulsions and tetanic crisis – cataracts - basal ganglia calcifications.
• Secondary amenorrhea and/or infertility.
• Reduced growth velocity (in children), short stature.
• AHO features (at least brachydactyly and/or heterotopic ossifications are required):
- Brachydactyly (shortening of fourth and/or fifth metacarpals defined as the metacarpal sign and/or shortening below -2SDS at the metacarpophalangeal profile pattern in at least one metacarpal bone or distal phalanx)
- Ectopic ossifications (either clinically evident or at X-ray)
- Obesity (BMI >30 kg/m^2 in adults and >97th centile in children)
- Round face
- Intellectual disabilities, defined in case of history of delayed motor and/or speech milestones or need of extra help in pre-school or mainstream school.

untreated, enhances the defect in the generation of 1,25-dihydroxyvitamin D consequent to renal resistance to PTH, further contributing to the decrease of serum calcium. The detection, during physical examination, of positive Chvostek sign (twitching of facial muscles after tapping the facial nerve just in front of the ear) and/or Trousseau sign (carpal spasm after maintaining an arm blood pressure cuff at 20 mm Hg above the patient's systolic blood pressure for 3min) may reveal hypocalcemia. Patients may develop features such as basal ganglia calcifications and cataracts as effects of chronic hypocalmia, hyperphosphatemia and, more importantly, elevated Ca × P product [9,10,44].

The management of PTH resistance has the objective to maintain calcemia and phosphatemia within normal ranges while avoiding hypercalciuria and preventing bone resorption. The main treatments are active vitamin D analogs, calcitriol or alfacalcidol, and calcium supplements.

Resistance to other hormones

The identification of PTH resistance leads to the investigation for other hormone resistances, thus genetic disorders causing a metabolic disorder. With interindividual variability in severity and time course, patients also display resistance to other GPCRs acting hormones, such as TSH, gonadotropins, and GHRH [13,45–55].

TSH resistance is seldom detected during the neonatal screening for congenital hypothyroidism, but it develops more often over childhood or adolescence. Clinically patients present mild resistance, characterized by elevated TSH levels, with normal/slightly low free thyroxine levels, no goiter and no antithyroid antibodies [47–49]. The treatment is L-thyroxin administration to reach a normal TSH level.

As for gonadotropins resistance, the relation with increased basal or GnRH-stimulated levels of circulating gonadotropins still needs to be confirmed, although female patients usually manifest hypogonadism, or rather delayed or incomplete sexual maturation, amenorrhea/oligomenorrhea and/or infertility [50].

Deficiency in GH secretion secondary to GHRH resistance was reported in a large subset of PHP patients. Additional hormone defects described in small series of PHP patients include prolactin deficiency, blunted plasma cAMP responses to glucagon and isoproterenol, resistance to calcitonin and reduced insulin sensitivity [50–55].

The current knowledge on ACRDYS confirmed that *PRKAR1A* defects were frequently associated with multihormone resistance, whereas, in case of *PDE4D* mutations, hormonal defects were present only in a subset of patients. Most patients displayed resistance to PTH and TSH, and a small percentage showed an altered response to FSH associated with cryptorchidism and/or lack of puberal spurt [56].

Additional clinical features

Albright hereditary osteodystrophy is a clinical entity encompassing a series of heterogeneous and nonspecific clinical findings including rounded face, short stature, early-onset central obesity, and variable degrees of mental retardation. Such clinical features are frequently described also in patients affected with acrodysostosis, making the differential diagnosis even more complicated [9,12,14,56].

The evaluation of auxological parameters allows to find short stature, defined as height below the 3rd percentile for chronological age, and obesity, defined as Body Mass Index (BMI) above the 97th percentile in children (SDS ≥ 1.88) and above 30 kg/m^2 in adults [12,56].

One of the most specific features of AHO are heterotopic intramembranous ossifications. Such calcified nodules are often limited to the dermis and subcutaneous tissues and can be found on physical examination as palpable hard nodules, whose number and extension are highly heterogeneous.

Brachydactyly, defined as the shortening of III, IV and V metacarpals, and I distal phalanx, derives from the premature closure of the growth plate and associated with coning of the epiphysis. Its presentation is highly variable and is often asymmetric, and, to avoid a misdiagnosis, the construction of the metacarpophalangeal pattern profile after posterioanterior left hand radiographs is used. It can be absent at birth, but it become apparent during infancy/childhood. Brachydactyly showed to be the most frequent feature of ACRDYS, as present in more than 90% of patients [56,57].

AHO seems to be associated also with musculoskeletal abnormalities including spinal cord compression and carpal tunnel syndrome [58,59]. In ACRDYS, cone-shaped epiphyses and facial dysmorphism are often observed [56].

Frequency and severity of neurocognitive abnormalities in PHP patients, such as mental retardation, developmental delay and emotional disorders, are not well established, with an apparent discrepancy between the adult (27%) and the pediatric populations (64%) [12,60]. Mental/behavioural defects seemed to have different frequencies between ACRDYS subtypes, affecting about half of *PRKAR1A* mutated patients and up to 95% of the *PDE4D* mutated patients [56].

Recent data suggested that patients with PHP may present intrauterine growth defects. A growth retardation leading to low birth weight and length was described in those with a paternally-inherited GNAS disease, while an opposite phenotype with increased intrauterine growth was documented in PHP1B subjects affected with the autosomal dominant form of the disorder [61,62]. Intrauterine growth retardation was described in about 15% of ACRDYS subjects bearing a *PRKAR1A* genetic variant [56].

Further additional recurring comorbidities, deserving investigation in larger cohorts in order to define their relationship with ACRDYS, are hearing loss, recurrent otitis media, intracranial hypertension, shypodeformity of knees and shoulders, and atophy/rhinitis/eczema [56].

Molecular diagnosis and genetic counseling

The non-responsives of target organs to hormones, despite sufficient/elevated hormone levels, mimics the deficiency of the hormone itself. Such resistances mostly derive from inactivating mutations affecting hormone receptors, while multiple hormone resistances associated with alterations of the GPCRs signaling are an unusual form of hormone resistance as molecular defects affect Gsα, Prkar1a and Pde4d proteins, or rather downstream effectors of the GPCR PTHR1. As previously stated, the clinical and molecular overlap among disorders affecting the cAMP pathway makes performing the correct molecular diagnosis challenging and time consuming, thus, in Fig. 3, we resume the flowchart to analyze patients after the clinical assessment.

GNAS genetic defects

The first *GNAS* inactivating mutation was described in 1990 and since then more than 200 genetic variants distributed through the *GNAS* gene have been discovered, both point mutations (missense, nonsense, frameshift, and splice site) and small/large deletions or insertions. The only mutational hot spot described up to now is a 4-bp deletion in exon 7, c.568_571del. All *GNAS* exons are affected with different frequency, although exons 1 and 7 host about 20% each. Most of these genetic defects are private mutations, and the few recurring *de novo* mutations suggest the derivation from a common molecular mechanism rather than from a founder effect [7,63–67].

GNAS genetic defects are subject to autosomal dominant inheritance, thus offsprings of a PHP patient have a 50% recurrence risk and the detection of pathogenetic variants provides the possibility of predictive genetic testing in relatives as well as prenatal diagnosis [63–69].

To note that the phenotypic overlap among different disorders affecting the cAMP pathway represents a challenge to perform differential diagnosis and, in case of negative *GNAS* mutation screening, patients should be screened also for the presence of GNAS imprinting and of genetic variants in *PRKAR1A* and *PDE4D* genes [12,15,16].

GNAS epigenetic defects

Reports about multi-generation families with PHP showing a marked excess of maternal transmission, suggested the involvement of genomic imprinting. The characterization of the GNAS locus and its transcripts demonstrated that Gsα expression is subject to tissue-specific imprinting and that PHP1B patients displayed a paternal-specific patterns of cytosine methylation at GNAS DMRs of their maternally inherited alleles. Most cases were sporadic, being the only affected individuals in a given family with no underlying known genetic lesion, thus the recurrence risk could not be determined. In a small subset of sporadic PHP1B (spor-PHP1B) patients, the LOI affecting GNAS DMRs was associated with uniparental disomy (UPD) of chromosome 20, which occurrence, in the absence of a parental translocation, was expected to be less than 1% [70–73].

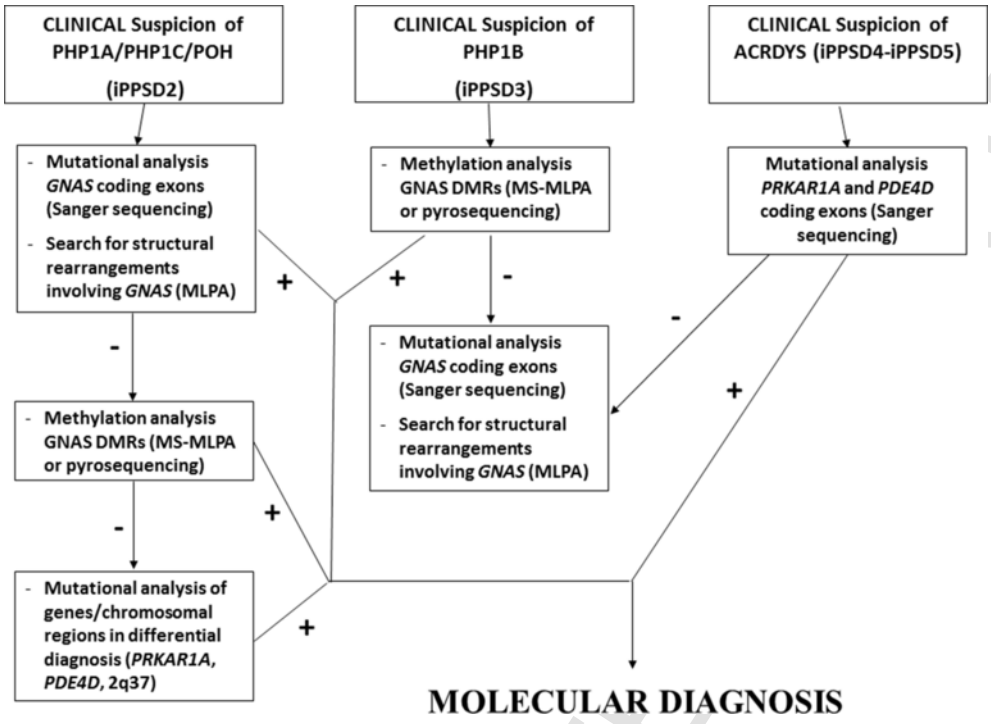

Fig. 3. Flowchart summarizing a molecular diagnostic algorithm for patients with multiple hormone resistance suspected of having a disorder linked to defective Gsα–cAMP signaling. According with the starting clinical suspicion, we propose how to perform a multistep analysis of patients to reach the molecular diagnosis.

The familial form of the disease is maternally transmitted in an autosomal dominant manner, with a 50% recurrence risk. Autosomal dominant PHP type 1B (AD-PHP1B) is typically characterized by an isolated loss of methylation at the exon A/B DMR due to microdeletions disrupting the ICR located into the *STX16* gene or, less frequently, by a LOI at all maternal GNAS DMRs due to deletions removing the NESP55 DMR [74–79].

PRKAR1A and PDE4D genetic defects

PRKAR1A and *PDE4D* heterozygous genetic variants, affecting different functional domains, were associated to ACRDYS. Such mutations are mainly private, and the only recognized mutational hot spot is the *PRKAR1A* c.1102C > T nonsense mutation, p.(Arg368X). As for the PDE4D gene, mutations are confined to single kindreds, with the exception of 4 recurring variants affecting the catalytic unit (c.803T > C, c.1586A > C, c.1835G > A and c.1850T > C) [40–42,56,80–85].

Genetic defects causing ACRDYS are autosomal dominant. The predictive genetic testing in relatives of mutated patients can be performed as offsprings have a 50% recurrence risk.

Classification: from the classical towards a novel nomenclature and classification

Since the first description of PHP, several clinical variants of this disorder have been reported and today the term Pseudohypoparathyroidism encompasses a group of rare, related and deeply impairing diseases, and performing a proper differential diagnosis among the various forms may be sometimes challenging.

The classical, still in use, classification is based on the presence/absence of specific clinical and biochemical signs, does not include molecular defects as a criterion to stratify patients and does not include all conditions deriving from Gsα/cAMP/PKA pathway molecular defects. The increasing knowledge of these disorders made this classification outdated and demonstrated the need for a novel and more effective one. Recently, a proposal for a new terminology has been proposed by the European network on PHP, together with a novel classification that should provide patients with an unambiguous diagnosis based on clinical/biochemical/molecular criteria [12,15,16]. "Inactivating PTH/PTHrpP signaling disorder" (iPPSD) is the proposed new nomenclature for this heterogeneous group of rare diseases and the different iPPSD subclusters encompassing disorders associated with multiple hormone resistance are reported below and resumed in Table 2.

Table 2
Classification of pseudohypoparathyroidism and related syndromes. Subtypes associated with multiple hormone resistance are highlighted in bold. OMIM, online Mendelian inheritance in man; AHO, Albright hereditary osteodystrophy; DMRs, differentially methylated regions; LoF, loss of function; LoI, loss of imprinting; patUPD, paternal uniparental disomy; BOCD, Blomstrand chondrodysplasia; HTNB, hypertension and brachydactyly syndrome.

Classical classification	Novel classification	OMIM	Phenotype	Main molecular determinants
BOCD EIKEN SYNDROME	iPPSD1	#215045 #600002	skeletal dysplasia, retarded ossification	*PTHR1* mutations
PHP1A	**iPPSD2**	**# 103580**	multiple hormone resistance, AHO	Maternal LoF *GNAS* mutations, *GNAS* deletions, LoI at GNAS DMRs
PPHP/AHO	**iPPSD2**	**# 612463**	AHO	Paternal LoF *GNAS* mutations, *GNAS* deletions
POH	**iPPSD2**	**# 166350**	heterotopic ossifications	Paternal LoF *GNAS* mutations
PHP1B	**iPPSD3**	**# 603233**	multiple hormonal resistance, rare signs of AHO	LoI at the GNAS DMRs (sporadic), isolated LoM at the A/B DMR (AD – maternal *STX16* deletion), patUPD20, maternal *NESP* and/or *AS* deletion
ACRDYS1	**iPPSD4**	**# 101800**	skeletal dysplasia, AHO-like features and multiple endocrine abnormalities	*PRKAR1A* mutations
ACRDYS2	**iPPSD5**	**# 614613**	skeletal dysplasia, AHO-like features and intellectual disabilities	*PDE4D* mutations
HTNB	iPPSD6	#112410	brachydactyly, hypertension	*PDE3A* mutations
/	iPPSDx	/	/	No (epi)genetic defect in known genes identified during investigation
/	iPPSDn+1	/	/	Novel gene/molecular defect to be discovered

PHP1A/PHP1C and POH, or iPPSD2

The iPPSD2 cluster includes all clinical presentations of loss-of-function Gsα mutations: Pseudohypoparathyroidism type 1A (PHP1A, MIM103580), Pseudohypoparathyroidism type 1C (PHP1C, MIM612462), Pseudopseudohypoparathyroidism (PPHP, MIM612463) and Progressive Osseous Heteroplasia (POH, MIM166350).

Patients with PHP1A, affected by maternally-derived point mutations in GNAS exons 113 or structural rearrangements involving part or the whole GNAS locus, clinically present both AHO features and resistance to several GPCRs-acting hormones (PTH, TSH, gonadotropins and GHRH) [7,66–69].

The same mutations, when affecting the paternal allele, lead to PPHP, in which AHO occurs in the absence of endocrine abnormalities. PHP1A and PPHP may coexist within the same family but never in the same sibship [63,64].

PHP1C is clinically indistinguishable from PHP1A, being characterized by multihormone resistance and the presence of signs of AHO. Actually the only way to differentiate these two PHP variants is the measurement of Gsα activity in erythrocytes', fibroblasts' or platelets' membranes, usually normal in PHP1C patients and 50% reduced in PHP1A subjects [86].

POH is a recently described rare disorder of mesenchymal differentiation, associated with paternally-inherited *GNAS* inactivating mutations, characterized by ectopic bone formation in dermis, skeletal muscle and deep connective tissues. Recent reports documented the existence of patients showing also typical AHO features, such as short stature and brachydactyly [87–89].

PHP type 1B, or iPPSD3

The iPPSD3 subgroup includes all disorders associated with changes in the methylation pattern of GNAS DMRs, including both primary epigenetic defects, or rather broad or partial GNAS loss of Imprinting (LOI), and conditions secondary to UPD(20)pat and deletions within *STX16* and/or *NESP* [70–79].

At its first description Pseudohypoparathyroidism type 1B (PHP1B, MIM603233) was presented as a clinical condition characterized by renal resistance to PTH in the absence of other endocrine or physical abnormalities. Subsequently, TSH resistance was also documented in large subsets of patients, thus identifying also this subtype as characterized by multi-hormone resistance. The recent description of GH deficiency in affected monozygotic twins suggested that also the GHRH-R signaling could be compromised [90–95].

ACRDYS type 1 and type2, or iPPSD4 and iPPSD5 respectively

iPPSD4 and iPPSD5 represent the two subtypes of Acrodysostosis type 1 (ACRDYS1, MIM101800) and type 2 (ACRDYS2, 614613) associated with *PRKAR1A* and *PDE4D* defects, respectively.

ACRDYS refers to a heterogeneous group of rare genetic congenital malformation syndromes, whose hallmarks are skeletal dysplasia with AHO-like features, such as brachydactyly type E, progressive growth failure, mental retardation and facial dysostosis (broad face with widely spaced eyes, maxillonasal hypoplasia and flattening of the nasal bridge).

The first case presenting also biochemical abnormalities dates back to 1977, but nowadays the presence of resistance to multiple hormones that bind GPCRs has been well documented, especially in patients carrying *PRKAR1A* mutations (ACRDYS1 or iPPSD4). To note that up to 20% of ACRDYS2 patients show an altered response to follicle-stimulating hormone, cryptorchidism and/or lack of puberal spurt [56].

Conclusions

Patients with PHP and related disorders face heterogeneous problems from early childhood to adulthood, including severe alterations of mineral metabolism potentially leading to seizures, other endocrine deficiencies leading to hypothyroidism, hypogonadism and GH deficit, important growth impairment independently of the hormonal status, ectopic ossifications with potential severe mobility limitation, skeletal issues, cognitive and psychomotor impairment. Given this highly heterogeneous clinical picture, clinicians often lack expertise to manage all these aspects.

In addition, this group of disorders is caused by different and complex genetic and epigenetic defects, so that often getting a correct molecular diagnosis may be also difficult and time-consuming for both patients, families and physicians.

Finally, there is a lot of confusion and overlap as to the nomenclature and classification of these heterogeneous but still closely related diseases.

Summary

Metabolic disorders deriving from the non-responsiveness of target organs to hormones, which manifest clinically similar to the deficiency of a given hormone itself, derive from molecular alterations affecting specific hormone receptors.

Pseudohypoparathyroidism (PHP) includes different metabolic disorders characterized by physical findings that variably comprise short bones, short stature, a stocky build, ectopic ossifications, and endocrine defects that commonly include resistance to multiple hormones. PHP and its related disorders vary with regards to clinical and endocrine presentation and severity between affected individuals with considerable clinical and molecular overlap.

As for its pathogenesis, PHP exemplifies an unusual form of hormone resistance as the underlying molecular defect is a partial deficiency of Gsα, a key regulator of cAMP signaling pathway, rather than the hormone receptor itself. Despite the first description of this disorder dates back to 1942, recent findings unveiled complex epigenetic alterations beside classical mutations at the *GNAS* complex gene as the molecular basis for PHP main subtypes. Moreover, mutations in the *PRKAR1A* and *PDE4D* genes, both crucial as *GNAS* for cAMP-mediated signalling, have been demonstrated in patients with acrodysostosis, a disease of bone formation and endocrine disturbances with many shared clinical characteristics.

In particular, resistance to hormones such as PTH, TSH, gonadotropins and GHRH may be variably present in this group of diseases, so that the clinical and molecular overlap among these different but related disorders represents a challenge for endocrinologists as to differential diagnosis and genetic counseling.

Practice points

- The term PHP encompasses a heterogeneous group of rare and impairing metabolic diseases, all characterized by end-organ resistance to the action of different hormones, primarily PTH. Endocrine alterations often include, with interindividual variability in severity and time course, also resistance to other hormones that act through GPCRs, such as TSH, gonadotropins, and GHRH.
- The lack of responsiveness to PTH, which results in hypocalcemia, hyperphosphatemia and inappropriately high serum PTH levels, usually develops over the first years of life, with high serum phosphate and elevated PTH generally preceding calcium reduction. The management of PTH resistance has the objective to maintain calcemia and phosphatemia within normal ranges, lowering PTH as much as possible while avoiding hypercalciuria.
- Most patients become clinically resistant to TSH over childhood or adolescence, but hypothyroidism may be sometimes detected at neonatal screening. Generally, TSH resistance is mild, with normal or slightly low thyroid hormone levels, no goiter and absence of antithyroid antibodies. Treatment with L-thyroxin is aimed to normalize TSH levels, as in any other form of primary hypothyroidism.

- Clinical evidence of hypogonadism, particularly in females, is usually manifested as delayed or incomplete sexual maturation, amenorrhea or oligomenorrhoea, and/or infertility.
- Patients frequently display additional heterogeneous features, referred to as Albright's hereditary osteodystrophy (AHO), such as brachydactyly, ectopic ossifications, short stature and mental retardation.
- The term acrodysostosis (ACRDYS) represents a group of rare skeletal disorders that may associate with the resistance to multiple hormones including PTH and TSH. Patients frequently display additional heterogeneous features, such as progressive growth failure with short stature, advanced bone age, obesity, severe brachydactyly, nasal and/or midfacial hypoplasia and variable intellectual/developmental/behavioural disabilities.
- Recently, the term "inactivating PTH/PTHrpP signaling disorder" (iPPSD) has been proposed to include all these heterogenous but similar rare disorders, together with a novel classification that should provide an unambiguous diagnosis based on both clinical and molecular criteria.

Research agenda

Given the lack of strong evidence-based data, particularly for management of these patients, international collaboration and long-term clinical trials looking at both the natural history and the outcome of treatments are urgently needed. In particular, the research agenda should focus on:

- Extensive and systematic data on growth pattern related to endocrine function, bone maturation, pubertal development and gonadal function, fertility, mineralization status.
- Identification of factors that contribute to the development and progression of ectopic bone formation.
- Identification of new genes involved in the PTH/PTHrP signaling cascade and their association with as-yet-unresolved cases with PHP and related disorders.
- Optimization of calcium, phosphate and PTH levels during active treatment for PTH resistance, especially related to poorly characterized long-term complications.
- Indications, doses, efficacy, optimal timing and indications for rhGH use in GH-deficient patients.
- Long-term quality of life.

Conflicts of interest

The authors declare no competing interests.

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References

[1] N. Wettschureck, S. Offermanns, Mammalian G proteins and their cell type specific functions, Physiol Rev 85 (4) (2005) 1159–1204.
[2] A.M. Spiegel, A. Shenker, L.S. Weinstein, Receptor-effector coupling by G proteins: implications for normal and abnormal signal transduction, Endocr Rev 13 (3) (1992) 536–565.
[3] A.M. Spiegel, Mutations in G proteins and G protein-coupled receptors in endocrine disease, J Clin Endocrinol Metab 81 (7) (1996) 2434–2442.
[4] A. Lania, G. Mantovani, A. Spada, G protein mutations in endocrine diseases, Eur J Endocrinol 145 (5) (2001) 543–559.
[5] A.G. Lania, G. Mantovani, A. Spada, Mechanisms of disease: mutations of G proteins and G-protein-coupled receptors in endocrine diseases, Nat Clin Pract Endocrinol Metabol 2 (12) (2006) 681–693.
∗[6] M.A. Levine, R.W. Downs, M. Singer, et al., Deficient activity of guanine nucleotide regulatory protein in erythrocytes from patients with pseudohypoparathyroidism, Biochem Biophys Res Commun 94 (1980) 1319–1324.
[7] J.L. Patten, D.R. Johns, D. Valle, et al., Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy, N Engl J Med 322 (20) (1990) 1412–1419.
[8] G. Mantovani, A. Spada, Mutations in the Gs alpha gene causing hormone resistance, Best Pract Res Clin Endocrinol Metabol 20 (4) (2006) 501–513.

∗[9] G. Mantovani, A. Spada, F.M. Elli, Pseudohypoparathyroidism and Gsα-cAMP-linked disorders: current view and open issues, Nat Rev Endocrinol 12 (6) (2016) 347–356.
[10] A. Linglart, C. Silve, A. Rothenbuhler, Multiple hormonal resistances: diagnosis, evaluation and therapy, Ann Endocrinol (Paris) 76 (2) (2015) 98–100.
[11] C. Silve, Acrodysostosis: a new form of pseudohypoparathyroidism?, Ann Endocrinol (Paris) 76 (2) (2015) 110–112.
[12] G. Mantovani, Clinical review: pseudohypoparathyroidism: diagnosis and treatment, J Clin Endocrinol Metab 96 (2011) 3020–3030.
[13] L.S. Weinstein, S. Yu, D.R. Warner, et al., Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting, Endocr Rev 22 (2001) 675–705.
[14] C. Silve, C. Le-Stunff, E. Motte, et al., Acrodysostosis syndromes, BoneKEy Rep 1 (225) (2012) 1–7.
[15] G. Mantovani, F.M. Elli, A. Spada, GNAS epigenetic defects and pseudohypoparathyroidism: time for a new classification?, Horm Metab Res 44 (10) (2012) 716–723.
∗[16] S. Thiele, G. Mantovani, A. Barlier, et al., From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network, Eur J Endocrinol 175 (6) (2016) P1–P17.
∗[17] F. Albright, C.H. Burnett, C.H. Smith, et al., Pseudohypoparathyroidism: an example of "Seabright-Bantam syndrome", Endocrinology 30 (1942) 922–932.
[18] F. Albright, A.P. Forbes, P.H. Henneman, Pseudopseudohypoparathyroidism, Trans Assoc Am Phys 65 (1952) 337–350.
[19] A.H. Tashjian Jr., A.G. Frantz, J.B. Lee, Pseudohypoparathyroidism: assays of parathyroid hormone and thyrocalcitonin, Proc Natl Acad Sci U S A 56 (4) (1966) 1138–1142.
[20] L.R. Chase, G.L. Melson, G.D. Aurbach, Pseudohypoparathyroidism: defective excretion of 3′,5′-AMP in response to parathyroid hormone, J Clin Invest 48 (10) (1969) 1832–1844.
[21] J.T. Potts, Parathyroid hormone: past and present, J Endocrinol 187 (3) (2005) 311–325.
[22] R.C. Gensure, T.J. Gardella, H. Jüppner, Parathyroid hormone and parathyroid hormone-related peptide, and their receptors, Biochem Biophys Res Commun 328 (3) (2005) 666–678.
[23] M.D. Stone, D.J. Hosking, C. Garcia-Himmelstine, et al., The renal response to exogenous parathyroid hormone in treated pseudohypoparathyroidism, Bone 14 (5) (1993) 727–735.
[24] D. Gardner, D. Shoback, Greenspan's basic & clinical endocrinology, 9th ed., McGraw Hill, New York, 2011232.
[25] K. Poole, J. Reeve, Parathyroid hormone – a bone anabolic and catabolic agent, Curr Opin Pharmacol 5 (6) (2005) 612–617.
[26] K. Taskén, B.S. Skålhegg, K.A. Taskén, et al., Structure, function, and regulation of human cAMP-dependent protein kinases, Adv Sec Messenger Phosphoprotein Res 31 (1997) 191–204.
[27] S.S. Taylor, J.A. Buechler, W. Yonemoto, cAMP-dependent protein kinase: framework for a diverse family of regulatory enzymes, Annu Rev Biochem 59 (1990) 971–1005.
∗[28] L.S. Weinstein, P.V. Gejman, E. Friedman, 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 87 (21) (1990) 8287–8290.
[29] M.A. Levine, W.S. Modi, S.J. O'Brien, Mapping of the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase (GNAS1) to 20q13.2–q13.3 in human by in situ hybridization, Genomics 11 (2) (1991) 478–479.
[30] S.J. Davies, H.E. Hughes, Imprinting in Albright's hereditary osteodystrophy, J Med Genet 30 (2) (1993) 101–103.
[31] R. Campbell, C.M. Gosden, D.T. Bonthron, Parental origin of transcription from the human GNAS1 gene, J Med Genet 31 (8) (1994) 607–614.
[32] B.E. Hayward, M. Kamiya, L. Strain, et al., The human GNAS1 gene is imprinted and encodes distinct paternally and biallelically expressed G proteins, Proc Natl Acad Sci U S A 95 (17) (1998) 10038–10043.
[33] B.E. Hayward, V. Moran, L. Strain, et al., Bidirectional imprinting of a single gene: GNAS1 encodes maternally, paternally, and biallelically derived proteins, Proc Natl Acad Sci U S A 95 (26) (1998) 15475–15480.
[34] L.S. Weinstein, S. Yu, C.A. Ecelbarger, Variable imprinting of the heterotrimeric G protein G(s) alpha-subunit within different segments of the nephron, Am J Physiol Ren Physiol 278 (2000) F507–F514.
[35] H. Zheng, G. Radeva, J.A. McCann, et al., Galphas transcripts are biallelically expressed in the human kidney cortex: implications for pseudohypoparathyroidism type 1b, J Clin Endocrinol Metab 86 (2001) 4627–4629.
[36] G. Mantovani, E. Ballare, E. Giammona, et al., The Gs alpha gene: predominant maternal origin of transcription in human thyroid gland and gonads, J Clin Endocrinol Metab 87 (2002) 4736–4740.
[37] G. Mantovani, S. Bondioni, M. Locatelli, et al., Biallelic expression of the Gsalpha gene in human bone and adipose tissue, J Clin Endocrinol Metab 89 (2004) 6316–6319.
[38] S. Klenke, W. Siffert, U.H. Frey, A novel aspect of GNAS imprinting: higher maternal expression of Galphas in human lymphoblasts, peripheral blood mononuclear cells, mammary adipose tissue, and heart, Mol Cell Endocrinol 341 (2011) 63–70.
[39] L.S. Weinstein, The stimulatory G protein alpha-subunit gene: mutations and imprinting lead to complex phenotypes, J Clin Endocrinol Metab 86 (10) (2001) 4622–4626.
∗[40] A. Linglart, C. Menguy, A. Couvineau, et al., Recurrent PRKAR1A mutation in acrodysostosis with hormone resistance, N Engl J Med 364 (23) (2011) 2218–2226.
∗[41] C. Michot, C. Le Goff, A. Goldenberg, et al., Exome sequencing identifies PDE4D mutations as another cause of acrodysostosis, Am J Hum Genet 90 (4) (2012) 740–745.
∗[42] H. Lee, J.M. Graham Jr., D.L. Rimoin, et al., Exome sequencing identifies PDE4D mutations in acrodysostosis, Am J Hum Genet 90 (2012) 746–751.
[43] K. Todorova-Koteva, K. Wood, S. Imam, et al., Screening for parathyroid hormone resistance in patients with non-phenotypically evident pseudohypoparathyroidism, Endocr Pract (2012) 1–21.
[44] S. Turan, E. Fernandez-Rebollo, C. Aydin, et al., Postnatal establishment of allelic Gαs silencing as a plausible explanation for delayed onset of parathyroid hormone resistance owing to heterozygous Gαs disruption, J Bone Miner Res 29 (3) (2014) 749–760.
[45] M.A. Levine, R.W. Downs Jr., A.M. Moses, et al., Resistance to multiple hormones in patients with pseudohypoparathyroidism. Association with deficient activity of guanine nucleotide regulatory protein, Am J Med 74 (4) (1983) 545–556.

[46] J.L. Wemeau, A.S. Balavoine, M. Ladsous, et al., Multihormonal resistance to parathyroid hormone, thyroid stimulating hormone, and other hormonal and neurosensory stimuli in patients with pseudohypoparathyroidism, J Pediatr Endocrinol Metab 19 (Suppl. 2) (2006) 653–661.
[47] M.A. Levine, T.S. Jap, W. Hung, Infantile hypothyroidism in two sibs: an unusual presentation of pseudohypoparathyroidism type Ia, J Pediatr 107 (1985) 919–922.
[48] J. Pohlenz, W. Ahrens, O. Hiort, A new heterozygous mutation (L338N) in the human Gsα (GNAS1) gene as a cause for congenital hypothyroidism in Albright's hereditary osteodystrophy, Eur J Endocrinol 148 (2003) 463–468.
[49] J.E. Pinsker, W. Rogers, S. McLean, et al., Pseudohypoparathyroidism type 1a with congenital hypothyroidism, J Pediatr Endocrinol Metab 19 (2006) 1049–1052.
[50] G. Mantovani, A. Spada, Resistance to growth hormone releasing hormone and gonadotropins in Albright's hereditary osteodystrophy, J Pediatr Endocrinol Metab 19 (2006) 663–670.
[51] E.L. Germain-Lee, Short stature, obesity, and growth hormone deficiency in pseudohypoparathyroidism type Ia, Pediatr Endocrinol Rev 3 (2006) 318–327.
[52] G. Mantovani, M. Maghnie, G. Weber, et al., Growth hormone-releasing hormone resistance in pseudohypoparathyroidism type Ia: new evidence for imprinting of the Gsα gene, J Clin Endocrinol Metab 88 (2003) 4070–4074.
[53] E.L. Germain-Lee, J. Groman, J.L. Crane, et al., Growth hormone deficiency in pseudohypoparathyroidism type 1a: another manifestation of multihormone resistance, J Clin Endocrinol Metab 88 (2003) 4059–4069.
[54] L. de Sanctis, J. Bellone, M. Salerno, et al., GH secretion in a cohort of children with pseudohypoparathyroidism type Ia, J Endocrinol Invest 30 (2007) 97–103.
[55] V. Vlaeminck-Guillem, M. D'Herbomez, P. Pigny, et al., Pseudohypoparathyroidism Ia and hypercalcitoninemia, J Clin Endocrinol Metab 86 (2001) 3091–3096.
*[56] F.M. Elli, P. Bordogna, L. de Sanctis, 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 31 (6) (2016) 1215–1224.
[57] L. de Sanctis, S. Vai, M.R. Andreo, et al., Brachydactyly in 14 genetically characterized pseudohypoparathyroidism type Ia patients, J Clin Endocrinol Metab 89 (4) (2004) 1650–1655.
[58] T.T. Roberts, S. Khasnavis, D.N. Papaliodis, et al., Spinal cord compression in pseudohypoparathyroidism, Spine J 13 (2013) e15–19.
[59] A.W. Joseph, A.H. Shoemaker, E.L. Germain-Lee, Increased prevalence of carpal tunnel syndrome in Albright hereditary osteodystrophy, J Clin Endocrinol Metab 96 (2011) 2065–2073.
[60] Z. Farfel, E. Friedman, Mental deficiency in pseudohypoparathyroidism type I is associated with Ns-protein deficiency, Ann Intern Med 105 (2) (1986) 197–199.
[61] A.C. Bréhin, C. Colson, S. Maupetit-Méhouas, et al., Loss of methylation at GNAS exon A/B is associated with increased intrauterine growth, J Clin Endocrinol Metab 100 (4) (2015) E623–E631.
[62] N. Richard, A. Molin, N. Coudray, et al., Paternal GNAS mutations lead to severe intrauterine growth retardation (IUGR) and provide evidence for a role of XLas in fetal development, J Clin Endocrinol Metab 98 (9) (2013) E1549–E1556.
[63] L.C. Wilson, M.E. Oude Luttikhuis, P.T. Clayton, et al., Parental origin of Gs alpha gene mutations in Albright's hereditary osteodystrophy, J Med Genet 31 (11) (1994) 835–839.
[64] J.M. Nakamoto, A.T. Sandstrom, A.S. Brickman, et al., Pseudohypoparathyroidism type Ia from maternal but not paternal transmission of a Gsalpha gene mutation, Am J Med Genet 77 (4) (1998) 261–267.
[65] F.M. Elli, L. deSanctis, B. Ceoloni, et al., Pseudohypoparathyroidism type Ia and pseudopseudohypoparathyroidism: the growing spectrum of GNAS inactivating mutations, Hum Mutat 34 (3) (2013) 411–416.
[66] S. Thiele, R. Werner, J. Grötzinger, et al., A positive genotype-phenotype correlation in a large cohort of patients with pseudohypoparathyroidism Type Ia and pseudopseudohypoparathyroidism and 33 newly identified mutations in the GNAS gene, Mol Genet Genomic Med 3 (2) (2015) 111–120.
[67] M.C. Lemos, R.V. Thakker, GNAS mutations in Pseudohypoparathyroidism type 1a and related disorders, Hum Mutat 36 (1) (2015) 11–19.
[68] I. Garin, F.M. Elli, A. Linglart, et al., Novel microdeletions affecting the GNAS locus in pseudohypoparathyroidism: characterization of the underlying mechanisms, J Clin Endocrinol Metab 100 (4) (2015) E681–E687.
[69] T. Mitsui, K. Nagasaki, M. Takagi, et al., A family of pseudohypoparathyroidism type Ia with an 850-kb submicroscopic deletion encompassing the whole GNAS locus, Am J Med Genet A 158A (1) (2012) 261–264.
*[70] J. Liu, D. Litman, M.J. Rosenberg, et al., A GNAS1 imprinting defect in pseudohypoparathyroidism type IB, J Clin Invest 106 (9) (2000) 1167–1174.
[71] M. Bastepe, A.H. Lane, H. Jüppner, Paternal uniparental isodisomy of chromosome 20q–and the resulting changes in GNAS1 methylation–as a plausible cause of pseudohypoparathyroidism, Am J Hum Genet 68 (5) (2001) 1283–1289.
[72] A. Dixit, K.E. Chandler, M. Lever, et al., Pseudohypoparathyroidism type 1b due to paternal uniparental disomy of chromosome 20q, J Clin Endocrinol Metab 98 (1) (2013) E103–E108.
[73] R. Takatani, M. Minagawa, A. Molinaro, 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 79 (2015) 15–20.
[74] M. Bastepe, L.F. Frohlich, G.N. Hendy, 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 112 (8) (2003) 1255–1263.
[75] M. Bastepe, L.F. Frohlich, A. Linglart, et al., Deletion of the NESP55 differentially methylated region causes loss of maternal GNAS imprints and pseudohypoparathyroidism type Ib, Nat Genet 37 (1) (2005) 25–27.
[76] A. Linglart, R.C. Gensure, R.C. Olney, et al., A novel STX16 deletion in autosomal dominant pseudohypoparathyroidism type Ib redefines the boundaries of a cis-acting imprinting control element of GNAS, Am J Hum Genet 76 (2005) 804–814.
[77] S. Chillambhi, S. Turan, D. Hwang, et al., Deletion of the noncoding GNAS antisense transcript causes pseudohypoparathyroidism type Ib and biparental defects of GNAS methylation in cis, J Clin Endocrinol Metab 95 (8) (2010) 3993–4002.
[78] N. Richard, G. Abeguilè, N. Coudray, et al., A new deletion ablating NESP55 causes loss of maternal imprint of A/B GNAS and autosomal dominant pseudohypoparathyroidism type Ib, J Clin Endocrinol Metab 97 (5) (2012) E863–E867.
[79] F.M. Elli, L. de Sanctis, E. Peverelli, et al., Autosomal dominant pseudohypoparathyroidism type Ib: a novel inherited deletion ablating STX16 causes loss of imprinting at the A/B DMR, J Clin Endocrinol Metab 99 (4) (2014) E724–E728.
[80] A. Linglart, H. Fryssira, O. Hiort, et al., PRKAR1A and PDE4D mutations cause acrodysostosis but two distinct syndromes with or without GPCR-signaling hormone resistance, J Clin Endocrinol Metab 97 (12) (2012) E2328–E2338.

[81] D.C. Lynch, D.A. Dyment, L. Huang, et al., Identification of novel mutations confirms PDE4D as a major gene causing acrodysostosis, Hum Mutat 34 (1) (2013) 97–102.
[82] F. Muhn, E. Klopocki, L. Graul-Neumann, et al., Novel mutations of the PRKAR1A gene in patients with acrodysostosis, Clin Genet 84 (6) (2013) 531–538.
[83] A. Lindstrand, G. Grigelioniene, D. Nilsson, et al., Different mutations in PDE4D associated with developmental disorders with mirror phenotypes, J Med Genet 51 (1) (2014) 45–54.
[84] T. Kaname, C.S. Ki, N. Niikawa, et al., Heterozygous mutations in cyclic AMP phosphodiesterase-4D (PDE4D) and protein kinase A (PKA) provide new insights into the molecular pathology of acrodysostosis, Cell Signal 26 (11) (2014) 2446–2459.
[85] N. Li, M. Nie, M. Li, et al., The first mutation identified in a Chinese acrodysostosis patient confirms a p.G289E variation of PRKAR1A causes acrodysostosis, Int J Mol Sci 15 (8) (2014) 13267–13274.
[86] M.A. Aldred, Genetics of pseudohypoparathyroidism types Ia and Ic, J Pediatr Endocrinol Metab 19 (2) (2006) 635–640.
[87] F.S. Kaplan, R. Craver, G.D. MacEwen, et al., Progressive osseous heteroplasia: a distinct developmental disorder of heterotopic ossification two new case reports and follow-up of three previously reported cases, J Bone Joint Surg 74A (1994) 425–436.
[88] M.C. Eddy, S.M. Jan De Beur, S.M. Yandow, et al., Deficiency of the alpha-subunit of the stimulatory G protein and severe extraskeletal ossification, J Bone Miner Res 15 (11) (2000) 2074–2083.
[89] N.S. Adegbite, M. Xu, F.S. Kaplan, et al., Diagnostic and mutational spectrum of progressive osseous heteroplasia (POH) and other forms of GNAS-based heterotopic ossification, Am J Med Genet A 146A (14) (2008) 1788–1796.
[90] D. Barret, N.A. Breslau, M.B. Wax, et al., New form of pseudohypoparathyroidism with abnormal catalytic adenylate cyclase, Am J Physiol 257 (1989) E277–E283.
[91] J.S. Winter, I.A. Hughes, Familial pseudohypoparathyroidism without somatic anomalies, Can Med Assoc J 123 (1986) 26–31.
[92] M.L. Nusynowitz, B. Frame, F.O. Kolb, The spectrum of the hypoparathyroid states: a classification based on physiologic principles, Medicine 55 (1976) 105–119.
[93] J. Liu, B. Erlichman, L.S. Weinstein, The stimulatory G protein α-subunit G s α is imprinted in human thyroid glands: implications for thyroid function in pseudohypoparathyroidism types 1A and 1B, J Clin Endocrinol Metab 88 (2003) 4336–4341.
[94] G. Mantovani, S. Bondioni, A. Linglart, et al., Genetic analysis and evaluation of resistance to thyrotropin and growth hormone-releasing hormone in pseudohypoparathyroidism type Ib, J Clin Endocrinol Metab 92 (2007) 3738–3742.
[95] S. Sano, H. Iwata, K. Matsubara, et al., Growth hormone deficiency in monozygotic twins with autosomal dominant pseudohypoparathyroidism type Ib, Endocr J 62 (6) (2015) 523–529.