From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network

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Abstract

Objective: Disorders caused by impairments in the parathyroid hormone (PTH) signalling pathway are historically classified under the term pseudohypoparathyroidism (PHP), which encompasses rare, related and highly heterogeneous diseases with demonstrated (epi)genetic causes. The actual classification is based on the presence or absence of specific clinical and biochemical signs together with an in vivo response to exogenous PTH and the results of an in vitro assay to measure Gsa protein activity. However, this classification disregards other related diseases such as acrodysostosis (ACRDYS) or progressive osseous heteroplasia (POH), as well as recent findings of clinical and genetic/epigenetic background of the different subtypes. Therefore, the EuroPHP network decided to develop a new classification that encompasses all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway.

Design and methods: Extensive review of the literature was performed. Several meetings were organised to discuss about a new, more effective and accurate way to describe disorders caused by abnormalities of the PTH/PTHrP signalling pathway.

Results and conclusions: After determining the major and minor criteria to be considered for the diagnosis of these disorders, we proposed to group them under the term ‘inactivating PTH/PTHrP signalling disorder’ (iPPSD). This terminology: (i) defines the common mechanism responsible for all diseases; (ii) does not require a confirmed genetic defect; (iii) avoids ambiguous terms like ‘pseudo’ and (iv) eliminates the clinical or molecular overlap
between diseases. We believe that the use of this nomenclature and classification will facilitate the development of rationale and comprehensive international guidelines for the diagnosis and treatment of iPPSDs.

**Introduction**

Pseudohypoparathyroidism (PHP) encompasses a group of rare, related, highly heterogeneous and deeply impairing disorders characterised by end-organ resistance to the action of parathyroid hormone (PTH) and in most instances associated with a demonstrated (epi)genetic component (1, 2, 3). PHP is historically the first hormone-resistance syndrome described by Albright et al. (4).

A better understanding of the PHP pathophysiology followed the identification of the PTH receptor (PTH1R) and its signal transduction pathway (**Fig. 1**) (5, 6). PTH1R, through its activation by two ligands, the PTH and the PTH-related peptide (PTHrP), regulates skeletal development, bone turnover and mineral ion homeostasis. In the kidney, binding of PTH to PTH1R stimulates the production of 1,25-dihydroxy vitamin D3, and inhibits phosphate reabsorption in the proximal tubule, while it increases calcium reabsorption in the distal nephron. In the growth plate,
PTHRP promotes endochondral ossification, by binding to PTH1R (7).

The Blomstrand chondrodysplasia (OMIM #215045), a lethal form of dwarfism (8), was the first disorder associated with biallelic loss-of-function mutations of the PTH1R gene (9). Subsequently, one report has described a milder phenotype in living children affected with Eiken disease (OMIM #600002), short stature, elevated PTH and mutations of PTH1R (10, 11).

A defect in the response of the proximal renal tubule to PTH is the hallmark of all forms of PHP. It manifests as hypocalcaemia, hyperphosphataemia and elevated circulating levels of PTH in the absence of vitamin D deficiency (5, 7, 12).

PTH receptor complexes with the stimulatory G protein (Gsa), leading to cAMP formation. Renal tubular response to exogenously administered PTH through measurement of serum and urinary cAMP levels permits the differentiation of PHP type 1 (PHP1), in which a blunted cAMP response is observed, from PHP type 2 (PHP2), where cAMP increase is conserved but the phosphaturic response is deficient (13). To date, only a handful of PHP2 cases have been reported, and the molecular defect responsible for this variant is still unknown. It has also been hypothesised that PHP2 could either be an acquired defect secondary to vitamin D deficiency (14), as calcium and vitamin D supplementation resulted in normalisation of the phosphaturic response to PTH in some patients (14, 15), or due to defects downstream the Gsa protein, as seen in patients with acродysostosis type 1 (ACRDYS1) (16).

In 1980, deficiency in the Gsa protein activity in erythrocytes from patients affected with PHP1 was demonstrated in vitro (17, 18). For years, this bioassay allowed the diagnosis of PHP, and contributed to PHP subclassification (see below).

PHP type 1 (PHP1) is further subdivided based on the presence (PHP1A and PHPIC; OMIM #103580 and #612462 respectively) (6, 17, 18, 19) or absence (PHP1B; OMIM #603233) (6, 20) of Albright hereditary osteodystrophy (AHO) (Table 1). AHO is a clinical entity initially described together with PHP in 1942, which encompasses heterogeneous clinical findings such as brachydactyly, rounded face, short stature, stocky build and subcutaneous ossifications (4, 21, 22). Additional features that may not directly relate to AHO, yet extensively associated with PHP1A individuals, include obesity, varying degrees of intellectual disability and resistance to several hormones, including TSH, GHRH and calcitonin (23, 24, 25, 26, 27, 28). The subcategory of PHP1C has all the characteristics of PHP1A, except that Gsa activity in erythrocytes was found comparable to controls (29, 30).

Interestingly, patients showing the physical features of AHO without any evidence of PTH resistance were also described by Albright et al. (21) 10 years after their first report of PHP. This new syndrome, named pseudopseudohypoparathyroidism (PPHP; OMIM #612463) may be present either in kindreds with PHP or as an isolated defect. It is possible that the 'bone phenotype' observed in AHO is largely mediated by the resistance to PTHrP at the growth plate during foetal and postnatal growth (31).

In 1990, the first heterozygous inactivating mutation in the gene coding for Gsa (GNAS), responsible for PHP1A, was described (32). Since then, several Gsa-coding mutations have been identified in all of its 13 exons with different frequency, with a detection rate of about 70% (33, 34, 35, 36, 37, 38, 39). Cases of deletions of 20q, including part or the whole GNAS gene, and an inversion at GNAS have been recently reported (40, 41, 42, 43, 44). Remarkably, similar mutations when paternally inherited, or occurring de novo on the paternal allele of GNAS may lead to PPHP or to progressive osseous heteroplasia (POH, OMIM #166350), a disorder characterised by heterotopic ossifications expanding into deep muscles and connective tissues (45, 46).

GNAS is a locus encoding several transcripts through alternative splicing. In most tissues, except for Gsa, the GNAS transcripts are of monoallelic origin due to the control of their expression by parent-specific differentially methylated regions (DMRs) (Fig. 2) (47). In thyroid, pituitary gland and most likely in the proximal tubule (36), Gsa is predominantly expressed from the maternal allele through a yet unexplained mechanism (48, 49). In the early 2000, the molecular defect of PHP1B was characterised. The most consistent defect common to all PHP1B patients is a paternal-specific pattern of cytosine methylation within the maternal GNAS A/B: transcriptional start site (TSS)-DMR (GNAS A/B:TSS-DMR; previously known as exon A/B or 1A), which could lead to a decreased expression of Gsa in the renal proximal tubules, hence PTH resistance (50). Fifteen to twenty percent of the PHP1B cases present familial history with an autosomal dominant mode of inheritance (AD-PHP1B) through the maternal lineage. Most AD-PHP1B show loss of imprinting (LOI) limited to the GNAS A/B:TSS-DMR (more precisely a loss of methylation (LOM)) associated with deletions on the maternal allele of cis-acting control elements within STX16 or NESP55 (51, 52, 53, 54, 55), although other
### Table 1  Former classification of PHP along with the other disorders affecting the PTH/PTHrP signalling pathway; note the overlap of phenotypes and molecular defects of the patients. Diseases included in the former classification are PHP1A, PHP1B, PHP1C and PPHP.

<table>
<thead>
<tr>
<th></th>
<th>PHP1A</th>
<th>PHP1C</th>
<th>PHP1B</th>
<th>BWS</th>
<th>No AHO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>AHO</td>
<td>AHO</td>
<td>No AHO</td>
<td>Mental retardation reported in 2 patients, lambdoid synostosis, early-onset obesity, macrocephaly</td>
<td>No AHO</td>
</tr>
<tr>
<td>Obesity</td>
<td>Subcutaneous</td>
<td>No obesity</td>
<td>Obesity may be present</td>
<td>No obesity</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Subcutaneous</td>
<td>No cognitive impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ossifications</td>
<td>Subcutaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hormone resistance</strong></td>
<td>Resistance to PTH, TSH, GHRH, calcitonin, epinephrine, glucagon and gonadotropins</td>
<td>Resistance to PTH, TSH, epinephrine and gonadotropins</td>
<td>PTH resistance, ± TSH resistance</td>
<td>PTH resistance, ± TSH resistance</td>
<td></td>
</tr>
<tr>
<td>Resistance to PTH, TSH, GHRH, calcitonin, epinephrine, glucagon and gonadotropins</td>
<td>Significantly below controls</td>
<td>Similar to controls</td>
<td>Mildly decreased when compared with controls</td>
<td>Mildly decreased when compared with controls</td>
<td>Similar to controls</td>
</tr>
<tr>
<td><strong>In vitro activity of Gsa</strong></td>
<td>Significantly below controls</td>
<td>Similar to controls</td>
<td>Mildly decreased when compared with controls</td>
<td>All activities are increased significantly compared with controls</td>
<td></td>
</tr>
<tr>
<td><strong>LOI at the GNAS DMRs</strong></td>
<td>Heterozygous mutation in the coding sequence of GNAS (maternal allele)</td>
<td>Heterozygous mutation in the coding sequence of GNAS (maternal allele)</td>
<td>Heterozygous mutation in the coding sequence of GNAS (p.Ile382del) (maternal allele)</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic lesion</strong></td>
<td>Heterozygous mutation in the coding sequence of GNAS (maternal allele)</td>
<td>Heterozygous mutation in the coding sequence of GNAS (maternal allele)</td>
<td>Heterozygous mutation in the coding sequence of GNAS (p.Ile382del) (maternal allele)</td>
<td>Unknown</td>
<td>Maternal deletion of NESP and/or AS or duplication of GNAS</td>
</tr>
<tr>
<td>References</td>
<td>(32, 33, 34, 35, 36, 37, 38, 39)</td>
<td>(112)</td>
<td>(50, 51, 52, 113)</td>
<td>(50, 51, 63, 74)</td>
<td>(59, 60, 61, 62, 63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(114)</td>
<td>(53, 54, 58, 115)</td>
<td></td>
</tr>
</tbody>
</table>
## References

Genetic lesion

LOI at the

In vitro

Clinical

overlap of phenotypes and molecular defects of the patients. Diseases included in the former classification are PHP1A, PHP1B, GNAS Gsa resistance presentation DMRs Former classification of PHP along with the other disorders affecting the PTH/PTHrP signalling pathway; note the

Significantly Resistance to Subcutaneous Cognitive Obesity AHO

PHP1A

36 allele) GNAS sequence of mutation in below controls gonadotropins glucagon and epinephrine, calcitonin, GHRH, PTH, TSH, ossifications impairment

33 37

34 38 39 (Heterozygous allele) (maternal p.Y391X, all in p.E392X, (p.E392K, GNAS sequence of mutation in controls compared with decreased resistance ± TSH and/or obesity subcutaneous (brachydactyly, patients

Recurrent 3-kb LOM at the

Mildly STX16 or 4.2-kb A/B:TSS-DMR controls with decreased when decreased ± TSH and/or obesity subcutaneous (brachydactyly, patients

51

51 63

MLID

European Journal of Endocrinology

115

of duplication or AS or NESP and/ deletion of

54 58

European Journal of Endocrinology

175:6

S Thiele and others

iPPSD, a novel classification for PHP

100

78

77

14

16 82 90, 91, 117, 118, 119

92

9, 11

10

34, 36, 44, (34, 36, 44, 100) (77) (39, 45, 46, 79, 80) (116) (14) (16, 82, 90, 91, 117, 118, 119) (90, 91) (92) (9, 11) (10)

AHO, Albright’s hereditary osteodystrophy; BWS, Beckwith–Wiedemann syndrome; MLID, multilocus imprinting defect; NA, not available; PHP, pseudohypoparathyroidism; PPHP, pseudopseudohypoparathyroidism.

### Table

<table>
<thead>
<tr>
<th></th>
<th>PPHP</th>
<th>POH</th>
<th>2q37.3 Deletion Syndrome</th>
<th>PHP2</th>
<th>Acrodysostosis</th>
<th>Blomstrand dysplasia</th>
<th>Eiken disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHO</td>
<td>AHO</td>
<td>Subcutaneous ossifications</td>
<td>Hypocalcaemia, osteomalacia</td>
<td>Severe AHO</td>
<td>AHO</td>
<td>Severe AHO</td>
<td>Lethal dwarfism</td>
</tr>
<tr>
<td>Subcutaneous ossifications</td>
<td>Subcutaneous ossifications</td>
<td>Cognitive impairment</td>
<td>PTH resistance</td>
<td>PTH resistance, and TSH in some patients</td>
<td>Hypertension</td>
<td>Short stature</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Mild</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Elevated PTH in one patient</td>
<td></td>
</tr>
<tr>
<td>Significantly below controls</td>
<td>Significantly below controls</td>
<td>None</td>
<td>Deletion of the 2q37.3 chromosomal region including HDAC4</td>
<td>Heterozygous mutation in the coding sequence of PRKAR1A or PDE4D</td>
<td>Heterozygous mutation in the coding sequence of PRKAR1A</td>
<td>Biallelic inactivating mutation in the coding sequence of PTH1R</td>
<td>Biallelic inactivating mutation in the coding sequence of PTH1R</td>
</tr>
</tbody>
</table>

34, 36, 44, 100 (34, 36, 44, 100) (77) (39, 45, 46, 79, 80) (116) (14) (16, 82, 90, 91, 117, 118, 119) (90, 91) (92) (9, 11) (10)
maternally inherited deletions have been identified affecting all four DMRs (GNAS-NESP:TSS-DMR, GNAS-AS1:TSS-DMR, GNAS-XL:Ex1-DMR and GNAS A/B:TSS-DMR) (56, 57, 58).

The remaining cases of PHP1B are sporadic. They present with broad LOI at GNAS, including the GNAS A/B:TSS-DMR. The molecular basis of this broad LOI is yet to be identified, with an exception of less than 10% of the patients who are affected by paternal complete or segmental uniparental disomy (UPD) of the chromosome 20, comprising the GNAS locus (59, 60, 61, 62, 63).

To summarise, the existing classification of PHP (Table 1) is based on the following criteria: (i) presence or absence of AHO differentiates PHP1A/PHP1C from PHP1B; (ii) presence or absence of hormonal resistance differentiates PHP1 from PPHP; (iii) in vivo response to exogenous PTH as for nephrogenic cAMP synthesis and phosphaturia separates PHP1 from PHP2 and (iv) in vitro assay measuring the Gsa protein activity from erythrocyte membranes differentiates between PHP1A and PHP1C.

As described above, the existing PHP classification does not include molecular defect as a criterion and fails to stratify PHP and AHO as well as include conditions such as acrodysostosis, POH and PTH1R-related chondrodysplasia. In this manuscript, we therefore propose to review the rationale of this nomenclature and recommend a novel classification for disorders impairing the PTH/PTHrP signalling pathway.

Methodology

The EuroPHP network met on three different occasions (October 2014, May 2015, November 2015) to discuss and agree on a novel classification. The aims of these meetings were (i) to identify the limitations in the current PHP classification; (ii) to formulate mandatory criteria for the new classification; (iii) to propose a comprehensive definition gathering all the disorders; (iv) to analyse the classifications used in other genetic/epigenetic conditions and (v) to generate a novel classification. The methodology comprised a thorough review of the current literature to facilitate comparison and form basis for the proposal of a new classification.

We have carefully considered a series of classifications proposed for various rare genetic/epigenetic disorders, including the reporting manuscripts that were taken into consideration for the design of a novel classification (summarised in Table 2). In brief, methodologies were similar. A group of experts in the field identified the deficiencies in the existing classification/terminology and the need for an update. Subsequently, agreement on a novel terminology and classification was reached and reported (64, 65, 66, 67, 68, 69, 70).

Challenges and limitations of the current classification

Recent clinical and molecular data gathered for these complex disorders have questioned the distinction...
of the different PHP and AHO subtypes in the existing classification (Table 1). We have selected the following limits of the current classification:

1. In a subset of patients with PHP1A and varying degree of AHO, LOI of GNAS identical to that of PHP1B has been reported, suggesting a molecular and clinical overlap between the two subtypes (71), further confirmed (72, 73, 74, 75).

2. PHP1B patients present with a moderate reduction in Gsa activity in erythrocyte membranes, reminiscent – yet less severe – to that observed in patients with PHP1A and PPHP (76).

3. Recently, mild resistance to PTH was described in patients affected with PPHP, carrying a paternal GNAS mutation (77), showing that the hormonal resistance is not only associated with maternally inherited GNAS mutations.

4. Different molecular defects have been identified in patients with PHP1C, i.e. LOI at GNAS and four loss-of-function mutations in the GNAS carboxyl-terminus leading to a conserved adenylyl cyclase receptor-independent activation but disrupted receptor-mediated activation (29, 30, 78).

5. Paternal GNAS mutations associated with progressive osseous heteroplasia are usually truncating mutations (79), yet they are identical to those found in families with PHP1A and/or PPHP (45). Also noteworthy is that a fraction of POH patients exhibits some of the typical AHO features and, conversely, some PHP1A patients carrying mutations on the maternal allele present with progressive deepening heterotropic ossifications. The hypothesis that POH should be considered as a form of PPHP is, therefore, debated (80, 81).

6. Heterozygous mutations in PRKAR1A – coding for the regulatory subunit of the protein kinase A (PKA) – and PDE4D – coding for phosphodiesterase type 4 – have been found in patients with acrodysostosis (16, 82, 83). Acrodysostosis refers to a heterogeneous group of rare diseases characterised by skeletal dysplasia and characteristic features, including brachyactyly, facial dysmorphism and, in some cases, mental retardation (84, 85, 86, 87, 88). Acrodysostosis differs from PHP by more generalised osseous abnormalities (87, 89). Resistance to PTH and/or TSH is present in about 60–70% of acrodysostosis patients with a PRKAR1A mutation, while, in case of a PDE4D mutation, such hormone resistances are found only in a smaller

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Table 2 Nonexhaustive review of classifications used in other conditions.

<table>
<thead>
<tr>
<th>Primary immunodeficiency diseases (69)</th>
<th>Skeletal dysplasia (66)</th>
<th>Autosomal dominant tubule interstitial kidney disease (67)</th>
<th>Endocrine diseases (68)</th>
<th>Diabetes mellitus (MODY) (70)</th>
<th>Osteogenesis imperfecta (64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-days meeting</td>
<td>Meeting, extensive review of the literature, and circulation of drafts of the manuscript</td>
<td>Meeting, agreement on the manuscript</td>
<td>Literature review</td>
<td>Meetings, agreement on the manuscript</td>
<td>Literature review</td>
</tr>
<tr>
<td>Groups of diseases according to the most fundamental defect presented as a table format</td>
<td>Groups of diseases defined by molecular, biochemical and/or radiographic criteria</td>
<td>Agreement on a novel name: ADTKD</td>
<td>Classification based on the underlying genetic defect: ADTKD-gene</td>
<td>Groups of diabetes by organ</td>
<td>Phenotypes on evolution, radiology, clinics and genetics</td>
</tr>
<tr>
<td>Allows a practical clinical framework for PID diagnosis</td>
<td>Disorders are caused by disturbances in related metabolic pathways or gene networks, Sheer number of conditions included</td>
<td>Provide information on the disease</td>
<td>Classification based on the underlying genetic defect: ADTKD-gene</td>
<td>Provide information on the disease mechanism</td>
<td>Provide information on the disease mechanism and genetics</td>
</tr>
<tr>
<td>The complexities of these conditions cannot easily be captured in the limited table format</td>
<td>The ‘hybrid’ nature of the classification, not clinical, not molecular</td>
<td>Use in communication with patients may not be easy</td>
<td>Allow numbering of new diabetes after identification of new genes for MODY (MODY1, MODY2, MODY3, MODY4...)</td>
<td>Very large groups of disease (type 2 diabetes for example)</td>
<td>Confusing as one causing gene may be in different categories</td>
</tr>
</tbody>
</table>
subset of 10–20%. Interestingly, few patients bearing a PRKAR1A mutation have been described in patients with a phenotype indistinguishable from PHP1A (90, 91).

7. Heterozygous mutations in PDE3A have been identified in patients affected with hypertension and brachydactyly type E (hypertension and brachydactyly syndrome (HTNB): OMIM #112410) (92).

8. Disorders associated with an impaired function of PTH1R, i.e. the Blomstrand and Eiken skeletal dysplasia, are currently not included in the classification.

Over the past two decades, it became obvious that clinical features such as AHO or in vitro assays such as Gsa bioactivity fail to differentiate between PHP subtypes. In addition, mutations of genes different from GNAS have been shown to lead to PTH and/or PTHrP resistance and GNAS mutations might trigger diseases different from PHP/PPHP (i.e. POH). These disorders are not encompassed by the current classification system.

For all these reasons, different independent studies from the authors of the present paper, as well as the ‘EuroPHP network’ concluded and agreed that a uniform terminology is required to create a functional working classification that reflects the current knowledge of the diseases (29, 93, 94).

**Terminology**

We propose the term of ‘inactivating PTH/PTHrP signalling disorder’, abbreviated as iPPSD, which encompass all disorders related to this pathway. We also propose that numbering will allow for both clinical features and molecular and genetic findings to be included. The advantages of this terminology are as follows: (i) it describes the common mechanism responsible for the diseases; (ii) it does not require a confirmed genetic defect; (iii) it avoids the ambiguous term like ‘pseudo’; (iv) it eliminates the clinical or molecular overlap between diseases and (v) it is flexible to incorporate new evolving information.

We recognise that the nomenclature ‘inactivating PTH/PTHrP signalling disorder’ might be initially difficult for patients and caregivers to remember. It would, therefore, be helpful to rely on the abbreviation iPPSD. Equally, the former terms ‘pseudohypoparathyroidism’ and ‘pseudopseudohypoparathyroidism’ were also long and challenging to use for communication. PTH/PTHrP-specific pathway was deliberately included in the name of the classification to avoid the misperception with disorders resulting from the inactivation of G protein-coupled receptors, i.e. inactivating mutations in the TSH receptor or in the FSH receptor. All nomenclature based on the cAMP signalling were carefully considered and rejected due to their generic nature.

**Identification of mandatory criteria for the new classification**

Basis for the newly proposed classification of iPPSD are:

- to provide patients with an unambiguous diagnosis;
- to base nomenclature on pathophysiology, i.e. the PTH1R/Gsa/cAMP/PKA pathway, and a standardised diagnostic pathway;
- to formulate basis to develop new therapeutic approaches;
- to be sufficiently flexible and adaptable to include emerging clinical and molecular information;
- to be simple and usable for the caregivers.

It is, therefore, of significant importance to define the category of iPPSD a patient belongs to, based on the characterisation of clinical/biochemical criteria, to facilitate a definitive diagnosis and, if possible, through molecular analysis, a more specific denomination within the classification.

We suggest three key clinical features as major criteria for the diagnosis of iPPSD. The proposed major criteria have minimum or no overlap with other conditions due to different mechanisms (Table 3, especially for the differential diagnoses).

We also propose a list of minor criteria that are associated with iPPSD. These are less specific to iPPSD compared with major criteria and can occur in other clinical conditions. Therefore, minor criteria need to be combined with one or more major criteria to establish the diagnosis of iPPSD.

**Major criteria**

**PTH resistance**

The hallmark of inactivating PTH/PTHrP signalling disorders is the resistance of the renal proximal tubule to the action of PTH. All genetic defects leading to a deficient PTH1R signalling in the kidney will, therefore, be named iPPSD.

**Ectopic ossifications**

Ectopic ossifications are superficial, subcutaneous nodules, defined as ectopic bone formation in the adipose or dermal tissue. Progressive osseous heterotopic calcifications often begin in the dermal and subcutaneous tissues and later
progress to the deeper tissues, such as muscles and tendons. In children, ectopic ossifications are highly suggestive of an inactivating GNAS mutation, i.e. iPPSD.

**Brachydactyly**

Brachydactyly refers to shortening of fingers, toes or both. Brachydactyly type E (BDE, OMIM #113300) encompasses variable shortening of the metacarpals/metatarsals, often with the involvement of phalanges (Fig. 3). It can either present in isolation or as part of a genetic disorder, most of which are included among iPPSD (95).

Brachydactyly can be challenging to identify in early childhood, and tends to become more evident during early puberty. Brachydactyly can be overlooked when all bones are short as in acrodysostosis since early childhood.

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**Table 3**: Definition of major and minor criteria for iPPSD and differential diagnoses.

<table>
<thead>
<tr>
<th>I. Major criteria</th>
<th>Assessment</th>
<th>Differential diagnosis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PTH resistance</td>
<td>Ionized calcium, total calcium phosphate, Magnesium, PTH, Vitamin D (25OHD), Creatinine, Urinary calcium, Urinary phosphate, PTH infusion test in challenging cases</td>
<td>Normocalcaemic hyperparathyroidism, Renal failure, Vitamin D deficiency or any kind of secondary hyperparathyroidism</td>
<td>(16)</td>
</tr>
<tr>
<td>2. Ectopic ossification</td>
<td>Detailed physical exam, X-rays</td>
<td>Fibrodysplasia ossificans progressiva (FOP, OMIM #135100), post-traumatic osteoma cutis</td>
<td></td>
</tr>
<tr>
<td>3. Brachydactyly type E (comprises the IV)</td>
<td>Clinical inspection (fist), hand and feet X-rays</td>
<td>Turner syndrome, tricho-rhino-phalangeal syndrome (TRPS), TRPS I, (OMIM #190350), TRPS-II (OMIM #150230) and TRPS-III, (OMIM #190351)</td>
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<th>II. Minor criteria</th>
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<td>TSH, T4l, antibodies, imaging</td>
<td>Mutations in the TSH receptor</td>
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<td>2. Other hormonal resistances</td>
<td>IGF-1 (GH stimulation test if necessary), calcitonin, LH, FSH, GnRH test</td>
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<td>3. Motor and cognitive retardation or impairment</td>
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<td>4. Intrauterine and postnatal growth retardation</td>
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<td></td>
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<td>5. Obesity/overweight</td>
<td>Weight SDS, BMI percentile, BMI z-score</td>
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<td>6. Flat nasal bridge and/or maxillar hypoplasia and/or round face</td>
<td>Clinical inspection</td>
<td></td>
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**iPPSD clinical diagnosis**

(a) Presence of one major criteria, either number 1 or 2;
(b) Presence of major criteria number 3 and at least 2 minor criteria

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*US in adults with hypothyroidism and no evidence for autoimmunity; thyroid imaging through thyroid scintigraphy and US in neonates diagnosed through screening for congenital hypothyroidism; †Minor criteria are nonspecific (obesity/cognitive impairment); for instance, the association of BDE+obesity or BDE+cognitive impairment would not be relevant for our classification. By raising the number of minor criteria from 1 to 2, we will reduce the risk of overdiagnosing patients with iPPSD.
While PTH resistance and ectopic ossifications are considered major criteria for iPPSD, brachydactyly is less specific and should, therefore, be combined with at least one major or two minor criteria to trigger the diagnosis of iPPSD.

**Minor criteria**

**Thyroid-stimulating hormone (TSH) resistance**

In iPPSD, TSH resistance is often mild and characterised by elevated TSH levels associated with free thyroxine ($T_4$) levels in a normal or low-normal reference range. This occurs in the absence of goitre and markers of autoimmune disease (26, 27). TSH resistance can sometimes be the first detected sign of iPPSD, especially in countries where screening for congenital hypothyroidism is routinely performed (96).

**Other hormone resistances**

Very few other hormone resistances have been demonstrated so far. Resistance to growth hormone-releasing hormone (GHRH), leading to growth hormone deficiency, is the most frequent additional resistance found in PHP1A, affecting as many as 60% of patients (97, 98, 99). Calcitonin resistance has been described without clinical features in patients affected with PHP1A (27). Elevated follicular-stimulating hormone (FSH) and luteinizing hormone (LH) levels were reported both by us and Namnoum et al. (78, 100). Glucagon and adrenaline resistances were demonstrated in patients...
with features of PHP and low Gsa bioactivity through in vivo testing (6, 101).

Motor and cognitive retardation or impairment

Psychomotor and cognitive alterations have been described in about 40 to 70% of the patients with a maternal coding mutation of GNAS (25, 34), as well as in some patients affected with acrodysostosis (83, 85, 86). Psychiatric manifestations have also been reported in these patients (102). Patients with paternal mutations of GNAS or epigenetic modifications of the GNAS DMRs seem unaffected (25, 63).

Intrauterine and postnatal growth retardation

Intrauterine growth retardation (IUGR) has been frequently observed in both maternal and paternal inherited inactivating GNAS coding mutations. However, IUGR is more pronounced in patients harbouring mutations on the paternal GNAS allele, mainly when affecting GNAS exon 2–13 mutations, compared with patients with GNAS exon 1/intron 1 mutations (103). IUGR has also been described in acrodysostosis with mutations in PRKAR1A or PDE4D, and in patients with mutations in PDE3A (16, 82, 90, 92). A LOI at the maternal GNAS A/B: TSS-DMR has been associated with increased intrauterine growth (104).

Postnatal growth retardation is a frequent sign in PHP1A and acrodysostosis. Growth hormone deficiency and premature closure of the epiphysis result in short stature (16, 82, 97, 105). Growth retardation has also been observed in PHP1B, although only in exceptional cases (71, 74), and in patients with Eiken dysplasia (10).

Obesity/overweight

Obesity or overweight may be the most nonspecific minor sign; however, it occurs very frequently in disorders with an impaired PTH/PTHrP signalling pathway and may help to differentiate between the different subtypes. Growth hormone deficiency, impaired lipolytic response of adrenaline (101) or decreased resting energy expenditure (106) contribute to the development of obesity in patients with mutations on the maternal allele of GNAS (23, 107). Obesity is also a frequent feature in patients affected with acrodysostosis (16, 90, 108).

Flat nasal bridge and/or maxillary hypoplasia and/or round face

Elements of facial dysmorphism have been associated with acrodysostosis (flat nasal bridge and/or maxillary hypoplasia) or with PHP1A (round face) (4, 86).

Diagnosis of iPPSD

We propose that a minimum of one of the major criteria is mandatory for the clinical diagnosis of iPPSD. PTH resistance or ectopic ossifications may lead to the diagnosis of iPPSD with or without the presence of minor criteria. However, brachydactyly type E (BDE) should be associated with at least one major or two minor criteria to suggest iPPSD, as it is a common feature of several other diseases and syndromes (Table 3).

The known molecular causes of PTH/PTHrP signalling disorders are:

- inactivating mutations of PTH1R;
- inactivating heterozygous mutations in the coding sequence of GNAS-Gsa;
- methylation changes of the DMRs of GNAS caused by
  - deletions or duplications at ICRs (STX16; NESP; GNAS-AS1);
  - paternal UPD of chromosome 20q;
  - unknown mechanism(s);
- heterozygous mutations of PRKAR1A;
- heterozygous mutations of PDE4D;
- heterozygous mutations of PDE3A.

In contrast to the former diagnostic classification based solely on the phenotype, once iPPSD has been identified (using criteria described Table 3), we propose to further subtype iPPSD based on the underlying molecular (epi) genetic defect. Therefore, the term iPPSD will refer to the pathophysiology of the PTH/PTHrP signalling abnormalities, while the number will refer to the underlying molecular mechanism (responsible for the pathology). We have numbered iPPSD subtypes starting with PTH1R mutations.

The novel classification of iPPSD

The European PHP network proposes the following classification (Fig. 4):

- iPPSD: clinical/biochemical diagnosis based on the major/minor criteria as defined above, in the absence of genetic investigation;
- iPPSD1: loss-of-function mutation in PTH1R;
- iPPSD2: loss-of-function mutation in Gsa;
iPPSD3: methylation change(s) at one or more GNAS DMRs, associated with or without a genetic (deletion) or cytogenetic (UPD) defect;

- iPPSD4: PRKAR1A mutation;
- iPPSD5: PDE4D mutation;
- iPPSD6: PDE3A mutation;
- iPPSDx: lack of genetic/epigenetic defect identified following molecular investigation of known genes described above;
- iPPSDn+1: the identification of a novel gene/molecular defect will lead to a disease named iPPSD7, then 8 and so on.

iPPSD3 encompasses all disorders associated with changes in the methylation patterns of the DMRs of GNAS, including UPD(20)pat and deletion within STX16, NESP etc. Of most significance is the common mechanism shared by these patients, i.e. the LOM at the GNAS A/B:TSS-DMR. Grouping them under iPPSD3 highlights this common mechanism. Secondly, we anticipated the difficulties in integrating the multiplicity of the epigenetic mechanisms within the classification system as this adds no further diagnostic value. However, the further specification of the epigenetic defect can remain part of a private exchange between the molecular laboratory, the patient and his/her physician.

We recommend the use of Arabic numerals to avoid the confusion with letters (II with the number 11 for example).

The advantages of this new nomenclature are: (i) it stratifies the disorders into clusters caused by the same mechanism; (ii) it is flexible and open to accommodate new defects to be discovered in the future and (iii) it simplifies the concept of the overlapping disorders under a single umbrella.

This classification, however, bears some limitations. We deliberately did not include the parental origin of the genetic/epigenetic defect, although some iPPSD are imprinting disorders – namely iPPSD2 and iPPSD3 – and their phenotypic expression depends on their parental inheritance. The main reason behind this is the association of PTH resistance and POH with both maternal and paternal inactivating GNAS mutations. Therefore, the mechanism of the two allelic GNAS mutations can be considered alike. However, in daily practice, the parental origin of the GNAS defect should be considered, particularly for genetic counselling. In fact, AHO and multiple hormone resistance including PTH resistance are largely associated with maternal GNAS coding defects, whereas isolated AHO and/or POH are more often associated with paternal GNAS coding defects.

Figure 4
Schematic representation of the new classification proposed by the European PHP network. According to the suggested new classification Blomstrand and Eiken chondrodysplasia, PHP type 1 and 2, PHP/AHO/POH and acrodysostosis clinically/biochemically diagnosed without genetic investigation are named iPPSD; Blomstrand and Eiken chondrodysplasia due to PTHR1-inactivating mutations are named iPPSD1; PHP1A, PHP1C, PPHP and POH clinically diagnosed and characterised by Gsa-inactivating mutations are termed iPPSD2; PHP1B clinically diagnosed and due to methylation changes at the GNAS DMRs is classified as iPPSD3; in the presence of acrodysostosis type 1 or PRKAR1A mutations, the disease is classified as iPPSD4. Acrodysostosis type 2 or PDE4D mutations are termed iPPSD5; PDE3A mutations are categorised as iPPSD6; patients lacking genetic or epigenetic defects at the known genes fall under the category of iPPSDx; any newly discovered genetic/molecular defects will be labelled as iPPSDn+1.
Another limitation of this classification is the inability to subclassify individuals with a pure clinical suspicion of iPPSD and lack of complete (epi)genetic testing. While such patients cannot be classified as iPPSxD or with a specific number, we recommend that they are classified as iPPSD.

The inclusion of the disorders involving the two main ligands of the PTH1R, i.e. hypoparathyroidism (109) and brachydactyly type E with short stature (mutations in PTHLH the gene encoding PTHrP (110, 111)) to the classification may be argued. However, we decided to exclude them due to several other issues such as (i) their different biochemical pattern including low levels of PTH responsible for hypoparathyroidism; (ii) the dramatic difference in the therapy of hypoparathyroidism and defects in PTH1R signalling respectively and (iii) the difference in research goals in the two disease groups.

Perspectives

We believe that the use of the new nomenclature will facilitate a more straightforward approach to the diagnosis of iPPSD, increase awareness of the red-flag signs of PTH resistance, ectopic ossifications and brachydactyly type E. It would allow for the classification of patients into local catalogues used by the different healthcare organisations in a more homogenous way, and enable future observational and research studies in the field.

We strongly believe that too many denominations for similar diseases and patients with phenocopies (PHP, PPHP, POH, ACRDYS, TRPS, BDE, AHO) have diluted and dispersed research advance, adding undue complexity to the causative mechanism and proved challenging for the experts in building a global research network in the field.

Regular use of the classification in daily practice or for scientific purposes will allow appropriate amendments in the best interest of the patients.

While producing this novel nomenclature and classification, we have identified the need to (i) disseminate this alternative classification to be positively enriched by the clinical and scientific community; (ii) validate the major/minor criteria in a series of patients affected by different iPPSxDs and (iii) develop international guidelines for the diagnosis and treatment of the iPPSxDs in the near future.

Declaration of interest

All the authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.


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iPPSD, a novel classification for PHP


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