Current Perspectives on Pseudohypoparathyroidism-New Classification

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Pseudohypoparathyroidism (PHP) is a rare disease caused by impairments in the parathyroid hormone (PTH) signaling pathway and was first described by Fuller Albright and colleagues in 1942 (1). The current classification is based on the presence or absence of Albright hereditary osteodystrophy (AHO) characterized by brachydactyly, rounded face, short stature, obesity, and subcutaneous ossifications and, the presence or absence of PTH or multiple hormonal resistance together with an in vivo response to exogenous PTH and the results of an in vitro assay to measure Gsα activity (2). However, this classification do not include recently described other related diseases like acrodysostosis (Acro) or progressive osseous heteroplasia (POH), as well as clinical and genetic/epigenetic background of the different subtypes.

The *GNAS* complex locus encodes the alpha-subunit of the stimulatory G protein (Gsα), a ubiquitous signaling protein mediating the actions of many hormones, and gives rise to other gene products, most of which exhibit exclusively monoallelic expression. Although, Gsα is expressed biallelically in most tissues, paternal Gsα expression is silenced in some tissues with poorly understood mechanisms that involve differential methylation within *GNAS* (2).

Current classification of the disease is given in the Table 1 below:

However, this classification could not include all features of the disease like in the following cases: PHP1b patients show mild TSH resistance and AHO features in several cases have and a recent study showed mildly diminished erythrocyte Gsα activity (3,4). In a subset of patients with PHP1a, also shows methylation defects in *GNAS* identical to that of PHP1b.

Additionally, mild resistance to PTH was described in patients having a paternal *GNAS* mutation, known as pseudopseudohypoparathyroidism (5), demonstrating that the hormonal resistance is not restricted to the maternally inherited mutations.

In this description of the disease, patients with methylation defects having AHO feature can be classified as PHP1c (6).

Additionally, two other diseases are caused by the defects involved in signaling pathway of Gsα, acrodysostosis caused by heterozygous mutations in PRKAR1A and PDE4D (7,8) and hypertension and brachydactyly syndrome (HTNB) caused by heterozygous mutations in PDE3A have been identified (9).

For all these reasons, the EuroPHP network suggested a new classification that encompasses all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway and proposed the name inactivating PTH/PTHrP signalling disorder (iPPSD) with the following classification (10).

iPPSD1: Loss of function mutation in PTH1R

iPPSD2: Loss of function mutation in Gsα coding exons

iPPSD3: Methylation change(s) at one or more *GNAS*, differentially methylated regions associated with or without a genetic (deletion) or cytogenetic (UPD) defect,

iPPSD4: PRKAR1A mutations

iPPSD5: PDE4D mutations

iPPSD6: PDE3A mutations

iPPSDx: Lack of genetic/epigenetic defect identified following molecular investigation of known genes described above.

As a conclusion, the new classification will cover the recent findings and lead to a more straightforward definition of the disease.

Table 1. Current classification of the disease

	Defect	Parental origin	PTH resistance	Additional hormone resistance	AHO features	Urinary cAMP and phosphate to PTH	Erythrocyte Gsα activity
PHP1a	Gsα coding mutation	Maternal	Yes	Yes	Yes	Blunted	Reduced
PHP1c	Gsα coding mutation	Maternal	Yes	Yes	Yes	Blunted	Normal
PPHP	Gsα coding mutation	Paternal	No	No	Yes	Normal	Reduced
POH	Gsα coding mutation	Paternal	No	No	No	Normal	Reduced
PHP1b	Methylation defect in DMR of *GNAS*	Maternal	Yes	No	No	Blunted	Normal

Gsα: alpha-subunit of the stimulatory G protein, PHP: pseudohypoparathyroidism, POH: progressive osseous heteroplasia, PTH: parathyroid hormone, AHO: Albright hereditary osteodystrophy, DMR: differentially methylated region, cAMP: cyclic adenosine monophosphate, PPHP: pseudopseudohypoparathyroidism

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