# From Pseudohypoparathyroidism to inactivating PTH/PTHrP Signalling Disorder (iPPSD) a novel classification proposed by the European EuroPHP-network

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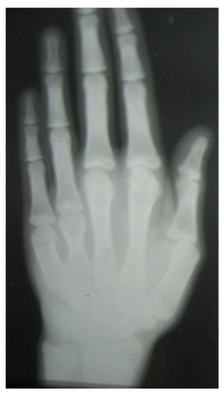
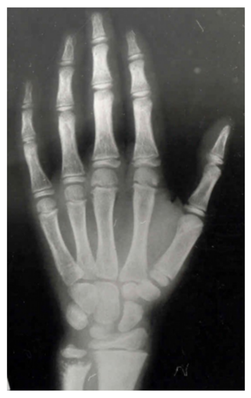
Disorders caused by impairments in the parathyroid hormone (PTH) signalling pathway are historically classified under the term pseudohypoparathyroidism (PHP), that encompasses rare, related but highly heterogeneous diseases with demonstrated (epi)genetic causes. A defect in the response of the proximal renal tubule to PTH is the hallmark of all forms of PHP. AHO comprises heterogeneous clinical findings such as brachydactyly, rounded face, short stature, stocky build and subcutaneous ossifications likely mediated by the resistance to PTHrP at the growth plate during fetal and post-natal growth.

The EuroPHP network

One objective of our network was to to review the limitations and challenges of the current nomenclature and recommend a novel classification for disorders impairing the PTH/PTHrP signalling pathway.



PHP1B



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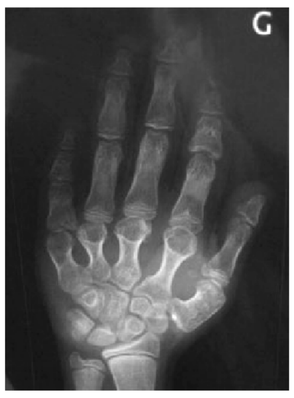
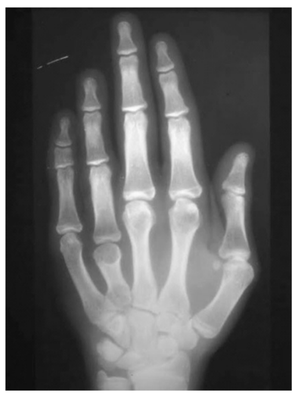


PHP1A



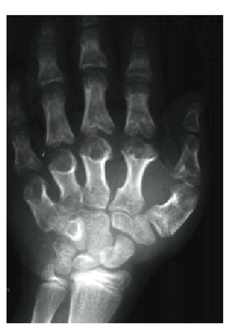
PHP1A

## Main limits of the current classification

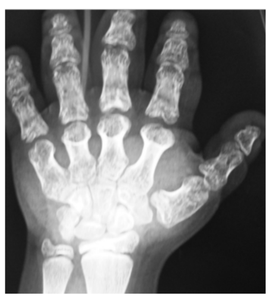
- fails to stratify PHP and AHO
- Does not include acrodysostosis, POH and PTH1R-related chondrodysplasia
- Does not incorporate the genetics

## Main demands for a new classification

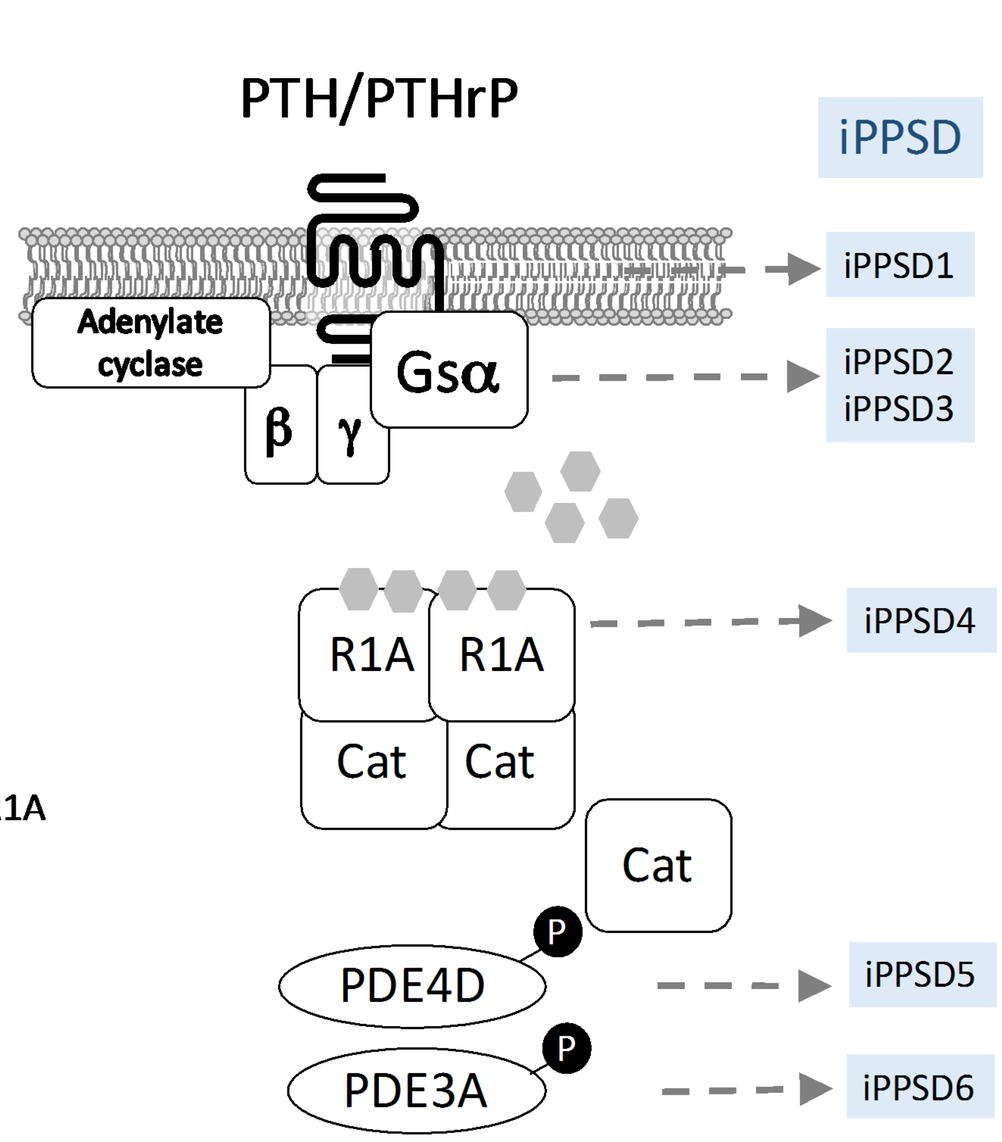
- Simple and flexible
- Define the common mechanism of the disease
- Non ambiguous
- Based on the clinical Dg, but includes genetics



ACRODYSOSTOSE, mutation PRKAR1A



ACRODYSOSTOSE, mutation PDE4D




| | PHP1A | PPHP | ADPHP1B and sporPHP1B | PHP1C |
|---|---|---|---|---|
| Clinical signs | AHO | AHO | no | AHO |
| PTH-Resistance | yes | no | yes | yes |
| In-vitro Gsα-activity | diminished | diminished | normal | normal |

**Table 1:**
**Current classification**
ADPHP1B: autosomal dominant form of PHP1B
SporPHP1B: sporadic form of PH1B

- Comprehensive review of the litterature
- Identification of the limitations
- Methodologies of other classifications
- Mandatory criteria

- 3 Meetings

- Proposal for a new name
- Nomenclature and classification

## Major criteria

PTH resistance
Subcutaneous ossifications
Brachydactyly type E*

## Minor Criteria

Thyroid Stimulating Hormone (TSH) resistance
Other hormone resistances
Motor and cognitive retardation or impairment
IUGR and post-natal growth retardation
Obesity/overweight/hyperphagia
Flat nasal bridge and/or maxillar hypoplasia and/or round face

*Minor criteria need to be combined with one or more major criteria to establish the diagnosis of iPPSD.*

**Brachydactyly should be combined with at least one major or two minor criteria to trigger the diagnosis of iPPSD*