Pseudohypoparathyroidism presenting in children at a tertiary hospital in Johannesburg, South Africa

N Madi*, FY Moosa*, KB Parbhoo*, JM Pettifor* and K Thandrayen*

Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, University of the Witwatersrand, Johannesburg, South Africa
MRC/Wits Developmental Pathways for Health and Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa
*Correspondence: Ntombizodwa.mahlaba2@wits.ac.za

Pseudohypoparathyroidism (PHP) represents a group of disorders due to end organ resistance to the actions of parathyroid hormone (PTH) and abnormalities in the PTH signalling pathway. PHP is characterised by hypocalcaemia and hyperphosphataemia, with or without a variable expression of physical features. The constellation of these physical features together are termed Albright hereditary osteodystrophy (AHO). Other disorders related to PTH resistance and PTH signalling pathway impairment are pseudopseudohypoparathyroidism (PPHP), progressive osseous heteroplasia (POH) or osteoma cutis and acrodysostosis.

PHP is due to genetic and/or epigenetic alterations in the PTH/PTHrP (parathyroid hormone related-protein) signalling pathway. The main genetic aberration is due to inactivating mutations in the GNAS gene (responsible for multiple gene products, including transcripts that encode the α-subunit of the stimulatory guanine nucleotide-binding protein [G protein] Gsα, resulting in Gsα protein abnormalities. Other genetic mutations associated with PHP have been identified in genes that regulate CAMP-dependent protein kinases, in enzymes that hydrolyse CAMP and cGMP, and in the mutations and loss of methylation of GNAS differentially methylated regions (DMRs).

PHP and disorders related to PTH resistance are primarily clinical diagnoses. In the majority of our patients, PHP was initially diagnosed clinically and biochemically. Genetic diagnoses were confirmed in two of the nine patients that are presented in this case series. Patients may also present with clinical features that are similar to rickets due to chronically elevated PTH levels that lead to bone resorption and demineralisation. The clinical features are those of AHO and intracranial calcifications, especially those of the basal ganglia, are frequently discovered on brain imaging.

In 1942, Fuller Albright and colleagues first described PHP and the features of AHO. AHO describes a collection of clinical features, including short stature, round facies, brachydactyly type E, central obesity, subcutaneous ossifications, intrauterine growth restriction, mental and developmental delay and other poorly defined abnormalities. The phenotype may occur with or without PTH hormone resistance.

PHP is classified into five subtypes: PHP Type 1A, PHP Type 1B, PHP Type 1C, PHP Type 2 and Pseudo-PHP, based on the presence or absence of AHO, the characteristic hormone resistance, and Gsα protein inactivity. PHP-Ia has the same clinical and endocrine features as PHP-Ic, but PHP-Ic has normal functional activity of Gsα protein, which is encoded by GNAS gene, in in vitro assays.

Pseudohypoparathyroidism type Ia (PHP-Ia) is a condition with resistance to multiple endocrine hormones that are coupled to G-protein. These include PTH (present as elevated PTH levels, hyperphosphataemia and hypocalcaemia with normal 25 hydroxyvitamin D and magnesium levels); TSH resistance (presenting with hypothyroidism and elevated TSH levels, without goitre or autoimmune thyroid disease); gonadotropin resistance (manifests as delayed puberty, menstrual disorders/irregularities, cryptorchidism, infertility, and elevated LH and FSH levels in both males and females), involvement of growth hormone-releasing hormone (GHRH), manifesting with short stature and/or poor growth due to growth hormone deficiency, and calcitonin resistance (manifesting as elevated calcitonin level, which is usually asymptomatic). Patients also present with obesity, due to decreased resting energy expenditure and hyperphagia, which appears to result from impaired Gα-coupled signalling in imprinted regions of the hypothalamus. Patients also have an AHO phenotype and reduced Gα activity in in vitro assays. PHP-Ia is
due to an autosomal dominant inherited mutation in the GNAS1 gene.\textsuperscript{11,12}

Pseudohypoparathyroidism type lc (PHP-lc) is a variant of PHP-la because they share the same clinical features and it is also due to GNAS1 gene mutation. In PHP-lc there is normal G\textsubscript{a} activity in vitro complementation assays.\textsuperscript{13}

Pseudohypoparathyroidism type lb (PHP-lb) was initially described as isolated resistance to PTH (which is the major endocrine abnormality), in the absence of the AHO phenotype and with normal levels of G\textsubscript{a} activity. But some patients with PHP-lb have biochemical characteristics and some features of the AHO phenotype that overlap with PHP-la, thus complicating the diagnosis. These patients have slightly elevated TSH levels due to partial resistance to TSH and generally normal (or low) serum thyroid hormones, mild brachydactyly, enhanced intrauterine growth, and the Madelung deformity. There are sporadic and familial forms of PHP lb. The sporadic forms display GNAS imprinting abnormalities that involve multiple DMRs and STX16 (Syntaxin-16) gene disruption. The familial forms are transmitted in an autosomal dominant manner and are associated with a methylation defect in the A/B exon of GNAS.\textsuperscript{9,14-19}

Pseudohypoparathyroidism type 2 is distinguished from PHP type 1 by the normal exogenous PTH response of renal cAMP. PHP-I is characterised by a blunted cAMP response to infusion of exogenous PTH, while PHP-II is diagnosed when there is an elevation of renal cAMP with deficient phosphaturia indicating a defect distal to cAMP generation in the PTH-mediated-transduction pathway in the target cells. It is not known which molecular defect causes PHP-II, but it has been postulated that there may be an acquired defect secondary to vitamin D deficiency, as treatment with vitamin D and calcium is able to normalise the phosphaturic response.\textsuperscript{19}

Pseudopseudohypoparathyroidism (PPHP) and progressive osseous heteroplasia (POH) and osteoma cutis (OC) phenotypes are due to a lack of expression/function of G\textsubscript{a}, the difference being in the origin of the inactivating GNAS pathogenic variants. PPHP results from lack of expression of the paternal allele, while POH and OC can be associated with pathogenic variants in either the maternal or paternal allele. Individuals with PPHP have normal calcium and PTH levels with features of AHO and decreased G\textsubscript{a} activity. Individuals may also have intrauterine growth restriction, ectopic ossifications, obesity and intellectual disabilities. Individuals with OC have subcutaneous and dermal ossifications, while those with POH have ossifications that extend to the deep connective tissues.\textsuperscript{20}

PHP-la,b and -lc are associated with reduced or absent expression/function of the protein G\textsubscript{a} (encoded by the maternal GNAS complex locus). GNAS DMR methylation changes, paternal uniparental disomy of chromosome 20q, and small deletions in STX16 are seen in patients with PHP-Ib.\textsuperscript{10,18}

The classification makes the diagnosis complex due to an overlap between the sub-types,\textsuperscript{7} which is evident in our case series as one patient’s diagnosis may fall into several subtypes of PHP. Molecular genetics is the gold standard for the diagnosis of PHP, for categorisation into the different subtypes and to guide management. In our clinical setting, molecular genetics confirmation is not available, due to resource constraints. Confirmatory diagnostic tests were performed at an international laboratory with informed consent or assent having been obtained from the parents/guardians and children respectively. The Human Research Ethics Committee of the University of the Witwatersrand granted approval for the case series to be reported (Ethics certificate no. M1911104).

The aim of our report is to describe the variable clinical features, clinical course and genetic results of nine patients (details shown in Table 1) who have been followed up at our paediatric Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto, South Africa.

**Case descriptions**

**Patients with features of AHO**

**Case 1**

A 10-year-old black African female who was being investigated for cor pulmonale secondary to obstructive sleep apnoea at the cardiology clinic was referred to elucidate the cause for her short stature and obesity. She had bilateral sensory neural hearing loss and tonsillar-adeno-hypertrophy. She had normal developmental milestones. Her younger brother is also being followed up at our clinic for PHP (Case 2).

She was overweight and stunted. She had subtle dysmorphic features: frontal bossing, a flat nasal bridge and a round facial profile. She had a shortened fourth metacarpal and a subcutaneous nodule was felt at the left lateral calf area. There were no clinical features of hypocalcaemia.

Biochemistry was consistent with PHP. Her renal function was normal but she had primary hypothyroidism (see Table 1). The thyroid antibody tests were negative. Radiographs of long bones revealed an exostosis of the left proximal tibia. Echocardiography and abdominal ultrasound were normal. The most likely type of PHP in this patient is PHP type 1A or 1C.

**Case 2**

This patient is the younger brother of case 1 and presented at the age of 3 months with a history of recent onset generalised tonic-clonic seizures. He was subsequently referred to our endocrine clinic for suspected congenital hypothyroidism and had age-appropriate developmental milestones.

He was overweight and stunted. He had a round face, a flat nasal bridge, abnormal ear creases and a shortened fourth metacarpal. There were no other skeletal abnormalities and his systemic examination was normal. Figure 1 shows the clinical features of the patient.

Biochemistry at the time of the seizures was consistent with the diagnosis of PHP and primary hypothyroidism (see Table 1).

The mother of cases 1 and 2 is short (151 cm) but she has no features of AHO. Her biochemistry results were normal. The most likely type of PHP in this patient is PHP type 1A or 1C. Genetic testing will be done on the whole family.

**Case 3**

An 11-year-old black African female presented with a third episode of generalised tonic-clonic seizures and was on anticonvulsants that were started at a primary health care clinic. She had failed a grade. She is the only child to her mother who is short (146.5 cm), but has no other features of AHO. There was no family history of AHO.
**Table 1:** Results of patients at first presentation to our clinic and their genetic results.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at presentation</th>
<th>Anthropometry</th>
<th>Total serum calcium (2.22–2.62 mmol/l)</th>
<th>Serum phosphate (age-dependent range in mmol/l)</th>
<th>PTH (1.6–6.9 pmol/l)</th>
<th>TSH (0.73–8.35 mIU/l)</th>
<th>T4 (11.9–25.6 pmol/l)</th>
<th>Major criteria for iPPSD</th>
<th>Minor criteria for iPPSD</th>
<th>iPPSD classification</th>
<th>Genetic abnormality</th>
<th>Implication of genetic result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 years</td>
<td>WAZ: +1</td>
<td>1.62</td>
<td>2.59 (1.20–1.80)</td>
<td>49.2</td>
<td>16</td>
<td>8.6</td>
<td>PTH resistance, brachydactyly</td>
<td>TSH resistance, cognitive retardation, obesity, flat nasal bridge, round face</td>
<td>iPPSD</td>
<td>Awaiting results</td>
<td>PHP 1A</td>
</tr>
<tr>
<td>2</td>
<td>3 months</td>
<td>HAZ: −2</td>
<td>1.23</td>
<td>2.28 (1.25–2.10)</td>
<td>16</td>
<td>Normal</td>
<td>6.1</td>
<td>PTH resistance, brachydactyly</td>
<td>TSH resistance, obesity, flat nasal bridge, round face</td>
<td>iPPSD</td>
<td>Awaiting results</td>
<td>PHP 1B</td>
</tr>
<tr>
<td>3</td>
<td>11 years</td>
<td>WAZ: +1.6</td>
<td>1.21</td>
<td>3.77 (1.20–1.80)</td>
<td>24.40</td>
<td>24.0</td>
<td>Normal</td>
<td>PTH resistance, brachydactyly</td>
<td>Cognitive retardation, obesity, flat nasal bridge, round face</td>
<td>iPPSD</td>
<td>Awaiting results</td>
<td>PHP 1A</td>
</tr>
<tr>
<td>4</td>
<td>8 months</td>
<td>HAZ: +2.6</td>
<td>2.09*</td>
<td>1.92 (1.25–2.10)</td>
<td>91.2</td>
<td>91.0</td>
<td>Normal</td>
<td>PTH resistance, ectopic ossifications</td>
<td>Overweight, motor and cognitive retardation</td>
<td>iPPSDx</td>
<td>No genetic abnormality identified</td>
<td>PHP 1B</td>
</tr>
<tr>
<td>5</td>
<td>4 years</td>
<td>HAZ: +1.5</td>
<td>1.75</td>
<td>2.84 (1.20–1.80)</td>
<td>2.31</td>
<td>10.5</td>
<td>Normal</td>
<td>PTH resistance</td>
<td>Cognitive retardation</td>
<td>iPPSDx</td>
<td>No genetic abnormality identified</td>
<td>PHP 1A</td>
</tr>
<tr>
<td>6</td>
<td>13 years</td>
<td>HAZ: −2.5</td>
<td>0.70</td>
<td>1.94 (0.95–1.75)</td>
<td>21.8</td>
<td>26.2</td>
<td>Normal</td>
<td>PTH resistance</td>
<td>Motor and cognitive retardation</td>
<td>iPPSD</td>
<td>No genetic abnormality identified</td>
<td>PHP 1B</td>
</tr>
<tr>
<td>7</td>
<td>7 years</td>
<td>HAZ: −1.2</td>
<td>1.93</td>
<td>2.31 (1.20–1.80)</td>
<td>27.1</td>
<td>38.1</td>
<td>Normal</td>
<td>PTH resistance</td>
<td>Obesity, motor and cognitive retardation</td>
<td>iPPSDx</td>
<td>No genetic abnormality identified</td>
<td>PHP 1A</td>
</tr>
<tr>
<td>8</td>
<td>1 year</td>
<td>HAZ: 0.08</td>
<td>1.46</td>
<td>2.18 (1.20–1.80)</td>
<td>27.1</td>
<td>33.7</td>
<td>Normal</td>
<td>PTH resistance</td>
<td>None</td>
<td>iPPSDx</td>
<td>No genetic abnormality identified</td>
<td>PHP 1B</td>
</tr>
<tr>
<td>9</td>
<td>9 years</td>
<td>HAZ: +4.4</td>
<td>1.74</td>
<td>2.90 (1.20–1.80)</td>
<td>None</td>
<td>10.3</td>
<td>Normal</td>
<td>PTH resistance</td>
<td>None</td>
<td>iPPSDx</td>
<td>No genetic abnormality identified</td>
<td>PHP 1B</td>
</tr>
</tbody>
</table>

- BMI: body mass index (kg/m²), HAZ: height for age Z-score, iPPSD: inactivating PTH/PTH-related protein signalling disorder, WAZ: weight for age Z-score, WHZ: weight for height Z-score, * blood results at eight years of age.
are awaiting the results. Testing has been done on the patient and her mother but we type of PHP in this patient is PHP type 1A or 1C. Genetic and grey-white matter interface calcifications. The most likely scan of the brain showed bilateral symmetrical basal ganglia pals and proximal phalanges.

and digits. On the right, there is mild shortening of the metacarpals and digits represented by small nubbins of tissue. At birth, he was noticed to have raised lesions on the scalp and over the prominences of the head. He had multiple symmetrical foci of calcifications in the basal nuclei, and white matter interface calcifications. The most likely type of PHP in this patient is PHP type 1A or 1C. Genetic testing has been done on the patient and her mother but we are awaiting the results.

Case 4
A white male who was born with a malformation of the left hand and with digits represented by small nubbins of tissue. At birth, he was noticed to have raised lesions on the scalp and over the next few months more lesions developed on the left calf, the abdomen and left knee. The lesions were biopsied at 2 months and showed subcutaneous heterotopic ossification. Biochemistry on admission is shown in Table 1. The CT scan of the brain showed bilateral symmetrical basal ganglia and grey-white matter interface calcifications. The most likely type of PHP in this patient is PHP type 1A or 1C. Genetic testing has been done on the patient and her mother but we are awaiting the results.

He was lost to follow up until eight years of age. When he returned to our clinic, he was attending remedial school and the skin lesions were minimal. Biochemistry showed hypocalcaemia, hyperphosphataemia and a high PTH. His renal and thyroid functions were normal (Table 1). Genetic testing revealed a mutation in exon 6 of the GNAS1 gene. The mutation is a four-base pair deletion (GACT), deleting Asp 173, and the first base pair of Cys 174. Genetic tests on the parents were normal. The genetic results confirmed PHP type 1A.

Case 5
A female patient of mixed ancestry background was referred for the orthopaedic surgeons for suspected metabolic bone disease at four years of age. She had bilateral genu valgum deformities. She was stunted but of normal weight. She had no other skeletal abnormalities and her systemic examination was normal. Her X-rays showed bilateral slipped femoral epiphyses and slipping of her distal tibial epiphyses (Figure 2a and b). There were irregularities at the left distal unrepaired metaphysis and medial aspect of the distal radial metaphysis, which are of unknown significance. None of her family members had clinical features of PHP. Biochemistry revealed findings in keeping with PHP (see Table 1). The most likely type of PHP in this patient is PHP type 1A or 1C, because of the features of AHO. Genetic testing revealed no abnormalities in the patient and her mother.

Patients without features of AHO

Case 6
A 13-year-old black African male presented with generalised tonic-clonic seizures. He had no clinical signs of hypocalcaemia (tetany, muscle spasms) and negative Trousseau and Chvostek signs. He was wasted and mildly stunted. He had no dysmorphic features, and no signs of AHO. He was unable to walk, with decreased power in the lower limbs but no other positive neurological findings. He did have a lower respiratory tract infection with digital clubbing and subsequently was confirmed to have pulmonary tuberculosis (TB) on sputum microscopy and cultures. Biochemistry on admission showed severe hypocalcaemia, an elevated PTH level and hyperphosphataemia (see Table 1). His renal function, thyroid function tests and albumin were normal. The ECG showed a slightly prolonged QT interval. The CT scan of the brain showed extensive bilateral calcifications in the basal ganglia and cerebral parenchyma, with age-inappropriate involutional changes and the brain MRI showed multiple symmetrical foci of calcifications in the basal nuclei, cerebellar hemispheres and cortex, with ventriculomegaly and prominent sulci (Figure 3).

Genetic testing showed loss of methylation at GNAS exon A/B, AS, XL and gain of methylation at exon NESP. There was no evidence of a deletion in GNAS or SXX16. These are all typical for the sporadic variant of PHP type 1B. There is no significant family history of PHP.

Case 7
A seven-year-old white female was referred for the treatment of rickets and progressive bowing of her legs. She had delayed developmental milestones and delayed dentition. She also had learning difficulties. She has one older sibling, who is well, and no other significant family history.

She had normal anthropometric measurements and was not dysmorphic. She had an obvious displacement of the right
wrist. She was toe-walking and had severe valgus deformity of both ankles and mild bilateral genu valgum at the knees. There were no clinical features of rickets. Biochemistry confirmed hypocalcaemia, hyperphosphataemia and hyperparathyroidism (Table 1). Her renal function was normal.

Her radiographs showed bilateral slipped femoral capital epiphyses and bilateral destruction of the distal tibial epiphysis. She has a Madelung deformity involving the right radial shaft (the radius was bowed with increased interosseous space and dorsal subluxation of the distal radioulnar joint). She had osteitis of the distal end of the clavicles and distal phalanges. The presumed type of PHP in this patient is PHP type 1B. Genetic testing was done on the patient, her mother and unaffected sister and no genetic abnormalities were identified.

Case 8
A black South African female was referred to us from our paediatric HIV clinic at one year of age for investigation of her obesity. She was on anti-retroviral therapy and on TB treatment for recurrent severe BCG disease with axillary adenitis (disseminated extra-pulmonary TB). She had been following up at our endocrine clinic since one year of age and was treated for subclinical hypothyroidism and obesity.

She had significant neurodevelopmental delay, and it became apparent that she had speech and motor delay at subsequent visits. At 10 years of age she presented with generalised tonic-clonic seizures that were secondary to hypocalcaemia. She had one older sibling, a sister, who had died at two years of age from suspected dilated cardiomyopathy. The sibling had no clinical features of AHO. Her mother and father are well and have no clinical features of PHP.

The biochemistry results at admission for the management of her seizures were in keeping with PHP (Table 1). The only radiological abnormality that was found was bilateral symmetrical distal ulna metaphyseal irregularities and lucencies of unknown significance. The CT scan of the brain showed bilaterally symmetrical basal ganglia, and subcortical and cortical calcifications. The most likely type of PHP in this patient is PHP type 1B. Genetic testing done on the patient and her mother are pending.

Case 9
A nine-year-old white male presented to the emergency department with generalised tonic-clonic seizures and had normal developmental milestones. His mother gave a history of him having muscle cramps of the lower limbs from the age of three years. There were no other affected family members. His anthropometry was normal. He had no features of AHO. His radiology investigations (X-rays of long bones, CT scan and MRI of the brain) were normal. Biochemistry was consistent with PHP (Table 1). The most likely type of PHP in this patient is PHP type 1B because of the absence of AHO phenotype, in the absence of being able to measure Gsα activity. Genetic testing was done on him and no genetic abnormality was identified.

Discussion
Since Albright first described PHP and AHO in 1942, more knowledge has been gained on the clinical and genetic profile of patients affected by this condition. Recent progress in genetic testing has contributed to a better understanding of the pathophysiologic basis of PHP. However, genetic testing is not widely available, and a classification has been published recently to include the suspicious clinical features that may lead to identification of cases (Table 2). Moreover, genetic abnormalities have not been identified in some forms of PHP. Of the nine children in this case series, results were available in five cases. In three of the five cases, a genetic abnormality was not detected. Genetic testing in two cases was associated with abnormalities previously reported in the literature, namely mutation in exon 6 of the GNAS 1 gene and loss of methylation at GNAS exon A/B, AS, and XL, and gain of methylation at exon NESP.
In 2016, a new classification system was established by the EuroPHP network that encompasses all the disorders of the PTH and/or PTHrP cAMP-mediated pathway. The new name proposed for the group of disorders is inactivating PTH/PTH-related protein signalling disorder (iPPSD) and, to assist in the diagnosis, the major and minor criteria were also defined (see Table 2).

The physical manifestations of PHP are highly variable; patients may present with features of AHO, and other features that vary amongst patients.

In our case series, all our patients had resistance to PTH, which is the defining criterion of PHP (see Table 2). Five patients (Cases 1–5) presented with some features of AHO. The most frequent features of AHO in our patients were round facies, type E brachydactyly and short stature. Genu valgum, a feature not associated with AHO, was found in two patients. Five of our patients had early-onset obesity (occurring in the first year of life, seen in cases 1–4 and 8), and three patients had thyroid stimulating hormone (TSH) resistance (cases 1–2 and 8).

Cases 1, 2 and 3 can be classified as having either PHP-Ia or PHP-Ic, but distinguishing between PHP-Ia and PHP-Ic is not possible as the facilities to measure $G_{o}$ activity are unavailable. Case 4 was suspected of having OC or POH due to the subcutaneous nodules that he presented with initially, but was confirmed on genetics, biochemistry and clinically (positive features of AHO) to have PHP-Ia. Case 5 can be classified as having PHP-Ia or PHP-Ic, because of the presence of features of AHO. Case 6 was confirmed as PHP-Ib on genetic testing with no clinical features of AHO, and initial biochemistry was suggestive of PHP. Case 7 can be classified as PHP-Ib because she had isolated PTH resistance and a Madelung deformity of her right wrist, assuming that the $G_{o}$ activity would be normal if measurable.

Figure 3: CT scan and brain MRI of case 6 showing multiple symmetrical foci of calcifications in the basal nuclei, cerebellar hemispheres and cortex, with ventriculomegaly and prominent sulci.
All our patients had biochemical evidence of PTH resistance (hypocalcaemia, hyperphosphataemia and elevated PTH levels). The diagnosis of PHP in our present case series was based on clinical features of AHO and appropriate neurodevelopmental delay. The diagnosis of PHP in our cases was confirmed by the clinical and biochemical profile, without genetic confirmation. The management principles of PHP can be found in an article by Germain-Lee and will not be discussed in this report.

The diverse clinical features of PHP make the diagnosis difficult to confirm but the majority of patients in this case series presented with seizures secondary to hypocalcaemia and had neurodevelopmental delay. The diagnosis of PHP in our setting was based on clinical features of AHO and appropriate biochemical testing for perturbations in mineral homeostasis (hypocalcaemia, hyperphosphataemia and elevated PTH levels). All our patients had biochemical evidence of PTH resistance. Genetic testing and testing for $G_{\alpha}$ activity cannot be performed locally in South Africa due to limited resources. Despite the inability to perform genetic testing and confirmation of the genetic mutations of the different types of PHP in our patients, correct timely identification of these conditions based on the major and minor criteria and treatment with calcium supplementation and calcitriol or 1α calcidiol is vital to prevent or reduce the complications associated with the condition.

### Ethics committee approval

The Human Research Ethics Committee of the University of the Witwatersrand granted approval for the case series to be reported (Ethics certificate no: M1911104).

### Conflicts of interest

All authors declare no conflict of interest.

### Disclosure statement

No potential conflict of interest was reported by the authors.

### ORCID

K Thandrayen ORCID http://orcid.org/0000-0002-4028-2749

JM Pettifor ORCID http://orcid.org/0000-0003-1155-0334

### References


### Table 2: Definition of major and minor criteria for iPPSD

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PTH resistance</td>
<td>1. TSH resistance</td>
</tr>
<tr>
<td>2. Ectopic ossification</td>
<td>2. Other hormonal resistance (LH, FSH, GHRH, Calcitonin)</td>
</tr>
<tr>
<td>3. Brachydactyly type E</td>
<td>3. Motor and cognitive retardation or impairment</td>
</tr>
<tr>
<td>4. Intrauterine and postnatal growth retardation</td>
<td>5. Obesity/overweight</td>
</tr>
<tr>
<td>6. Flat nasal bridge and/or maxillary hypoplasia and/or round face</td>
<td></td>
</tr>
</tbody>
</table>

iPPSD clinical diagnosis: (a) presence of one major criterion, either number 1 or 2 or (b) presence of major criterion number 3 and at least 2 minor criteria.

### Table 3: The novel classification of iPPSD (European PHP network)

<table>
<thead>
<tr>
<th>iPPSD</th>
<th>Clinical/biochemical diagnosis based on the major/minor criteria described in Table 2, without any genetic investigation/diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPPSD 1</td>
<td>Loss-of-function mutation in PTH1R</td>
</tr>
<tr>
<td>iPPSD 2</td>
<td>Loss-of-function mutation in $G_{\alpha}$</td>
</tr>
<tr>
<td>iPPSD 3</td>
<td>Methylisation change(s) at one or more GNAS DMRs, associated with or without a genetic deletion (STX16, NESP55, AS etc.) or cytogenetic (UPD) defect. The loss of methylisation at the GNAS A/B is the common mechanism shared by these patients</td>
</tr>
<tr>
<td>iPPSD 4</td>
<td>Mutation in PRKAR1A leading to reduced PKA activity</td>
</tr>
<tr>
<td>iPPSD 5</td>
<td>Gain-of-function mutation in PDE4D mutation</td>
</tr>
<tr>
<td>iPPSD 6</td>
<td>Gain-of-function mutation in PDE4A mutation</td>
</tr>
<tr>
<td>iPPSDn</td>
<td>Absence of any genetic/epigenetic defect after molecular investigations of known genes described above but fitting the criteria for iPPSD</td>
</tr>
<tr>
<td>iPPSDn+1</td>
<td>Identification of a new gene and/or molecular defect will increment the number of iPPSD types by one, i.e. iPPSD7, iPPSD8, etc.</td>
</tr>
</tbody>
</table>

PTH1R: PTH receptor, DMRs: differentially methylated regions, PKA: protein kinase A, UPD: uniparental disomy.


Received: 11-06-2020 Accepted: 28-08-2020