Pseudohypoparathyroidism (PHP) is a heterogeneous condition, principally known to cause parathyroid hormone (PTH) resistance, and sometimes other peptide hormone resistance. PHP1a is also associated with Albright's hereditary osteodystrophy (AHO), a phenotype including obesity, short stature, brachydactyly and subcutaneous ossifications. It results from heterozygous inactivating mutations on the maternally derived GNAS allele.

PHP1b is associated with methylation defects affecting the upstream overlapping GNAS imprinted gene cluster. This can be sporadic, or familial, when usually associated with a maternally inherited imprinted STX16 deletion.

We characterised the phenotype of PHP patients at two UK tertiary care centres and investigated phenotype-genotype correlations.

**Methods**

Case notes were retrospectively reviewed for patients with PHP and a known genetic abnormality, at two tertiary care centres.

Comparisons were made between PHP1a and PHP1b; PHP1a missense vs other variants, and PHP1b STX16 familial deletions vs sporadic widespread methylation defects. T-tests were used for parametric data and X² tests to analyse non-parametric data.

**Background**

Characterisation and phenotype-genotype associations of a large cohort of patients with pseudohypoparathyroidism type 1a and 1b

Prentice P1,2, Wilson L1, Gevers E2, Buck J3, Raine J4, Rangasami J1, McGloin H4, Peters C5, Amin R1, Gan H1, Hughes C2, Brain C4, Dattani M1, Allgrove J4

1Great Ormond Street Hospital for Children, London, UK, 2Royal London Hospital – Barts Health NHS Trust, London, UK, 3Ipswich Hospital - East Suffolk and North Essex NHS Foundation Trust, UK, 4Whittington Health NHS Trust, London, UK, 5West Middlesex University Hospital, London, UK

**Results**

Of 18 patients older than 12 years, 44% have type 2 diabetes or severe insulin insensitivity (average BMI SDS 2.88).

Figure 1: Presentation in PHP1a and PHP1b

**Mis sense vs other variants**

Of 31 patients with PHP1a, 15 have mis sense mutations; 16 other variants (frameshift/deletion/splicing/initiator codon). Those with mis sense mutations are shorter but of similar BMI SDS. 47% of those with mis sense mutations have PTH resistance, compared with 100% of those with other variants (table 1).

Table 1: Comparison between missense and other variants in PHP1a

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>PTH resistance</th>
<th>BMI SDS</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>74.2%</td>
<td>4.7</td>
<td>93.5%</td>
</tr>
<tr>
<td>Other variants</td>
<td>46.7%</td>
<td>2.6</td>
<td>93.3%</td>
</tr>
</tbody>
</table>

**STX16 deletions vs other variants**

10 patients with STX16 deletions and methylation defects only in GNAS exon 1A/B are taller and heavier than those with sporadic methylation defects. Similar numbers are on allacalculid and levothyroxine (table 2).

Table 2: Comparison between STX16 mutations and widespread methylation defects in PHP1b

<table>
<thead>
<tr>
<th>Variant Type</th>
<th>BMI SDS</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>STX16 deletion</td>
<td>1.1</td>
<td>100%</td>
</tr>
<tr>
<td>Other variants</td>
<td>0.9</td>
<td>80.0%</td>
</tr>
</tbody>
</table>

**Key messages**

This is one of the largest PHP cohorts reported to date and highlights some notable findings:

- 16% of PHP1a patients were diagnosed with congenital hypothyroidism.
- 44% of PHP1a patients over 12 years of age have T2D or insulin insensitivity.
- PHP1a missense variants may cause a milder phenotype with significantly less PTH resistance (47% vs. 100%).
- POH is not confined to paternally derived GNAS mutations but can be associated with PHP1a.
- One third of PHP1b patients have TSH resistance.
- Patients with STX16 mutations are taller and heavier than sporadic methylation abnormalities but there is little difference in hormonal complications.