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

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Background

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 intragenic 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 X^2 tests to analyse non-parametric data.

Results

56 patients, from 41 kindreds, were identified; 31 with PHP1a and 25 with PHP1b.

PHP1a

The PHP1a cohort (55% female, 71% White), currently 16.3 +/- 10.4 years of age, presented at 3 +/- 6 years. The majority presented with TSH resistance/hypothyroidism (Figure 1); 36% of whom had congenital hypothyroidism. The average time from presentation to genetic diagnosis was 2 +/- 3 years.

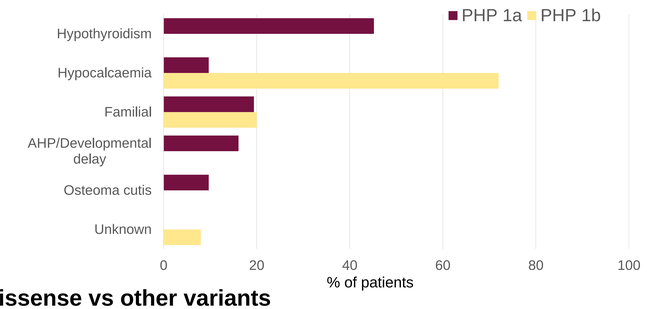
94% of the cohort currently have hypothyroidism; 74% have PTH resistance.

Results

Additionally, 6 have GHRH resistance, 1 had precocious puberty and 2 were treated for delayed puberty.

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



Missense vs other variants

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

Table 1: Comparison between missense and other variants in PHP1a

	PHP 1a cohort (N=31)	Missense (N=15)	Other variants (N=16)	P value
Height SDS	**-0.9 +/- 1.9**	**-1.9 +/- 2.2**	**0.08 +/- 0.9**	**0.002**
Weight SDS	1.7 +/- 2.1	1.3 +/- 2.6	2.0 +/- 1.4	0.3
BMI SDS	2.6 +/- 1.6	2.6 +/- 1.7	2.5 +/- 1.5	0.9
PTH resistance	**74.2%**	**46.7%**	**100%**	**0.0006**
Hypothyroidism	93.5%	93.3%	93.8%	1.0
Ossifications	53.6%	33.3%	68.8%	0.07

Two patients with splicing/frameshift mutations have progressive osseous heteroplasia (POH).

PHP1b

The PHP1b cohort (56% female, 44% White), currently aged 17.1 +/- 7.8 years presented later than PHP1a patients, at a mean age of 9 years, the majority with hypocalcaemia (Figure 1).

Results

They are taller (p=0.008), with lower BMI (p=0.005). 32% have TSH resistance.

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 alfacalcidol and levothyroxine (table 2).

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

	PHP 1b cohort (N=25)	Widespread methylation defect (N=15)	STX16 mutation (N=10)	P value
Height SDS	**0.4 +/- 1.3**	**-0.1 +/- 1.1**	**1.1 +/- 1.3**	**0.03**
Weight SDS	**1.3 +/- 1.3**	**0.7 +/- 1.1**	**2.2 +/- 1.0**	**0.004**
BMI SDS	**1.5 +/- 1.0**	**1.1 +/- 0.9**	**2.1 +/- 0.8**	**0.01**
PTH resistance	92.0%	100%	80.0%	0.07
Hypothyroidism	32.0%	26.7%	40.0%	0.5

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.

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