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Evidence of hormone resistance in a pseudo-pseudohypoparathyroidism patient with a novel paternal mutation in *GNAS*

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Abstract

Context—Loss-of-function *GNAS* mutations lead to hormone resistance and Albright's hereditary osteodystrophy (AHO) when maternally inherited, i.e. pseudohypoparathyroidism-Ia (PHPIa), but cause AHO alone when located on the paternal allele, i.e. pseudoPHP (PPHP).

Objective—We aimed to establish the molecular diagnosis in a patient with AHO and evidence of hormone resistance.

Case—The patient is a female who presented at the age of 13.5 years with short stature and multiple AHO features. No evidence for TSH or gonadotropin-resistance was present. Serum calcium and vitamin D levels were normal. However, serum PTH was elevated on multiple occasions (64–178 pg/mL, normal: 9–52) and growth hormone response to clonidine or L-DOPA was blunted, suggesting hormone resistance and PHP-Ia. The patient had diminished erythrocyte Gsα activity and a novel heterozygous *GNAS* mutation (c.328 G>C; p.A109P). The mother lacked the mutation, and the father's DNA was not available. Hence, a diagnosis of PPHP also appeared possible, supported by low birth weight and a lack of AHO features associated predominantly with PHP-Ia, i.e. obesity and cognitive impairment. To determine the parental origin of the mutation, we amplified the paternally expressed A/B and biallelically expressed Gsα transcripts from the patient's peripheral blood RNA. While both wild-type and mutant nucleotides were detected in the Gsα amplicon, only the mutant nucleotide was present in the A/B amplicon, indicating that the mutation was paternal.

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Conclusion—These findings suggest that PTH and other hormone resistance may not be an exclusive feature of PHP-Ia and could also be observed in patients with PPHP.

Key Terms

Pseudohypoparathyroidism; pseudopseudohypoparathyroidism; *GNAS*; hormone resistance

Pseudohypoparathyroidism (PHP) refers to parathyroid hormone (PTH) resistance particularly in the renal proximal tubule, leading to hypocalcemia, hyperphosphatemia, and elevated serum PTH [1–4]. PHP type Ia is caused by maternally inherited inactivating mutations in *GNAS*, the gene encoding the alpha-subunit of the stimulatory G protein (Gsα). In addition to PTH resistance, PHP-Ia patients show resistance to certain other hormones, including thyroid stimulating hormone (TSH), gonadotropins, and growth hormone releasing hormone (GHRH). These patients also demonstrate the features of Albright's hereditary osteodystrophy (AHO), a constellation of physical features including short stature, obesity, brachydactyly, ectopic ossification, and cognitive impairment. The same Gsα mutations are also found in patients with pseudoPHP (PPHP), who show AHO without PTH or other hormone resistance. In PPHP patients, these mutations are located on the paternal allele. Studies have shown that certain AHO features are associated primarily with PHP-Ia, including obesity and cognitive impairment [5,6], and that PPHP patients can present with intrauterine growth retardation that is much severer than that observed occasionally in PHP-Ia patients [7].

Case Report

The female patient presented at the age of 13.5 years with multiple AHO features, including short stature, shortening of the third and fourth metacarpals on both hands, round face, and a subcutaneous nodule of 3 cm diameter on sacral region on physical examination. Additionally, she had acne on face and hirsutism with a Ferriman-Gallwey score of 15 (Normal < 8); however, serum androgen, FSH, and LH levels were within normal ranges [FSH:8.3 mIU/mL (3.5–12.5), LH:4.4 mIU/mL (1.6–8.3)]. The patient had menarche at the age of 12.5 year and had been having regular menstrual cycles. Her bone age was 15 years old. Her height was 143.9 cm (−2.61 SDS), while her mid-parental height was 155 cm (−1.38 SDS). Her healthy sister was 169 cm tall (+1.08 SDS). The patient was not obese (BMI of 19 kg/m^2, −0.54 SDS) and did not have cognitive impairment with normal neurodevelopmental parameter during infancy and childhood and she had been attending high school with academic proficiency.

She was born from a healthy mother, with a birth weight of 1 kg at term. She had a twin, but intrauterine death of the twin occurred 15 days before the delivery; the cause of death was not determined. There was no family history of AHO features or hormone resistance. The karyotype was 46 XX. Biochemical analysis showed no evidence for resistance to TSH [TSH: 1.88 uIU/mL (0.51–4.3), f-T4: 1.58 ng/dL (0.93–1.7)]. The plasma PTH was markedly elevated (146 pg/ml) with mildly elevated phosphorus levels (Fig. 1). Serum Ca (9.9 mg/dL) and vitamin D (33 μg/L; normal ≥20) values were within the normal range (Fig. 1), and, urinary Ca/Cre ratio was diminished (0.016 mg/mg). Bone mineral density of spine showed z-score of −0.5 on L1-L4 at initial evaluation and height adjusted z-score was 2.1.

Considering the biochemical evidence for PTH resistance, the patient was prescribed 800 IU of vitamin D per day. On follow-up visits, however, the patient continued to have elevated PTH with high-normal serum phosphorus; serum Ca and vitamin D levels were normal (Fig. 1). Therefore, the treatment was supplemented with 1000 mg oral elemental Ca, which led to a reduction in serum PTH levels and serum phosphorus levels. The PTH levels, however, remained at the upper end of the normal range. The patient was later taken off the treatment, leading to an increase in serum PTH levels with normal or low-normal serum phosphorus. Subsequently, high dose vitamin D treatment (12,000 IU/day) led to normalization of PTH (Fig. 1). Calcitriol treatment was not considered, since PTH normalization could be achieved with cholecalciferol and calcium supplementation, which is less costly than calcitriol.

Two years after our evaluation of the patient, at age 15.5 years, she stopped growing and reached a final height of 144.8 cm (−2.95 SDS). Growth hormone stimulation tests performed at that age with clonidine and L-DOPA showed peak growth hormone (GH) levels of 5.3 and 3.7 ng/mL, respectively (Normal response ≥ 10 ng/mL for children, > 6 ng/mL for transition adolescents). Serum IGF-I was 237 ng/mL (−2.7 SD), and IGFBP-3 was 4.6 μg/mL (−1.25 SD) for age.

Molecular and Genetic Analyses

Because of the phenotypic features of AHO and biochemical evidence for PTH resistance, a diagnosis of PHP-Ia was originally considered. Consistent with this diagnosis, analysis of patient's erythrocytes showed diminished Gsα activity (46.7% vs normal range 85–115%). Accordingly, a nucleotide sequence analysis of the patient's leukocyte DNA revealed a novel heterozygous mutation in *GNAS* (c.328 G>C; p.A109P), affecting the C-terminal end of the Gsα alpha-helical domain (Fig. 2A). However, this novel mutation was not detected in her mother's DNA (Fig. 2A). Although it was possible that the mutation occurred on the maternal allele of the patient *de novo*, a diagnosis of PPHP also appeared possible given that the patient lacked obesity and cognitive impairment, i.e. AHO features typically associated with PHP-Ia [5, 6]. Moreover, she had severe IUGR, a finding often found in PPHP patients [7]. Due to the importance of the correct diagnosis with respect to the patient's clinical follow-up and genetic counseling, we sought to determine whether the mutation was located maternally or paternally. DNA from the father was not available for genetic analyses. To determine the allelic origin of the mutation, we took advantage of the fact that the mutation was present not only in the Gsα transcript but also in other *GNAS* transcripts that show monoallelic expression (A/B, XLαs, or NESP55) [8–11]. RT-PCR was performed by using total RNA extracted from the patient's peripheral blood. While the maternally expressed NESP55 or the paternally expressed XLαs transcripts could not be amplified, the paternally expressed A/B transcript and the biallelically expressed Gsα transcript were amplified through the use of specific forward and common reverse primers (Fig. 2B). Sequence analyses showed that, whereas both the wild-type guanine and the mutant cytosine nucleotides were present in the Gsα amplicon, only the mutant cytosine nucleotide was present in the A/B amplicon (Fig. 2C), indicating that the mutation was located on the paternal allele (primer sequences are available upon request). The study was approved by Marmara University Ethics Committee and informed written consent was obtained from the patient and her family for these DNA analyses.

Discussion

PHP-Ia results from maternal inactivating mutations affecting Gsα, a ubiquitously expressed signaling protein mediating the actions of many hormones and other endogenous molecules through the generation of cyclic AMP [3]. The transcript encoding Gsα is biallelically expressed in most tissues; however, the paternal Gsα allele is repressed in certain tissues, including proximal renal tubules, thyroid, gonads, and pituitary [12]. Because of the predominant maternal expression of Gsα in a tissue-specific manner, it has hitherto been thought that *GNAS* mutations in PHP-Ia patients lead to PTH and other hormonal resistance only after transmission from the mother or when they occur *de novo* on the maternal allele. Based on our current understanding, the same *GNAS* mutations do not lead to PTH and/or other hormone resistance but cause AHO alone when located on the paternal allele, i.e. PPHP. AHO is thought to occur due to Gsα haploinsufficiency caused by ~50% reduction of Gsα activity in tissues in which Gsα expression is normally biallelic. However, it has been reported that some AHO features, i.e. obesity and cognitive impairment, develop primarily after maternal inheritance of the *GNAS* mutations (PHP-Ia) [5, 6], consistent with findings in mice that Gsα expression is predominantly maternal in certain parts of the brain [13]. In addition, a recent study indicated that inactivating *GNAS* mutations are associated with intrauterine growth retardation (IUGR), and that this defect is significantly more severe in those with paternal (PPHP) than maternal (PHP-Ia) mutations [7]. The loss of one of the paternal *GNAS* gene products, XLαs, is implicated in the pathogenesis of IUGR in PPHP patients [7].

Our patient had a novel *GNAS* mutation and presented with AHO features, blunted growth hormone response to stimulation, and evidence for subclinical PTH resistance. While these findings suggested PHP-Ia, the identified mutation was not present in the mother. Moreover, the presence of severe IUGR and the absence of obesity and cognitive impairment were suggestive of PPHP. We therefore performed the differential diagnosis between PHP-Ia and PPHP by performing RT-PCR on patient's blood RNA and found the mutation on the paternally expressed A/B transcript. This approach was undertaken previously to determine the allelic origin of *GNAS* mutations associated with McCune-Albright syndrome and pituitary adenomas [14–16] but was not employed before for this purpose. Thus, in patients with *GNAS* mutations for whom the clinical features are not able to distinguish PHP-Ia from PPHP, and when the parental DNA samples are unavailable or lack the mutation, the analysis of RNA from the patient's blood samples can be performed to establish the molecular diagnosis.

The markedly reduced erythrocyte Gsα activity indicates that the novel A109P mutation leads to loss-of-function. Despite carrying this inactivating *GNAS* mutation on the paternal allele, the patient showed consistent elevation of PTH with mildly elevated or high-normal serum phosphorus and normal calcium levels. The elevation of PTH was not associated with vitamin D deficiency. These findings are consistent with mild PTH resistance at the level of proximal tubule, the site at which patients with PHP-Ia show resistance to the actions of PTH. On the other hand, both PTH and phosphorus levels declined by the 12-month follow-up, and these changes corresponded to the addition of calcium supplements to the treatment, suggesting that the PTH resistance was transient and/or the biochemical values at

presentation reflected, at least partly, insufficient calcium intake or an altered set-point of calcium for PTH stimulation. Note that the patient's serum calcium levels remained close to the upper end of the normal range.

The PTH levels in our patient did not elevate as much as the original levels after stopping the treatment, and serum phosphorus remained normal. Thus, it is possible that the loss of paternal Gsα expression might lead to PTH resistance in young PPHP patients, and PTH resistance could resolve with age. Accordingly, normocalcemic elevation of PTH has been observed in two mouse models of paternal *Gnas* exon 1 knock-out, and in one of those models, serum PTH was elevated in 3-week old but not in adult mice [17, 18]. We have shown that the contribution of the paternal allele to Gsα expression in the mouse renal proximal tubule is higher during the early postnatal period than in adulthood (50% vs. 34%, respectively), indicating the importance of the paternal allele in younger ages [18].

Our patient also showed some evidence for growth hormone deficiency. When the growth hormone stimulation tests were performed, she had just reached her final height and, therefore, was considered to be in the transition period from adolescent to young adult. This is a period from mid-to-late teens until 6–7 years following achievement of final height [19]. As such, the results of the growth hormone stimulation tests are considered to be abnormal. The blunted response in these tests could partly reflect resistance to GHRH, which is also an unexpected finding, as GHRH resistance is typically found in PHP-Ia patients due, presumably, to the predominant maternal expression of Gsα in the anterior pituitary combined with maternal loss-of-function *GNAS* mutations [2–4]. However, a PPHP case has previously been reported to have growth hormone deficiency and a blunted response to GHRH stimulation [20]. It thus appears that, at least in some cases, paternal Gsα mutations lead to GHRH resistance. This finding could indicate that, as in early postnatal renal proximal tubules [21], the paternal allele contributes significantly to Gsα expression in the pituitary somatotrophs; however, no evidence currently supports this possibility. Alternatively, the GHRH resistance in our patient could reflect the deficiency of XLαs, considering that this paternally expressed Gsα variant shares exons 2–13 with Gsα, can mimic the actions of the latter, and is found abundantly in the pituitary [12].

It appears unlikely that the hormone resistance in our patient depends on the specific protein defect, such as one that exerts a dominant negative effect, because the Gsα activity (46.7%) was above the minimum Gsα activity levels in other PHP-Ia or PPHP patients analyzed in our facility (41.5% and 42.6%, respectively). The mean ± S.D. values were 59.7±9.4% (n=72) and 60.1±9.5% (n=22) for the PHP-Ia and PPHP cohorts, respectively, and the Gsα activity of our patient was not significantly lower than the mean value obtained after combining the two cohorts (z-score: 1.40; p=0.08, one-tailed).

Other cases of PPHP who show evidence for PTH resistance have been described, and similar to our patient, those cases had normal calcium levels [22–26]. Detailed follow-up and extensive tests were not performed in most of those cases, and vitamin D levels were measured in only one, which was within the normal range (Table 1). Erythrocyte Gsα activity was assessed in two PPHP patients with elevated PTH and found to be reduced; however, the levels were higher than in our patient [23]. Another patient, who had a

paternally inherited *GNAS* defect, showed normal serum calcium and PTH but demonstrated blunted urinary cAMP and phosphate excretion in response to exogenously administered PTH [24]. The same patient also showed gradually increasing serum phosphorus levels and was clinically diagnosed with normocalcemic PHP-Ia [24]. Thus, it appears likely that in some patients with paternal *GNAS* defects, there may be proximal tubular PTH resistance. In addition, some of the reported PPHP patients with evidence of PTH resistance showed evidence of growth hormone deficiency and mild TSH resistance [22–24]. It thus appears possible that PPHP is sometimes misdiagnosed as PHP-Ia. Indeed, there are several cases reported as PHP-Ia who could instead be PPHP, since the parental origin of the genetic defect was not confirmed and serum calcium was normal [21, 27–29].

In conclusion, the findings in our PPHP patient, together with data from the literature, suggest that hormone resistance is not exclusively present in PHP-Ia. PTH resistance in renal proximal tubules and certain other hormonal deficiencies could also result from paternal *GNAS* mutations. Hence, PHP-Ia and PPHP can be clinically difficult to distinguish, and it is important to evaluate hormone resistance in both patients with paternal and maternal *GNAS* mutations. Moreover, the most effective diagnostic tool in a patient with AHO and an inactivating *GNAS* mutation is the establishment of the parental origin of the mutation, which can be accomplished by RT-PCR amplification of different *GNAS* transcripts from the patient's blood RNA.

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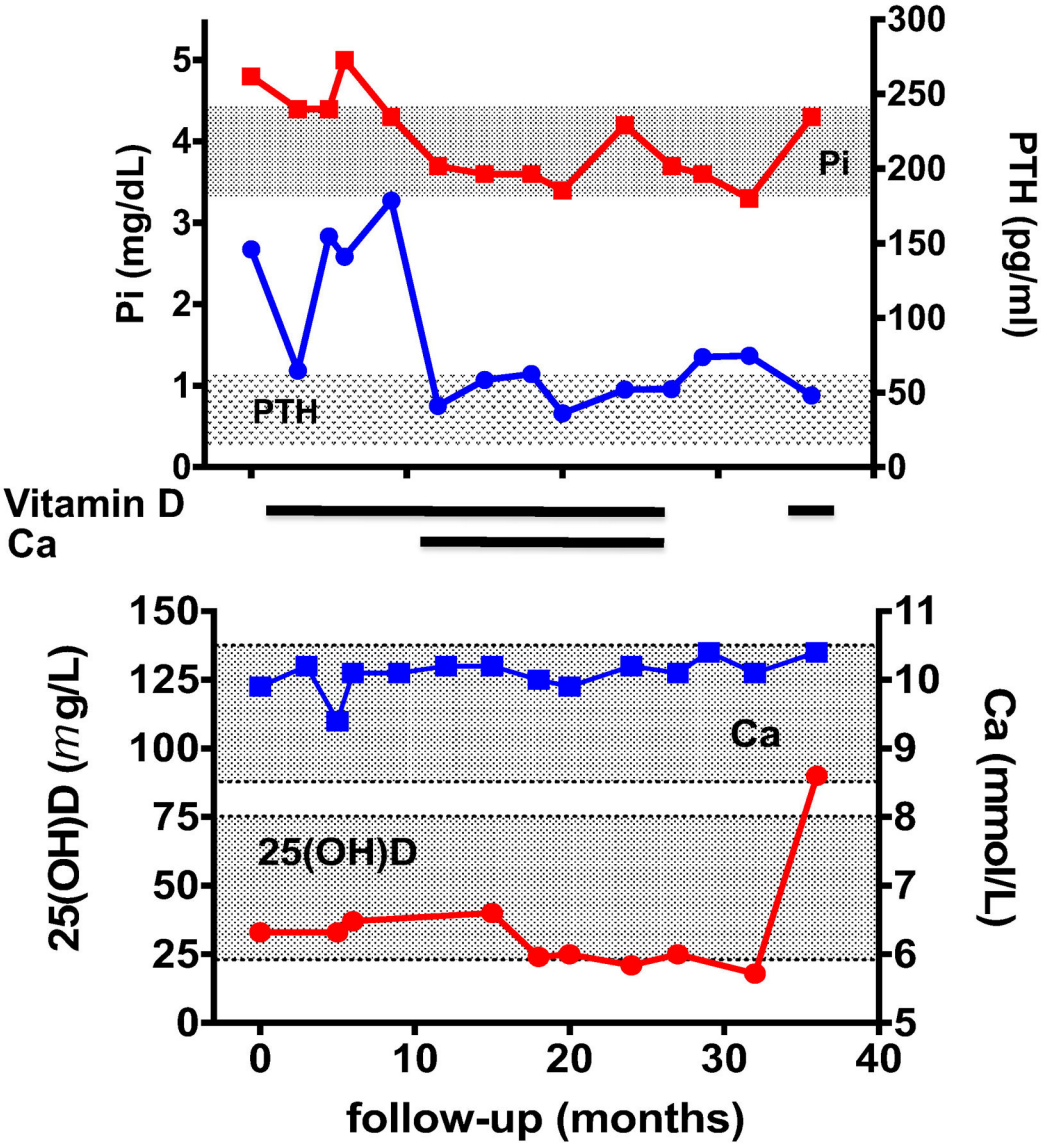

Figure 1.
Serum PTH, phosphorus (Pi), 25(OH)D and Ca values of the patient at presentation and over the follow-up period. Normal ranges are shown in shaded boxes.

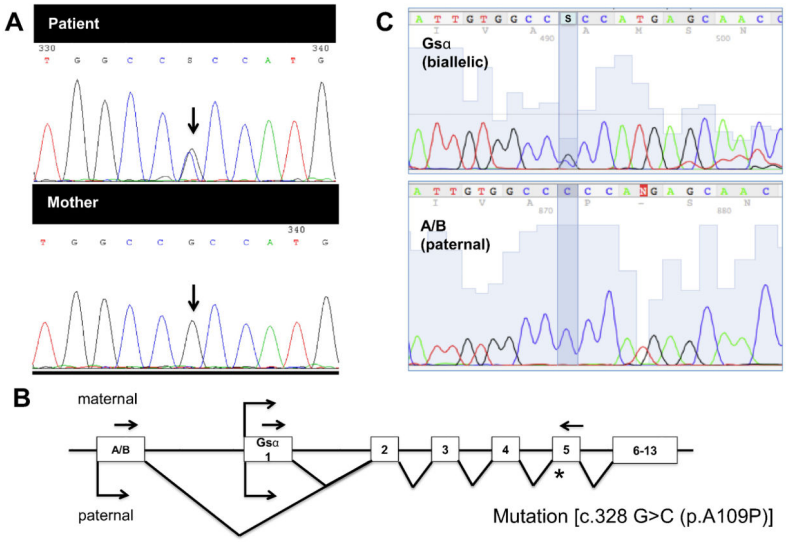

Figure 2.

Novel *GNAS* mutation on the paternal allele. (A) Nucleotide analysis of leukocyte DNA revealed a novel heterozygous *GNAS* mutation (c.328 G>C; p.A109P) in the patient (top) with no nucleotide change in the mother (bottom). (B) Partial schematic representation of *GNAS* showing exons that lead to A/B and Gsα transcripts; arrows, locations of PCR primers. (C) Sequence traces of the two RT-PCR amplicons indicating both the wild-type and the mutant nucleotides in Gsα and only the mutant nucleotide in A/B.

Table 1

Our PPHP patient and previously described PPHP patients with evidence of PTH resistance.

Case (*GNAS* defect)	**Age (yr)**	**Presentation**	**Erythrocyte Gsα activity**	**Ca (mmol/L)**	**P (mmol/L)**	**PTH (pg/mL)**	**25 OH Vit D**	**Other hormonal resistance**
Case presented herein (c.328 G>C; p.A109P)	14	Osteoma Cutis	46.7% (85–115%)*	2.48 (2.2–2.6)	1.55 (1.1–2)	146 pg/ml (9–52)	33 μg/L (20–70)	TSH normal, GH deficiency
Lau, et al. [22] **(c.1007–1017dupGACCCACGCGT)**	5/12	POH	ND**	Normal	Normal	12–40 pmol/L (1.1–5.8)	ND	TSH normal, Low IGF-1 level
Lebrun, et al. Pt #5 [23] **(c.85C>T; p.Q29X)**	14	POH	73% (80–110%)	2.3 (2.2–2.6)	1.8 (1.1–2)	88 pg/ml (10–71)	ND	Mild TSH elevation
Lebrun, et al. Pt #1 [23] **(c.345_346insT)**	10/12	POH	82% (80–110%)	2.6 (2.2–2.6)	2 (1.5–2.2)	63 pg/ml (10–60)	ND	Mild TSH elevation
Schuster, et al. [24] **(ND)**	14/12	Osteoma Cutis	ND***	Normal	High	Normal	ND	Blunted PTH-induced urinary cAMP, Exaggerated TSH response to TRH
Aldred, et al. Pt #1 [25] **(Complete paternal deletion)**	9	Dysmorphic Child	ND	2.6****	1.82****	5.6 pmol/L (1–5)	25 μg/L (14–76)	TSH normal
Ward, et al. Pt #1 [26] **(ND)**	1	Osteoma Cutis	ND	2.27 (2.25–2.75)	1.95 (1.3–2.3)	5.5 nmol/L (0.5–5.0)	ND	TSH normal, No molecular analysis.
Ward, et al. Pt #2 [26] **(ND)**	1 7/12	Osteoma Cutis	ND	2.43 (2.25–2.75)	1.81 (1.3–2.3)	7.6 nmol/L (0.5–5.0)	49 nmol/L (51–250)	TSH normal, No molecular analysis, Short-stature and brachydactyly in paternal side

* Normal ranges are in parentheses.

** ND, Not determined.

*** the patient's father showed reduced Gsα activity.

**** within the normal range.