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CASE REPORT

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Atypical presentation of pseudohypoparathyroidism with absence of mutations in the *GNAS* gene: a case report

Tao Wen[1†], Qian Liu[1†], Xiangfa Liu[1], Rongjiao You[1], Xingyue Li[1], Rongxuan Li[1], Lixi Tan[1], Jing Cheng[1], Mingfan Hong[1] and Zhongxing Peng[1*]

Abstract

Background This case report aimed to broaden the understanding of pseudohypoparathyroidism (PHP) manifestations when typical mutations in the *GNAS* gene are absent. The clinical, biochemical, and genetic investigations of a PHP case revealed diagnostic challenges and emphasized the importance of comprehensive genetic analysis for early diagnosis and appropriate management, as well as improved patient outcomes.

Case presentation The case involved a 21-year-old man who has experienced recurrent limb convulsions and episodes of altered consciousness since the age of eight. Recent assessments during frequent hospitalization uncovered findings consistent with PHP, including hypocalcemia, hyperphosphatemia, elevated parathyroid hormone level, and short stature. Notably, genetic testing did not reveal mutations in the *GNAS* gene, which could be typically associated with PHP. Diagnostic tests revealed mild abnormalities in the electroencephalogram and multiple abnormal signals in brain magnetic resonance imaging, specifically in the caudate, lenticular, dentate, and thalamus nuclei. Cranial computed tomography scan confirmed symmetrical calcifications in the basal ganglia. Biochemical analysis revealed severely altered calcium and phosphorus metabolism. Routine endocrine and neurological evaluations yielded results within normal ranges. Genetic testing identified a novel missense mutation in the *GHSR* gene, which has not been reported in the database and may reasonably explain some of the patient's phenotypic features.

Conclusions While mutations in the *GNAS* gene are the primary genetic markers for PHP, the presence of other genetic mutations in some cases complicates the clinical analysis. This case highlights the need for a comprehensive genetic screening approach in patients with PHP-like symptoms who do not exhibit mutations in the *GNAS* gene, to avoid misdiagnosis and ensure timely intervention.

Clinical trial number Not applicable.

Keywords Pseudohypoparathyroidism, Parathyroid hormone resistance, *GNAS* gene, *GHSR* gene, Case report

†Tao Wen and Qian Liu contributed equally to this work and share first authorship.

*Correspondence:
Zhongxing Peng
Pzx802@163.com
[1]Department of Neurology, The First Affiliated Hospital of Guangdong Pharmaceutical University, 19 Nonglinxia Road, Guangzhou, China

Background

Pseudohypoparathyroidism (PHP) is a rare endocrine disorder that is characterized by the body's resistance to the biological activity of parathyroid hormone (PTH), leading to hypocalcemia, hyperphosphatemia, and elevated PTH level [1]. PHP is mainly associated with mutations in the *GNAS* gene, encoding the α-subunit of the stimulatory G protein (Gsα) that is crucial for the PTH signaling pathway [2]. The characteristic features of PHP include short stature with a stocky build, brachydactyly, subcutaneous ossifications, and dental anomalies. When these manifestations are linked to mutations in the *GNAS* gene, they are collectively referred to as Albright's hereditary osteodystrophy (AHO) [3, 4].

Despite the established connection between mutations in the *GNAS* gene and PHP [5], a subset of patients exhibited the classic phenotypic features of PHP without detectable mutations in the *GNAS* gene [3]. This raises the possibility of alternative genetic pathways contributing to the disease, underscoring the complexity of its etiology and the need for more accurate diagnostic methods [3]. The present case involved a young male patient diagnosed with PHP based on both biochemical and clinical assessments. However, genetic testing revealed an absence of mutations in the *GNAS* gene. This study aimed to enhance understanding of PHP in cases without mutations in the *GNAS* gene, discuss potential genetic and epigenetic factors, and emphasize the importance of a comprehensive diagnostic approach to effectively manage such atypical cases.

Case presentation

A 21-year-old male patient was admitted to the Neurology Department of The First Affiliated Hospital of Guangdong Pharmaceutical University (China) for persistent convulsions affecting the right ocular region and limbs, a condition that he had experienced for 13 years. The convulsions, which initially occurred every two years during exercise and lasted for 4–5 s per episode, were significantly intensified over the past four years. Recently, the frequency of the seizures had escalated to approximately three episodes every two days. The patient's treatment was commenced on September 19, 2020, when he was admitted to another hospital following unsuccessful attempts at self-management due to persistent symptoms. He was diagnosed with intermittent episodic anxiety and treated with a regimen of sertraline, buspirone, diazepam, and Tianzhi granules. However, there was no notable improvement in his symptoms. Additional diagnosis was undertaken on December 22, 2020, when he underwent cranial magnetic resonance imaging (MRI). The MRI revealed symmetrical abnormal signals in the bilateral basal ganglia, suggestive of metabolic or hypoglycemic encephalopathy. Concurrent electroencephalogram (EEG) results indicated mild abnormalities. Despite these findings, no definitive diagnosis was made at that time. He had no history of hypoxia, head injury, or relevant family medical issues. He was a full-term only child, born to non-consanguineous parents without complications. His father's height was 170.0 cm, his mother's height was 155.0 cm, and his estimated target height was 169.0 cm.

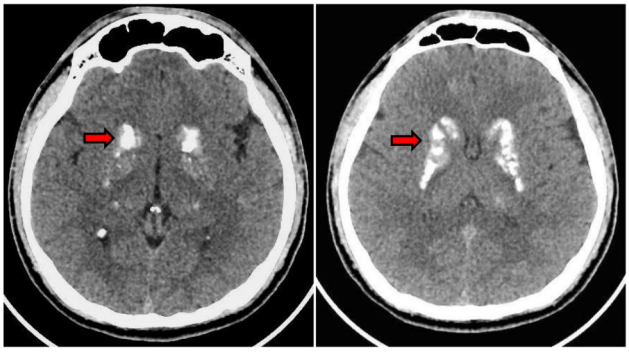

Fig. 1 Cranial computed tomography (CT) scan of the patient. This image displays symmetrical high-density shadows in the bilateral basal ganglia, which could be indicative of calcifications

Upon physical examination, the patient was alert and oriented, responding appropriately to inquiries. He was 159.0 cm (-2.25 SDS) in height and weighed 47.0 kg (-2.08 SDS). His physical development was normal, with no visible goiter, and no abnormalities detected during cardiopulmonary and abdominal examinations. He demonstrated normal muscle strength and tone in all limbs, with no evidence of muscle atrophy or joint deformity. The auxiliary examinations provided the following results: Biochemical tests indicated calcium level of 1.56 (2–2.88) mmol/L, inorganic phosphorus level of 2.14 (0.9–1.34) mmol/L, PTH level of 26.20 (1.59–7.42) pmol/L, 25-hydroxy vitamin D level of 41.1 (70–250) nmol/L, β-collagen degradation product level of 0.531 (<0.3) ng/mL, total type I collagen amino terminal extender peptide level of 108.8 (<36.4) ng/mL, and N-MID osteocalcin level of 36.15 (<26.3) ng/mL. The growth hormone level was 0.837 (0.033–2.470) ng/ml. There were no significant abnormalities in thyroid-thyrotropic hormone metabolism, sex hormones, adrenal corticosteroids, or in adrenocorticotropic hormone. EEG showed slight abnormalities, while cranial computed tomography (CT) revealed extensive symmetrical intracranial calcification (Fig. 1). Cranial MRI exhibited multiple symmetrical patchy abnormal signals across the caudate, lenticular, dentate, and thalamus on both sides, alongside localized soft tissue swelling, sinus inflammation, and slight nasal septum deviation (Fig. 2). Further evaluations, including thyroid and parathyroid ultrasound, adrenal CT, and other imaging and laboratory tests revealed no significant abnormalities. Psychometric

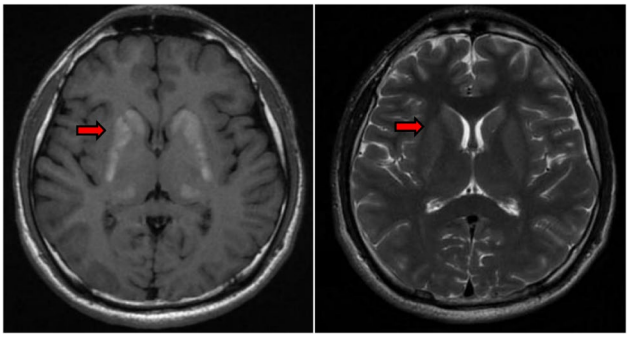

Fig. 2 Magnetic resonance imaging (MRI) of the patient's skull: T1 (left) and T2 (right) sequences. The image shows multiple symmetrical patchy abnormal signals across the bilateral lenticular, caudate, dentate, and thalamus areas, illustrating the extent of neurological involvement

assessment yielded a Self-Rating Anxiety Scale score of 45 (normal range, 20–49), a Self-Rating Depression Scale score of 48.75 (borderline), and a Mini-Mental State Examination score of 27 (normal range, 24–30) [6].

Genetic analysis: Blood samples were sent to Guangzhou Kingmed Center for Clinical Laboratory for genetic sequencing. DNA was extracted from peripheral blood samples using column-based methods, and sequencing techniques were applied to analyze genes associated with growth hormone deficiency and short stature. Genetic testing identified a c.925T > A (p.Phe309Ile) missense mutation in the exon region of the growth hormone secretagogue receptor (*GHSR*) gene (Fig. 3), suggesting a heterozygous state without typical mutations in the *GNAS* gene. This variant has not been reported in the HGMD database or the gnomAD population database. According to the ACMG guidelines, although it is classified as a variant of uncertain significance, it may reasonably account for certain phenotypic features found in the patient.

The patient was diagnosed with pseudohypoparathyroidism, which was characterized by hypocalcemia, elevated PTH level, and hyperphosphatemia. Secondary causes, such as neck surgery or radiation-induced damage, were ruled out. Treatment included sodium valproate for epilepsy and a combination of calciger and calcitriol for calcium supplementation. This treatment regimen led to notable improvements in calcium (2.01 mmol/L) and PTH (16.91 pmol/L) levels, resulting in the complete resolution of the patient's symptoms before discharge. The patient was discharged and followed up monthly for two years. He adhered to the medication regimen and experienced occasional twitching once a month, and no other significant discomfort was reported.

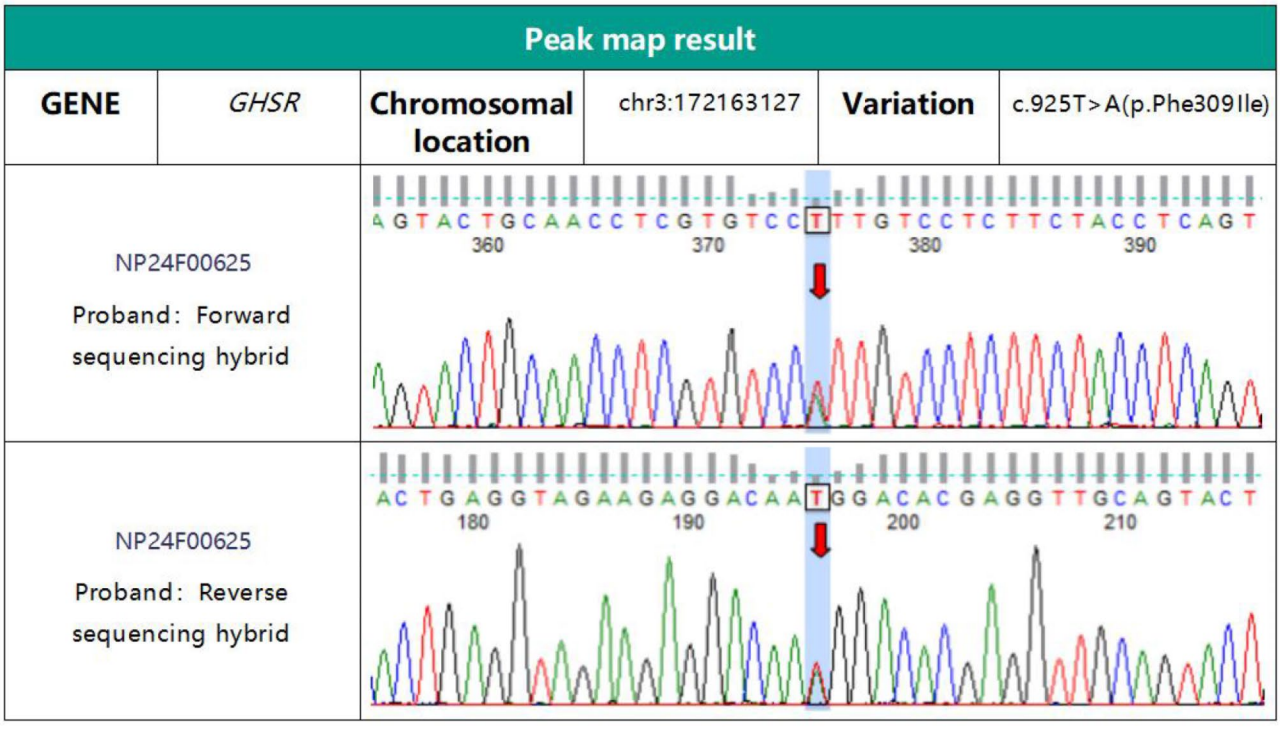

Fig. 3 Sanger sequencing results of the *GHSR* gene. This image illustrates the sequencing results for the growth hormone secretagogue receptor (*GHSR*) gene located on chromosome 3 at position 172,163,127, exon 2 (NM_198407.2). It identifies a c.925T > A (p.Phe309Ile) missense mutation in the exon region of the *GHSR* gene. This particular mutation has not been cataloged in the Human Gene Mutation Database (HGMD) or the Genome Aggregation Database (gnomAD). At present, it is classified as a variant of unknown clinical significance due to the limited evidence

Discussion and conclusions

PHP is characterized by end-organ resistance to PTH, resulting in clinical manifestations, such as hypocalcemia, hyperphosphatemia, and elevated PTH level. This resistance can occur at multiple levels of the PTH signaling pathway, primarily due to mutations or epigenetic alterations in the *GNAS* locus, which encodes the stimulatory G protein alpha subunit (Gsα) [7]. The *GNAS* complex is critical for PTH signal transduction, consisting of 13 exons and 12 introns with over 170 mutation sites identified [8, 9]. The primary pathogenesis of PHP involves Gsα dysfunction, either through direct mutations leading to its inactivation or through receptor unresponsiveness at the target organs. This dysfunction may lead to the compensatory parathyroid gland hyperplasia and the increased PTH secretion [10]. The hormone's signal is transduced through the activation of adenylate cyclase, which converts ATP to cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A, initiating multiple downstream effects to increase blood calcium level. Disruptions in this pathway, notably involving the Gsα component, result in PHP [11, 12].

Clinically, PHP is classified into type I and type II, with type I being more frequent and subdivided into type Ia (PHPIa) and type Ib (PHPIb) based on the presence of Albright's hereditary osteodystrophy (AHO) and hormone resistance profile [10]. Several studies have reported that mutations in the *GNAS* gene are frequently observed in PHP patients, with some estimates indicating a mutation rate of up to 50–70% in PHP1a cases [3, 10]. PHPIa is typically associated with mutations that affect the maternal allele of the *GNAS* gene, leading to the well-known physical manifestations of AHO, such as short stature and brachydactyly [3, 13]. Conversely, PHPIb mainly lacks these physical features, while includes biochemical features of PTH resistance. In the present case, the patient exhibited chronic convulsions and calcifications in the basal ganglia on CT scan, indicative of neurological involvement, which can be found in severe PHP cases where extensive extracellular calcium deposition occurs. His laboratory findings confirmed the biochemical criteria for PHP, and no mutations were found in the *GNAS* gene, suggesting an alternative genetic etiology [14].

Mutations in the *GHSR* gene may lead to isolated growth hormone deficiencies with phenotypic overlaps with PHP, particularly when *GHSR*-related signaling pathways are disrupted. *GHSR*, a G protein-coupled receptor (GPCR), plays a crucial role in regulating growth hormone secretion and is implicated in various cellular pathways, including those governing food intake and energy homeostasis [15, 16, 17]. Mutations in the *GHSR* gene could disrupt these pathways, as dysfunction of the GHSR receptor may impair normal hormone signaling and indirectly influence calcium metabolism. However, the exact mechanism by which *GHSR* mutations contribute to hypocalcemia remains elusive, requiring further research to explore its potential relationship with calcium metabolism.

The clinical diagnosis of PHP relies on genetic and biochemical assessments. Notably, other potential causes of PHP may exist, such as methylation changes, affecting GNAS-DMRs, particularly GNAS A/B: TSS-DMR. The lack of methylation analysis is a limitation of this study. Furthermore, whether *GHSR* gene variants are associated with the PHP phenotype should be further determined. This underscores the ongoing need for research to elucidate the genetic complexity of PHP and the potential contributions of additional genes to its pathogenesis [18]. In clinical practice, this necessitates a comprehensive diagnostic approach, including comprehensive genetic testing and consideration of non-traditional genetic pathways, particularly when classical mutations are absent.

In conclusion, PHP presents a diagnostic challenge due to its complex genetic and epigenetic landscape. This case not only improves the understanding of PHP's genetic diversity, but also highlights the importance of considering alternative genetic mechanisms in patients with typical biochemical features of PHP, while without mutations in the canonical *GNAS* gene. Early recognition and treatment are crucial to manage the metabolic disturbances in PHP and to prevent long-term complications.

Abbreviations

PHP	Pseudohypoparathyroidism
PTH	Parathyroid hormone
MRI	Magnetic resonance imaging
EEG	Electroencephalogram
CT	Computed tomography
AHO	Albright's hereditary osteodystrophy
GHSR	Growth hormone secretagogue receptor
GPCR	G protein-coupled receptor
cAMP	Cyclic adenosine monophosphate
Gsα	G protein α-subunit
PHPIa	Pseudohypoparathyroidism type Ia
PHPIb	Pseudohypoparathyroidism type Ib

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Author contributions

TW and ZXP conceptualized and designed the study. TW collected the data, drafted the initial manuscript, and reviewed and revised it. QL, XFL, RJY, XYL, RXL, LXT, JC, and MFH coordinated and supervised data collection and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability

The datasets generated and analyzed during the current study are available in the NCBI ClinVar repository, ClinVar accession number: SCV005402452. https:/

/www.ncbi.nlm.nih.gov/clinvar/variation/3383212/?oq=SCV005402452&m=NM_198407.2(GHSR):c.925T%3EA%20(p.Phe309Ile).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The First Affiliated Hospital of Guangdong Pharmaceutical University (number: 2024-IIT-93). All study procedures were conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent to participate in this study was provided by the patient.

Consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare no competing interests.

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