

# A patient with pseudohypoparathyroidism type 1A previously misdiagnosed as hereditary multiple exostosis: A case report

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**Abstract.** Pseudohypoparathyroidism type 1A (PHP1A), a rare hereditary disorder, is featured by end-organ resistance to parathyroid hormone and Albright's hereditary osteodystrophy. Heterozygous mutation of guanine nucleotide-binding protein  $\alpha$  stimulating (*GNAS*) gene causes the half decreased bioactivity of the G $\alpha$ s protein levels. Due to the diverse early clinical manifestations of PHP1A, a diagnosis of PHP1A is often easily overlooked and misdiagnosis or missed diagnosis is common. The present study described a girl who was initially diagnosed with hereditary multiple exostoses, but was afterwards confirmed with PHP1A. Moreover, genetic analysis indicated a new mutation (c2277deIC) of the gene.

## Introduction

Pseudohypoparathyroidism (PHP) is a rare hereditary disease and historically the first hormone resistance syndrome (1). It is estimated that the prevalence of PHP is approximately 0.34–1.1 per 100,000 (2–4). In patients with normal renal function, hyperphosphatemia as well as hypocalcemia are related to a decreased calcemic and phosphaturic response to injection of bovine parathyroid extract, in contrast to those with primary hypoparathyroidism, triggering the hypothesis of resistance to PTH action (2–4). PHP can be classified into pseudohypoparathyroidism type 1A (PHP1A), pseudoPHP (PPHP) and PHP type 1B (PHP1B), caused by maternal and paternal *GNAS* mutations and abnormal

methylation at maternal guanine nucleotide-binding protein  $\alpha$  stimulating (*GNAS*) promoter(s), respectively (5). Maternal loss-of-function mutations at *GNAS* exons 1–13 cause PHP type 1A (PHP1A). When patients have a similar phenotype to PHP1A but do not have a mutation in *GNAS*, other related disorders need to be considered. Phenotypic studies in patients with PHP1A reveal the presence of Albright Hereditary Osteodystrophy (AHO), including brachydactyly, subcutaneous ossifications, round facies as well as short stature (2). Due to the variable manifestations of early clinical of PHP1A, the diagnosis of PHP1A is often easily overlooked, with frequent misdiagnosis or missed diagnosis. To this end, this case report described a girl who was initially diagnosed with hereditary multiple exostoses (HMEs), but was afterwards confirmed with PHP1A. Moreover, genetic analysis indicated a new mutation (c2277deIC) of *GNAS* gene from maternal *GNAS* mutations.

## Case report

A 12-year-old girl presented to the inpatient department of Hangzhou Children's Hospital in February 2019, complaining of recurrent convulsions for 1.5 months and frequent episodes of four days. In February 2017, she was admitted at the Department of orthopedic of Jinhua Central Hospital due to double-footed mass for more than seven years. At that time, she was diagnosed with HMEs (double heel) and further received operation.

The physical examination of the girl showed short stature (height 135 cm), central obesity (weigh 34 kg), rounded face and mild mental retardation. The girl denied any family history of heterotopic ossification or inherited diseases. Additionally, her parents and two brothers were none of them were diagnosed with AHO, with normal serum concentration of calcium and phosphorus.

X-rays of hand and foot indicated: i) local cortical rough defect in left ulna and distal humerus, local mild periosteal reaction; ii) exogenous small osteophytes on the lateral side of the left heel and the ulnar side of left hand and iii) multiple small soft-tissue calcifications of the left palm, wrist and ankle (Fig. 1). Cerebral computed tomography (CT) revealed extensive symmetric calcifications

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Figure 1. X-ray of hand and foot shows. (A) Local cortical rough and defect in left ulna and distal humerus, local mild periosteal reaction. (B) Exogenous small osteophytes on the lateral side of the left heel and the ulnar side of left hand. (C and D) Multiple small soft-tissue calcifications of the left palm, wrist and ankle.

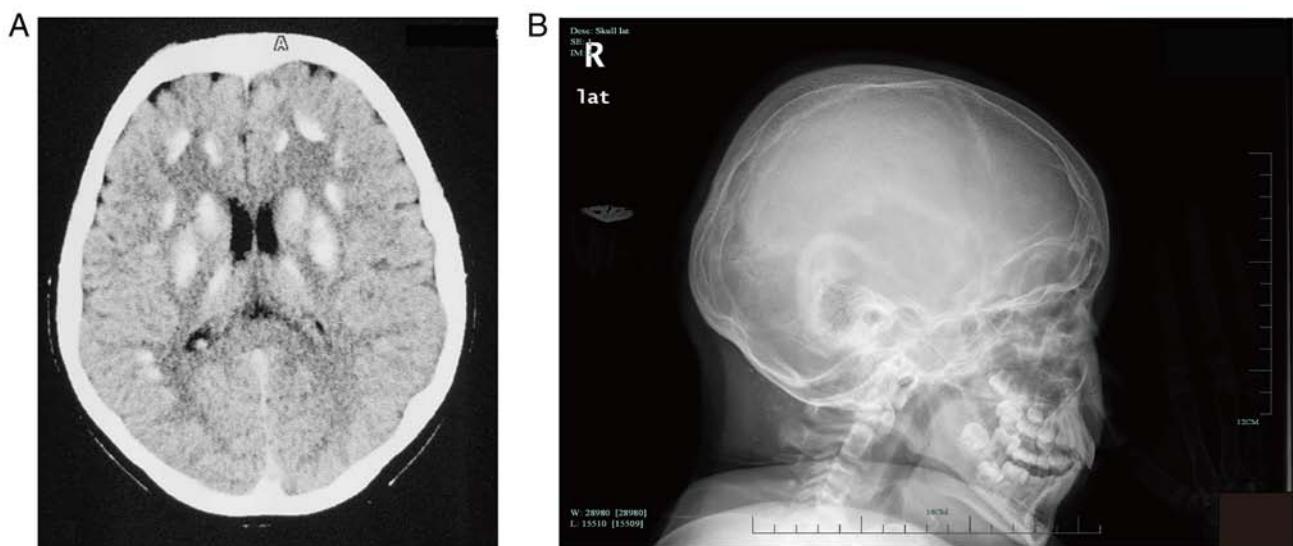


Figure 2. Cerebellar calcifications. (A) CT scan and (B) X-ray.

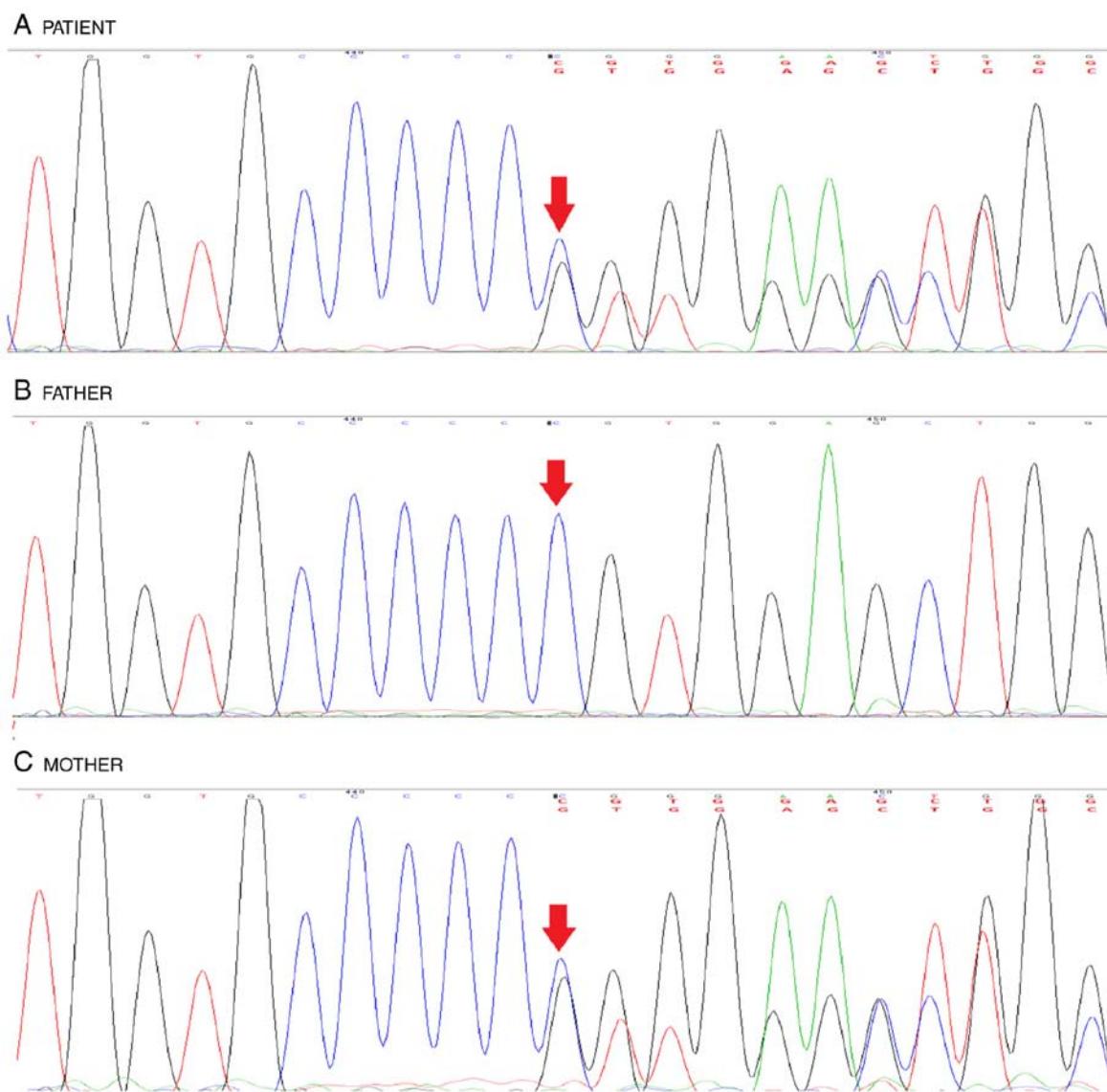


Figure 3. c.2277delC was observed in lymphocytes of the patient, in the mother's blood sample but not detected in the father. (A) Patient. (B) Father. (C) Mother.

in the basal ganglia, thalami and cerebellar hemispheres (Fig. 2). Abdominal ultrasound showed left kidney crystallization and left liver calcification. Laboratory examination showed hypocalcemia, blood levels of calcium 1.68 mmol/l (normal range 2.08-2.6 mmol/l), hyperphosphatemia, phosphorus 2.48 mmol/l (normal range 0.96-1.62 mmol/l), magnesium 0.73 mmol/l (normal range ~0.65-1.25 mmol/l) and parathyroid hormone 981.00 ng/l (normal range ~0-88.00 ng/l), alkaline phosphatase (ALP) 318 U/l (normal range ~0-500), 24 h urinary calcium 0.07 mmol/24 h (normal range ~0-6.25 mmol/24 h), serum 25-hydroxy vitamin D (37.02 nmol/l, normal range: 25-1251 nmol/l). Serum levels of thyroid hormone were normal, the values of TSH reveal TSH resistance (free T<sub>3</sub>: 6.01 pmol/l, normal range: ~3.00-7.50 pmol/l; free T<sub>4</sub>: 11.96 pmol/l, normal range: ~8.37-29.60 pmol/l; TSH: 5.69 mU/l, normal range: ~0.4-4.00 mU/l). Serum insulin-like growth factor-1 (IGF-1) was normal 318.5 ng/ml (normal range: 126-678 ng/ml). Sex hormones, growth hormone and cortisol rhythm were also normal.

Genetic counseling and analysis were offered to the girl and her family members after signing informed consent. DNA samples isolated from blood specimens were analyzed by Sanger sequencing as well as multiplex ligation-dependent probe amplification (MLPA), aiming to determine whether there was a *GNAS* gene mutation, in line with standard protocols. As a result, heterozygous c.2277delC (p.Val760TrpfsTer16) frameshift mutation was detected. The targeted mutation analysis of the *GNAS* gene revealed a defined mutation with PHP1A, PPHP or POH, depending of the allele involved. After analysis of clinical manifestations and gene types, the patient was diagnosed with PHP. Moreover, her mother was detected to harbor *GNAS* gene mutation (Fig. 3).

MLPA analysis further eliminated the additional pathogenic mechanism with *GNAS* locus, including deleted or aberrant methylation profiles. However, the present study was unable to conduct further research to examine the expression or activities of Gα protein.

The patient was treated with intravenous and oral calcium replacement therapy to target hypocalcemia, with

administration of 1, 25 hydroxyl vitamin D3 (0.04 µg/kg/d). Serum calcium level, pituitary hormones as well as thyroid function were regularly monitored until no episodes of hypothyroidism, hypocalcemia or seizure.

## Discussion

Target-organ resistance to other hormones are commonly observed in patients with PHP1A, acting through G<sub>α</sub>-coupled receptors, particularly TSH (6). There are also studies concerning resistance to gonadotrophins as well as GHRH (6,7). There are diverse presentation and different degrees of severity in PHP1A as well as its relevance among different individuals, in which there are considerable overlapping of clinical and molecular features between the different types (3). Patients with PHP1A are burdened with half decreased activity of G<sub>α</sub> subunit, due to decreased amounts of G<sub>α</sub> (2). The human G<sub>α</sub> gene (*GNAS*), contains 13 exons located at 20q13, with cDNA length of approximately 1.2 kb (4). Heterozygous mutation of the coding region of *GNAS* gene can lead to attenuated bioactivity of G<sub>α</sub> protein levels (8). In the present study, a heterozygous c2277delC (p.Val760TrpfsTer16) frameshift mutation was detected in the patient. However, her mother harbored a heterogeneous mutation in the *GNAS* gene and yet had no signs or symptoms of AHO. These discrepancies in the phenotype depending on the transmitting parent are explained by a tissue-specific imprinting of *GNAS*. When the mutation is carried by the maternal allele, there is a partial to complete deficit in G<sub>α</sub> depending on the severity of the mutation (9).

Another feature of PHP1A is the development of heterotopic subcutaneous ossifications. When in isolation, the condition is termed osteoma cutis, which is the first sign of a more severe PHP disorder. There is no definitive treatment and removal can cause regrowth that is worse (10,11). Nevertheless, the diagnosis might remain uncertain under the majority of clinical situations, due to the misdiagnosis of these clinical symptoms as nonspecific in the normal population. By retrospectively analyzing the medical history concerning the evolution of disease progression throughout the patient's lifetime: TSH resistance caused PTH resistance-related hypocalcemia as well as hypothyroidism in early stage, followed by bilateral heel disease and worsening hypocalcemia and recently recurrent seizures.

The clinical manifestations of PHP-1A are variable and the rate of misdiagnosis is high. Due to different complaints, the patients were admitted in different departments. The child had been treated with a double-pedal mass for 7 years. Considering congenital multiple osteochondroma (double heel), attention should be paid to blood calcium, blood phosphorus and PTH levels during the operation and physical examination should be carried out to determine whether there is physical development. In delayed and AHO performance; the disease is mostly the first consultation in neurology and emergency departments, often with convulsions as the main complaint, so when patients with suspected seizures are examined, blood calcium, blood phosphorus and brain CT should be detected. Careful examination of the presence or absence of AHO performance, for patients with normal renal

function but with low calcium, hyperphosphatemia, should involve checking the blood calcium, blood phosphorus and PTH level to assist in the diagnosis, as well as early calcium and active vitamin D3, to correct hypocalcemia and to ensure the diagnosis as soon as possible, to prevent death caused by severe low calcium convulsions. The present study indicated the clinical significance of early diagnosis of PHP1A, which serves a critical role in proper therapeutic approaches and long-term management strategies, essential for both the patient and the family. Notably, proper genetic counseling also serves a significant role in establishment of effective communication with the family, rendering efficient information exchange and the successful performance of genetic analysis. Therefore, multidisciplinary screenings, along with individualized therapeutic strategies are strongly recommended to enhance the clinical outcomes in real-world practice (3,12). In practice, clinicians should use a combination of phenotypic and genotypic information to suggest and confirm the diagnosis of PHP1A.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

JZ and MG obtained and analyzed the patient's information and wrote the manuscript. SZ, SW, LW and WS obtained and analyzed the patient's information and reviewed the discussion part of the clinical manifestations and imaging features. JZ, MG, LW and WS confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Hangzhou Children's Hospital (approval number 201901, Hangzhou, China).

## Patient consent for publication

Written informed consent to publish this case report was obtained from the patient and her family.

## Competing interests

The authors declare that they have no competing interests.

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