JIG Journal of Interdisciplinary Genomics

https://doi.org/10.22742/JIG.2023.5.2.29
Journal of Interdisciplinary Genomics 2023;5(2):29-31
eISSN 2671-6771

# Pseudohypoparathyroidism: Clinical Review of Diagnosis and Genetic Etiology

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Pseudohypoparathyroidism (PHP) is very rare and shows heterogeneity with impaired genetic components. PHP is characterized by parathyroid hormone resistance to target organ, related with a *GNAS* (guanine nucleotide-binding protein α-subunit) mutation and epimutation. PHP receptor is coupled with the stimulatory G protein which activates cyclic adenosine monophosphate formation. PHP type 1A is caused by inactivating mutations on the maternal allele of the *GNAS* whereas paternal allele mutations cause pseudopseudohypoparathyroidism. PHP type 1B is caused by abnormal patterns of methylation in differentially methylated region which can be divided into partial or complete. This disease has some difficulties to diagnose according to these different molecular alterations caused by complex genetic and epigenetic defects. According to this different molecular alterations, genetic confirmation must be done to discriminate their etiology.

Key words: GNAS, Hypocalcemia, Parathyroid hormone, Pseudohypoparathyroidism

**REVIEW ARTICLE**

**Received:** October 10, 2023
**Revised:** October 25, 2023
**Accepted:** October 30, 2023

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## INTRODUCTION

Pseudohypoparathyroidism (PHP) is very rare and shows heterogeneity with impaired genetic components. Its exact prevalence is unknown because of rarity, the estimated prevalence as 0.34 in 100,000 and 1.1 in 100,000 in Japan [1] and Denmark [2] respectively. PHP is characterized by parathyroid (PTH) resistance to target organ, related with a *GNAS* (guanine nucleotide-binding protein α-subunit) mutation and epimutation. PHP comprises OMIM #103580 for PHP type 1A (PHP-1A), #603233 for PHP type 1B (PHP-1B), and #6212462 type 1C (PHP-1C), which share common features of hypoparathyroidism [3].

To understand PHP pathophysiology, it is necessary to identify the PHP receptor and its signaling pathway. PHP receptor is coupled with the stimulatory G protein (Gs) which activates cAMP formation. Some cases show the resistance of other hormones (such as thyroid stimulating hormone (TSH), gonadotropin, calcitonin and growth hormone-releasing hormone) which have receptors coupled to Gs [4,5].

Albright hereditary osteodystrophy (AHO) comprises heterogeneous clinical manifestations such as ectopic ossification, round face, central obesity, short stature, brachydactyly and mental retardation. AHO was described with PHP in 1942, PHP type 1 is differentiated to the presence (PHP-1A and PHP-1C) and absence (PHP-1B) of AHO [6,7].

## CLINICAL PRESENTATIONS AND GENETIC CAUSES

### PHP-1A and PHP-1C

PHP-1A has multiple hormone resistances as well as PTH and TSH, gonadotro-

pin, and growth hormone releasing hormone (GHRH) which act via Gs-coupled receptor. The PTH resistance to renal proximal tubule leads to hypocalcemia, hyperphosphatemia, and elevated circulating PTH, generally preceding hypocalcemia usually over 1st years of life. PHP-1A shows clinical features of AHO, but these clinical features are very vague, it is diagnosed based on severe hypocalcemic symptoms such as seizure, tetany, paresthesia during childhood, requiring more calcium [3, 8]. Along with PHP resistance, almost PHP-1A patients have TSH resistance which is generally mild. But some patients are misdiagnosed only as congenital hypothyroidism by newborn screening test [9]. PHP-1A patients, especially females, have hypogonadism which is diagnosed as delay puberty, amenorrhea, or infertility. Almost all PHP-1A have an autosomal dominant pattern and caused by heterozygous loss-of function mutation in the *GNAS* gene [10,11]. Interestingly, patients inheriting from maternal mutation present phenotype of AHO as well as multiple hormone deficiency. However, patients inheriting from paternal mutation of this gene, show only AHO features without multiple hormone resistance (pseudo-pseudohypoparathyroidism, PPHP) [12].

*GNAS* is an imprinting gene which encodes Gsα coupled to PTH receptor, and locus is located on chromosome 20q13.22. This Gsα have a predominant maternal expression in specific maternal expression in some endocrine tissues, therefore is known as tissue-specific paternal imprinting of gene. This parent-of-origin-specific difference, *i.e.*, tissue-specific hormone responsive is expected in renal proximal tubule, thyroid, and ovary. The *GNAS* gene contains 13 exons which can be affected by loss-of function alterations [13]. Altered translation initiation or aberrant mRNA splicing by small insertion/deletions or amino acids substitutions have been reported. PPHP patients usually coexist, those patients have no hormone resistance but a partial deficiency (50%) of Gsα activity in various cell (fibroblast, erythrocytes) and show only the AHO. The diagnosis of PPHP with only phenotype is very difficult. The phenotype of PHP-1C is like PHP-1A, which is the AHO and multiple hormone resistance, but there is no deficiency of Gsα activity in various cell which PHP-1A showed. Few inactivating mutations is reported about PHP-1C.

### PHP-1B

PHP-1B is characterized with resistance to PTH and normal Gsα activity without AHO features. Recently mild TSH elevations have been reported. These defects are often sporadic but caused by familial with an autosomal dominant pattern. Interestingly, like PHP-1A, PTH resistance develops with maternal inheritance, whereas paternal inheritance is not related with hormone resistance. There are no clinical differences between sporadic and familial mutations. PHP-1B is caused by methylation defects of the imprinted *GNAS* cluster. *GNAS* locus comprises several transcripts like the Gsα extra-large variant (XLαs), the neuroendocrine protein (NESP 55), untranslated exon A/B, and an additional antisense transcript. The familial form of PHP-1B is associated with loss of methylation at GNAS exon A/B or microdeletions on the cis-acting control elements on *STX16* gene in maternally inheritance with autosomal dominant pattern [14,15].

## *GNAS* GENE AND IMPRINTING

The human *GNAS* gene comprises 13 exons and maps to chromosome 20q13. The mutations, loss-of-function, are developed in any coding region. Insertions, deletions, amino acids substitutions, nonsense, point mutations can alter translation initiation and aberrant mRNA splicing. PHP subtypes are caused by autosomal dominantly inheritance (mainly) or de novo mutation or epigenetic alterations (sporadic or familial). *GNAS* is imprinting gene, biallelic expression is shown in most cells but maternal expression is primarily observed in thyroid, renal proximal tubule, pituitary, and ovary cells. Therefore, this tissue specific monoallelic expression determines clinical outcome that depends on origin of paternal *GNAS* mutations.

PHP-1A is caused by inactivating mutations on the maternal allele of the *GNAS* whereas paternal allele mutations cause PPHP. Point mutation is easily detected by sequencing but genomic rearrangement needs analysis like multiple ligation-dependent probe amplification (MLPA) or comparative genomic hybridization [16,17].

PHP-1B is caused by abnormal patterns of methylation in the differentially methylated regions (DMR) which can be divided into partial or complete. *GNAS* has four different DMRs which are one paternally methylated DMR and three maternally methylated DMR. About 15%–20% are familial among the PHP-1B, and the methylation defect is generally limited at *GNAS* A/B:TSS-DMR. Methylation defects can be usually detected by methylation-sensitive MLPA [18].

## CONCLUSION

Patients with PHP and related disorders develop a wide spectrum of clinical manifestations from early infancy to adulthood.

These symptoms include changed mineral metabolisms, which can cause seizures and other endocrine deficiencies. These highly heterogeneous features need early accurate genetic confirmation. This disease has some difficulties to diagnose according to these different molecular alterations caused by complex genetic and epigenetic defects. Therefore, patients sometimes need time-consuming to be established for a correct molecular diagnosis. This review might be helpful to diagnosis PHP and more genetic analysis for *GNAS* gene seems to be necessary.

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