

Pseudopseudohypoparathyroidism With a Novel Mutation in the GNAS Gene Showing Thin Bones of Extremities and Ossification of Enteses

Hidetaka Hamasaki^a, Takahiko Mukaino^b, Hiroshi Kaneko^c, Toshikatsu Mitsui^d,
Sumie Moriyama^a, Tomonobu Hasegawa^d, Hidekatsu Yanai^{a, e}

Abstract

Pseudopseudohypoparathyroidism (PPHP) is an extremely rare disorder caused by mutations in the *GNAS* gene. PPHP as well as pseudohypoparathyroidism (PHP) shows Albright hereditary osteodystrophy (AHO) such as mental retardation, round face, short stature, central obesity, short fingers and toes. Here we report a patient with PPHP and type 2 diabetes who had a novel mutation in the *GNAS* gene and showed atypical heterotopic ossification, ossification of enteses, and also thin bones of extremities, in addition to characteristic clinical features for AHO.

Keywords: Albright hereditary osteodystrophy; Ossification of enteses; Pseudopseudohypoparathyroidism; Thin bones; Type 2 diabetes

Introduction

Pseudopseudohypoparathyroidism (PPHP) is an extremely rare disorder caused by mutations in the *GNAS* gene [1]. Mutations in *GNAS*, the imprinted gene complex encoding the α -subunit of the stimulatory G protein (*G α s*) are responsible for some inherited disorders such as pseudohypoparathyroidism (PHP) and PPHP [2]. These disorders usually show heterotopic ossification as a clinical feature of Albright

hereditary osteodystrophy (AHO) [3]. However, *GNAS*-associated disorders of heterotopic ossification have a broad clinical spectrum [4, 5], and its phenotype has not been fully understood. Progressive osseous heteroplasia (POH), another disorder of ectopic extraskeletal ossification, is dermal and subcutaneous ossification. The bone formation is more severe and ossification progresses into muscle and deep connective tissue during childhood [6]. To date, some cases with features of both AHO and POH-like heterotopic ossification have been described [7]. In this report, we describe a patient with PPHP and type 2 diabetes with a novel mutation in the *GNAS* gene that shows atypical heterotopic ossification and thin bones of extremities.

Case Report

A 46-year-old woman was admitted for the treatment of type 2 diabetes. She was diagnosed as having type 2 diabetes 2 years ago. She had mental retardation and epileptic seizure in early childhood. Her gait was unstable until she became 6 years old. Her father, paternal grandmother and aunt also had mental retardation. Her body height, weight, body mass index and abdominal circumference were 149.5 cm, 76.2 kg, 34.2 kg/m² and 92 cm, respectively. She showed round face, short stature, central obesity and short fingers and toes, suggesting the existence of AHO. She also has pleasant nature, supporting the diagnosis of AHO. Surprisingly, her bones of extremities were very thin (Fig. 1), with normal bone density. Normal serum levels of calcium, inorganic phosphorus and intact parathyroid hormone (PTH), and a negativity of the Ellsworth-Howard test suggested the existence of PPHP. Interestingly, ossification of enteses was also observed (Fig. 2). DNA sequence analysis showed a novel mutation in exon 1 (c.137 T > G, L46P) of the *GNAS* gene (Fig. 3). She was heterozygous for this mutation.

Discussion

PPHP is caused by mutations in the *GNAS* gene and is inherited in an autosomal dominant fashion. When inherited

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^aDepartment of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan

^bDepartment of Neurology, Kyushu University, Fukuoka, Japan

^cDepartment of Rheumatology, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan

^dDepartment of Pediatrics, Keio University School of Medicine, Tokyo, Japan

^eCorresponding author: Hidekatsu Yanai, Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Chiba 272-8516, Japan.

Email: dyanai@hospk.ncgm.go.jp

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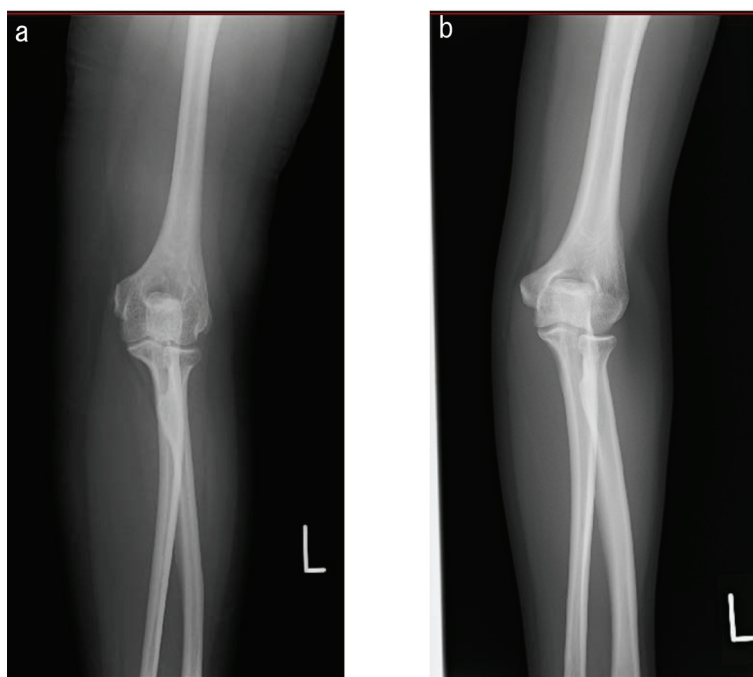


Figure 1. Radiograph of arm in a patient with pseudopseudohypoparathyroidism. Arm of (a) a patient and (b) a 35-year-old normal woman with body height 154 cm, body weight 46 kg and body mass index 19.4 kg/m².

paternally, heterozygous *GNAS* mutations affecting *GNAS* exons that encode *G α s*, cause PPHP characterized by the clinical features including round face, short stature, central obesity, subcutaneous ossifications and short fingers and toes

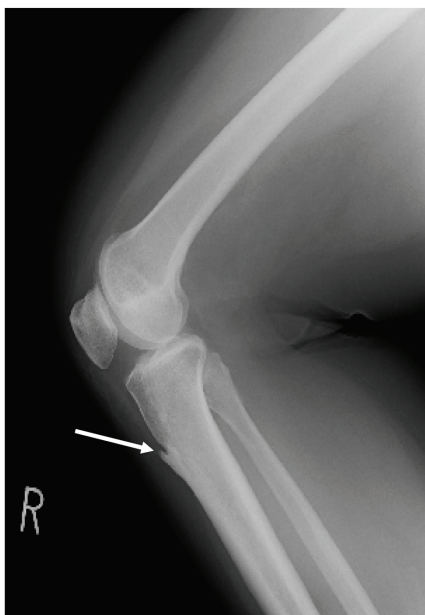


Figure 2. Radiograph of knee in a patient with pseudopseudohypoparathyroidism. Arrow indicates ossification of entheses.

observed in AHO in the absence of hormones resistance [3]. When inherited maternally, heterozygous mutations cause PHP type Ia (PHP Ia) [8]. Our patient was heterozygous for a novel mutation of the *GNAS* gene. It is exactly unknown whether her father had the same mutation of the *GNAS* gene, because her father already died. Her father also had mental retardation and clinical features similar to our patient, suggesting that her *GNAS* gene mutation might be possibly inherited paternally. PPHP is a genomic imprinting disorder resulting from decreased activity of *GNAS*, and is usually inherited from the father [2]. *GNAS* is a complex imprinted gene locus that encodes the signaling protein *G α s* which couples receptors for hormones and neurotransmitters to activation of adenylyl cyclase [9].

Pure POH (no other AHO features) is also caused by a paternal inheritance of *GNAS* mutations [10]. Ossification of entheses as observed in our patient may be a partial clinical presentation of POH due to a mutation in exon 1 (c.137 T > G, L46P) of the *GNAS* gene. Our patient also showed thin bones of extremities; however, it remains unknown whether the *GNAS* mutation influenced bone thinness of extremities or not.

A precise prevalence of PPHP has not ever been reported because PPHP is an extremely rare disease. Furthermore, PPHP complicated with type 2 diabetes is also quite rare [11]. The genetic association between PPHP and type 2 diabetes is also unidentified. To our knowledge, this patient is the first case with PPHP to show thin bones of extremities,

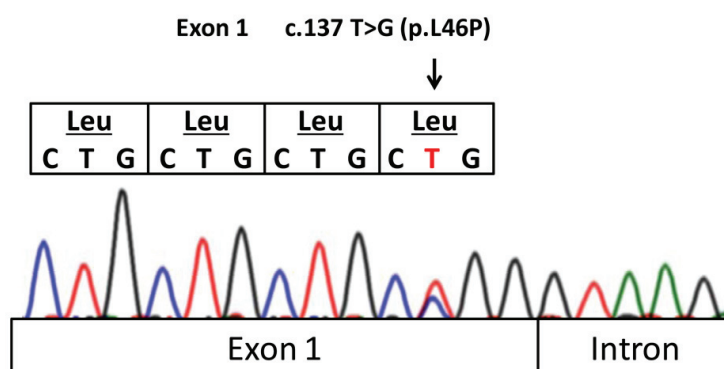


Figure 3. A novel mutation of the *GNAS* gene in a patient with pseudopseudohypoparathyroidism.

ossification of entheses, in addition to characteristic clinical features for AHO. We should investigate more cases to elucidate the pathophysiology of PPHP.

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Conflict Interests

The authors declare that they have no competing interests.

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