



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

# AAACE Clinical Case Reports

journal homepage: [www.aaace.com](http://www.aaace.com)



## Case Report

# Skeletal Complications With GNAS Mutation: An Unusual Case With Osteoma Cutis, Gout, and Synovial Chondromatosis in a Patient With Pseudopseudohypoparathyroidism

Jane Rhyu, MD<sup>\*</sup>, Shalini P. Bhat, MD

Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

## ARTICLE INFO

### Article history:

Received 6 August 2020  
Received in revised form 21 November 2020  
Accepted 30 November 2020  
Available online 7 January 2021

### Key words:

bone diseases  
endocrine  
genetics  
parathyroid disorder

## ABSTRACT

**Objective:** We present a patient with pseudopseudohypoparathyroidism (PPHP) who developed both gout and synovial chondromatosis, in addition to the classical Albright's hereditary osteodystrophy phenotype.

**Methods:** The patient's clinical course, laboratory data, and imaging are presented.

**Results:** The patient is a 40-year-old male with no pertinent family history who presented with findings of Albright's hereditary osteodystrophy, including short stature, obesity, rounded face, shortened fourth and fifth digits, and osteoma cutis (heterotopic subcutaneous ossification), which required surgical removal for pain relief. Genetic testing confirmed a GNAS mutation, and labs showed normal parathyroid hormone, calcium, and phosphorus levels, diagnostic of PPHP. The patient later developed gout and synovial chondromatosis, a rare benign process where the synovial membrane forms calcified loose bodies within the joint.

**Conclusion:** The patient case highlights the musculoskeletal complications of PPHP. Though PPHP has been rarely associated separately with gout or synovial chondromatosis, this is the first reported patient to have developed both conditions. This case raises the significance of multidisciplinary follow up for potential orthopedic complications. Moreover, the case underscores the importance of genetics and epigenetics in skeletal health, independent of calcium homeostasis in the blood.

© 2021 AAACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Pseudopseudohypoparathyroidism (PPHP) is a rare, inherited condition that presents with the characteristic phenotype of Albright's hereditary osteodystrophy (AHO) that also occurs in pseudohypoparathyroidism (PHP), without the parathyroid resistance syndrome and associated laboratory abnormalities that occur in the latter.<sup>1–3</sup> AHO consists of a constellation of physical exam findings, including a short stocky physique, round face, early-onset obesity, brachydactyly, osteoma cutis, and possible

mild developmental delay.<sup>1,4,5</sup> While PHP is characterized by elevated parathyroid hormone (PTH) levels, hypocalcemia, hyperphosphatemia, and low calcitriol levels, these labs are normal in PPHP.<sup>1,4,5</sup>

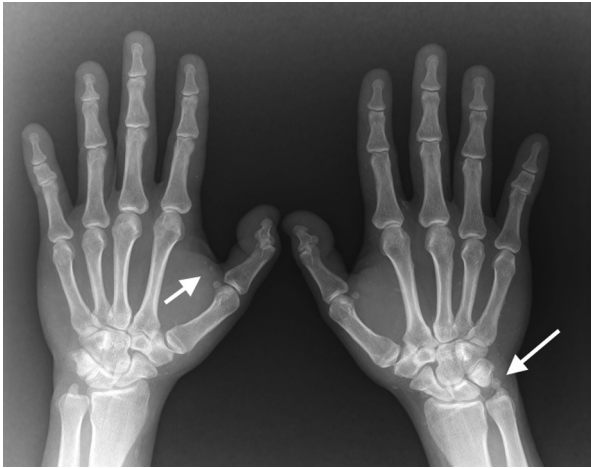
Both PPHP and PHP are caused by mutations in the GNAS locus of chromosome 20q13.3, which undergoes imprinting.<sup>1,3</sup> Due to differential expression in tissues and primarily maternal expression in the kidney, mutations in the maternal allele lead to PHP.<sup>1,3</sup> Due to haploinsufficiency in the bone, mutations in either maternal or paternal allele lead to the AHO phenotype.<sup>1,3</sup>

Though PPHP is rare, occurring in approximately 0.79 per 100 000 individuals,<sup>6</sup> the condition provides a significant insight into the role of GNAS and epigenetic expression in musculoskeletal development. We describe a case of a patient who developed gout and synovial chondromatosis as potential complications of PPHP, in addition to the usual AHO phenotype. Our case highlights a wide range of potential musculoskeletal complications in PPHP, which is

*Abbreviations:* AHO, Albright's hereditary osteodystrophy; GS $\alpha$ , stimulatory G protein alpha subunit; PHP, pseudohypoparathyroidism; POH, progressive osseous heteroplasia; PPHP, pseudopseudohypoparathyroidism; PTH, parathyroid hormone.

<sup>\*</sup> Address correspondence and reprint requests to Dr. Jane Rhyu, Division of Endocrinology, Diabetes, and Metabolism, Department of Internal Medicine, David Geffen School of Medicine at University of California Los Angeles' Los Angeles, CA 90095.

E-mail address: [jrhyu@mednet.ucla.edu](mailto:jrhyu@mednet.ucla.edu) (J. Rhyu).



**Fig. 1.** Bilateral hand x-ray. The bilateral hand x-ray shows soft tissue calcifications (with a few areas indicated by the arrow on the left of the figure) and shortening of the fourth metacarpals and fifth middle phalanges, consistent with pseudopseudohypoparathyroidism (PPHP). The x-ray also reveals ossification adjacent to the right ulnar styloid process, representing a probable accessory ossicle (indicated by the arrow on the right of the figure).

typically believed to have a relatively benign course owing to a lack of biochemical abnormalities.

**Case Report**

The patient is a 40-year-old male with type 2 diabetes, hypertension, hyperlipidemia, fatty liver, obesity, osteoma cutis, normal cognition, and no pertinent family history of PPHP or PHP. He reported having subcutaneous calcifications in his skin since childhood and required a prior surgical removal of calcium deposits in his right foot to alleviate pain.

Physical exam was notable for characteristics of AHO, including short stature, obesity, rounded face, and shortened digits. Numerous soft tissue calcifications were visible in the patient’s upper and lower extremities, and x-rays showed diffuse soft tissue calcifications (Fig. 1 and 2). Hand x-rays showed shortened fourth metacarpals and fifth middle phalanges (Fig. 1), and foot x-rays showed shortened proximal phalanges and first metatarsals (Fig. 2).

Due to the presence of tissue calcium deposits in his extremities, the patient underwent genetic testing, which revealed a GNAS gene c.636delC frameshift mutation in exon 8. Other family members did not undergo genetic testing. Given that labs were unremarkable, with normal levels of PTH, calcium, and phosphorus (Table), the patient was diagnosed with PPHP. Furthermore, labs revealed normal levels of thyroid, insulin-like growth factor 1, testosterone, and gonadotropin. The patient’s history was notable for the development of gout, which was diagnosed on arthrocentesis. The patient later also developed right knee pain. Examination of the knee revealed multiple, palpable free bodies, and a knee x-ray and MRI showed innumerable intraarticular, ossified loose bodies, highly suggestive of synovial chondromatosis (Fig. 3).

Synovial chondromatosis is a rare, benign neoplastic process where the synovial membrane hypertrophies and forms nodules that detach, leading to loose, calcified chondral bodies within the joint space, bursa, or tendon sheath.<sup>7</sup> The mainstay of treatment for synovial chondromatosis is surgical resection, though the extent of surgery and need for associated synovectomy are more controversial.<sup>7</sup> Recurrence rates for synovial chondromatosis can range from 3% to 25%, which may reflect the completeness of resection.<sup>7</sup>



**Fig. 2.** Left foot x-ray. Soft tissue calcifications are diffusely noted throughout the foot, along with a foreshortened and tubular first metatarsal and, to a lesser extent, foreshortened second, third, and fourth proximal phalanges.

The patient required consultations with multiple specialties, including endocrinology, rheumatology, and orthopedics. The patient’s gout was treated with allopurinol. However, due to progressive right knee pain, the patient was advised to have an arthroscopic removal of the loose bodies and synovectomy for the management of his synovial chondromatosis.

**Discussion**

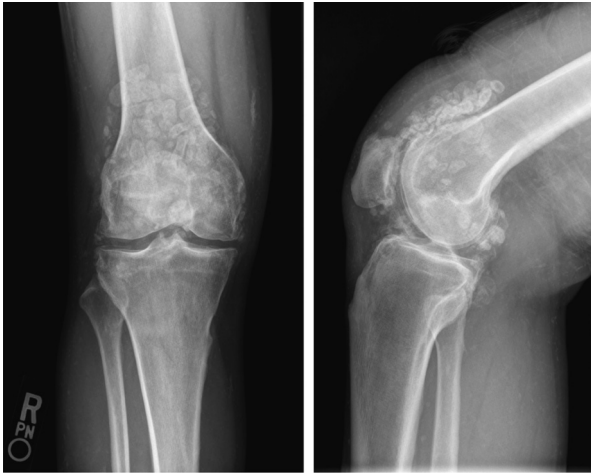
This case highlights skeletal complications that occur in AHO and associated downstream effects of mutations in the GNAS locus on the musculoskeletal system. Both PPHP and PHP are caused by mutations in the GNAS locus of chromosome 20q13.3, which encodes several imprinted transcripts, the most abundant of which is the stimulatory G protein alpha subunit (G $\alpha$ s) and several spliced variants.<sup>1,3</sup>

G $\alpha$ s is a ubiquitous signaling protein that acts as a molecular switch for signal transduction.<sup>5</sup> G $\alpha$ s activates the downstream generation of cAMP, which functions as a signal transducer by mediating the intracellular effects of multiple hormones and neurotransmitters.<sup>1,3</sup> The G $\alpha$ s transcript is biallelically expressed in most tissues, with a reduction in the paternal allele expression through an unclear mechanism in some target organs, including the renal proximal tubule, pituitary and various other nuclei in the brain, thyroid, brown adipose tissue, and gonads.<sup>1</sup>

As the kidney primarily expresses the maternal allele, mutations in the maternal allele lead to PHP, associated PTH resistance, biochemical abnormalities, and AHO phenotype.<sup>1,3</sup> Mutations in the paternal allele conversely lead to PPHP and AHO phenotype without PTH resistance, as haploinsufficiency in the bone leads to AHO regardless of a parenteral origin.<sup>1,3</sup> Similarly, due to the

**Table**  
Lab Trends for Calcium Homeostasis

Date	Calcium (8.4-10.2 mg/dL)	Albumin (3.2-4.8 g/dL)	Magnesium (1.8-2.4 mg/dL)	Phosphorus (2.5-4.9 mg/dL)	Creatinine (0.66-1.28 mg/dL)	25-hydroxy vitamin D (30-140 ng/mL)	Parathyroid hormone (14-72 pg/mL)
Month 1	9.4	4.39		3.6	0.77		
Month 8	9.8	4.5		3.5	0.73	24.3	
Month 14	9.5	4.5	1.9	3.7	0.78	27.6	32.2
Month 15	9.9	4.5		4.1	0.83		21.5



**Fig. 3.** Right knee x-rays. The right knee x-rays show the presence of numerous intraarticular calcified loose bodies, consistent with synovial chondromatosis. It is also notable for soft tissue swelling, suprapatellar joint effusion, a small proximal patellar enthesophyte, and mild arterial calcification.

primarily paternal expression in target organs, PHP is also characterized by resistance to thyroid-stimulating hormone, gonadotropins, and growth hormone-releasing hormone, whereas such hormone resistance is not present in PPHP.

GNAS mutations can lead to a spectrum of diseases with varying musculoskeletal manifestations, including PPHP with its associated AHO phenotype and another disorder called progressive osseous heteroplasia (POH).<sup>8</sup> POH leads to the heterotopic ossification of subcutaneous and deeper connective tissue and skeletal muscle.<sup>8</sup> In rare cases, patients can have a combined POH and AHO phenotype.<sup>8</sup>

This is the first reported case of a patient with PPHP who developed both gout and synovial chondromatosis. There have been rare cases with 1 of the 2 conditions individually with PPHP previously reported. Typically, hyperparathyroidism has been associated with gout, possibly attributed to a decreased renal excretion of uric acid.<sup>9</sup> In a prior case, the presence of gout with PPHP led to the postulation that nonrenal mechanisms may contribute to a heterogeneous pathogenesis of gout,<sup>10</sup> given normal PTH levels. In another case of a patient with PPHP and synovial chondromatosis of the knee who underwent a total knee arthroplasty,<sup>11</sup> it was underscored that since both PPHP and synovial chondromatosis share commonalities of soft tissue calcification and ossification, their coexistence did not seem coincidental.<sup>11</sup>

The presence of both gout and synovial chondromatosis in the patient highlights the possibility of a joint and synovial disease in PPHP due to GNAS-related abnormalities. Though the exact pathophysiology remains unknown, synovial chondromatosis represents a benign neoplastic process that leads to loose, lobulated bodies of hypercellular and atypical hyaline cartilage.<sup>12</sup> Studies in mice have shown that *GS $\alpha$*  expression in chondrocytes is biallelic and plays an essential role in growth plate chondrocyte

differentiation, contributing to the skeletal abnormalities of AHO.<sup>13</sup> Chondrocyte abnormalities from GNAS mutations may contribute to a higher predisposition toward synovial chondromatosis.

The pathogenesis of gout is multifactorial, including abnormalities in urate balance leading to overproduction or underexcretion. Our patient’s risk factors for gout included diabetes,<sup>14</sup> hypertension,<sup>15</sup> and obesity.<sup>15</sup> However, the majority of people with hyperuricemia do not develop gout, and local joint and cartilage factors may play roles in crystal formation.<sup>16</sup> In vitro studies have shown that the addition of gout patients’ synovial fluids to supersaturated solutions promotes monosodium urate crystallization, independent of uric acid concentration in the synovial fluid; this effect did not occur in patients with rheumatoid arthritis or degenerative arthritis.<sup>16</sup>

An abnormal synovial milieu in the setting of GNAS mutation may predispose toward crystallization and synovial chondromatosis. In particular, GNAS-related mutations involve the abnormal differentiation of mesenchymal stem cells or early progenitors,<sup>8,17</sup> which are also present in the synovial fluid.<sup>18</sup> The abnormal differentiation of mesenchymal stem cells in the subcutaneous fat or dermis is believed to lead to heterotopic ossification.<sup>8</sup> Animal studies have demonstrated a loss of GNAS to promote ectopic osteoblast differentiation,<sup>17</sup> POH-like skeletal anomalies,<sup>17</sup> and an increased osteogenic potential in adipose soft tissue stromal cells.<sup>2</sup> Similarly, synovial mesenchymal stem cells have chondrogenic potential,<sup>18,19</sup> which has implications in the pathogenesis of synovial chondromatosis. In another crystalline arthropathy, calcium pyrophosphate dehydrate crystals were synthesized mainly at the site of chondrogenesis after total knee arthroplasty,<sup>20</sup> supporting the hypothesis that cartilage damage or proteins and other macromolecules originating from the synovium or cartilage increase the risk for gouty attacks.<sup>16</sup> Similarly, the secretion of factors from abnormal synovial mesenchymal stem cells may increase the risk for gout. These studies, along with the disease manifestations in PPHP, PHP, and POH, support GNAS as a key mediator in regulating mesenchymal cell fate and associated skeletal abnormalities, heterotopic ossification, and possibly synovial and joint disease.<sup>2</sup>

**Conclusion**

This is the first reported case to show an association of PPHP with both gout and synovial chondromatosis. Though patients with PPHP are classically believed to have a relatively benign course due to the lack of biochemical abnormalities and normal calcium homeostasis, our patient case emphasized the need for close, multi-disciplinary follow up for musculoskeletal complications. The case also highlights the role of GNAS mutations and epigenetics in musculoskeletal differentiation and ectopic calcification, independent of serum calcium homeostasis.

**Disclosure**

The authors have no multiplicity of interest to disclose.

## References

1. Tafaj O, Jüppner H. Pseudohypoparathyroidism: one gene, several syndromes. *J Endocrinol Invest*. 2017;40(4):347–356.
2. Pignolo RJ, Xu M, Russell E, et al. Heterozygous inactivation of *GNAS* in adipose-derived mesenchymal progenitor cells enhances osteoblast differentiation and promotes heterotopic ossification. *J Bone Miner Res*. 2011;26(11):2647–2655.
3. Turan S, Bastepe M. *GNAS* spectrum of disorders. *Curr Osteoporos Rep*. 2015;13(3):146–158.
4. Wilson LC, Trembath RC. Albright's hereditary osteodystrophy. *J Med Genet*. 1994;31(10):779–784.
5. Shore EM, Ahn J, Jan de Beur S, et al. Paternally inherited inactivating mutations of the *GNAS1* gene in progressive osseous heteroplasia. *N Engl J Med*. 2002;346(2):99–106.
6. Haldeman-Englert CR, Hurst ACE, Levine MA. Disorders of *GNAS* inactivation. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews [Internet]*. Seattle: University of Washington; 1993–2021. <https://www.ncbi.nlm.nih.gov/books/NBK459117/>. Accessed November 30, 2020.
7. Murphey MD, Vidal JA, Fanburg-Smith JC, Gajewski DA. Imaging of synovial chondromatosis with radiologic-pathologic correlation. *Radiographics*. 2007;27(5):1465–1488.
8. Bastepe M. *GNAS* mutations and heterotopic ossification. *Bone*. 2018;109:80–85.
9. Hui JY, Choi JWJ, Mount DB, Zhu Y, Zhang Y, Choi HK. The independent association between parathyroid hormone levels and hyperuricemia: a national population study. *Arthritis Res Ther*. 2012;14(2):R56.
10. Newcombe DS. Endocrinopathies and uric acid metabolism. *Semin Arthritis Rheum*. 1972;2(3):281–300.
11. Fraser Jr MR, Sechriest VF. Total knee arthroplasty in a patient with pseudopseudohypoparathyroidism. *Orthopedics*. 2011;34(8):e413–e417.
12. Habusta SF, Tuck JA. Synovial chondromatosis. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2020. <https://www.ncbi.nlm.nih.gov/books/NBK470463/>. Accessed September 9, 2020.
13. Bastepe M, Weinstein LS, Ogata N, et al. Stimulatory G protein directly regulates hypertrophic differentiation of growth plate cartilage in vivo. *Proc Natl Acad Sci*. 2004;101(41):14794–14799.
14. Pan A, Teng GG, Yuan JM, Koh WP. Bidirectional association between diabetes and gout: the Singapore Chinese Health Study. *Sci Rep*. 2016;6:25766.
15. Evans PL, Prior JA, Belcher J, Mallen CD, Hay CA, Roddy E. Obesity, hypertension and diuretic use as risk factors for incident gout: a systematic review and meta-analysis of cohort studies. *Arthritis Res Ther*. 2018;20(1):136.
16. Martillo MA, Nazzari L, Crittenden DB. The crystallization of monosodium urate. *Curr Rheumatol Rep*. 2014;16(2):400.
17. Regard JB, Malhotra D, Gvozdenovic-Jeremic J, et al. Activation of Hedgehog signaling by loss of *GNAS* causes heterotopic ossification. *Nat Med*. 2013;19(11):1505–1512.
18. de Sousa EB, Casado PL, Neto VM, Duarte MEL, Aguiar DP. Synovial fluid and synovial membrane mesenchymal stem cells: latest discoveries and therapeutic perspectives. *Stem Cell Res Ther*. 2014;5(5):112.
19. Neybecker P, Henrionnet C, Pape E, et al. Respective stemness and chondrogenic potential of mesenchymal stem cells isolated from human bone marrow, synovial membrane, and synovial fluid. *Stem Cell Res Ther*. 2020;11(1):316.
20. Sato R, Nakano S, Takasago T, et al. Chondrogenesis in the synovial tissue is associated with the onset of pseudogout after total knee arthroplasty. *Arthroplast Today*. 2015;2(3):101–104.