

A novel variant in the *GNAS* complex locus causes Albright hereditary osteodystrophy with pseudopseudohypoparathyroidism



Jeffrey S. Smith, MD, PhD,^{a,b,c,d,e} Abdulrahman A. Aldeeri, MD,^{a,e,f,g,h} Scott A. Elman, MD,^{a,b,c,d,e}
Joel B. Krier, MD,^{a,f} and Joseph F. Merola, MD, MMSc^{a,e}
Boston, Massachusetts, and Riyadh, Saudi Arabia

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INTRODUCTION

Albright hereditary osteodystrophy (AHO) is an autosomal dominant disorder characterized by short stature, brachydactyly, and subcutaneous ossifications, caused by reduced expression or function of the G protein *Gαs*.¹ *Gαs* is a product of one of several *GNAS* transcripts and couples to many 7-transmembrane-spanning hormone receptors, including the parathyroid hormone (PTH) receptor, follicle-stimulating hormone receptor, and luteinizing hormone receptor. *Gαs* modulates adenylyl cyclase to increase intracellular cyclic adenosine monophosphate to further amplify cellular signaling.² Homozygous variants that abolish *Gαs* are embryonically lethal in mice.³ In most tissues, *Gαs* is biallelically expressed, and heterozygous variants produce sufficient *Gαs* to compensate for a defective allele. In some tissues, however, *Gαs* is paternally imprinted and expressed only by the maternal allele. Therefore, heterozygous variants may affect only certain tissue types, depending on the parent of origin of the affected allele. For example, resistance to certain hormones, such as PTH, can be observed in maternally, but not paternally, inherited *GNAS*-inactivating variants.³ Imprinting explains why patients with variants inactivating the maternal allele exhibit pseudohypoparathyroidism (PHP), which is

Abbreviations used:

AHO: Albright hereditary osteodystrophy
PHP: pseudohypoparathyroidism
PTH: parathyroid hormone

characterized by the AHO phenotype in addition to tissue-selective resistance to *Gαs*-dependent hormones. *STX16* is a gene located near *GNAS* that has a role in imprinting via methylation of *GNAS* locus alternative transcripts. Maternally inherited deletions in *STX16* have been associated with PHP type 1b and occasionally mild brachydactyly without other AHO features.⁴ Apart from imprinting-related differences, individuals with similar *GNAS* variants can have differences in the severity of endocrine resistance and/or the extent of the AHO phenotype. The poorly understood genotype-phenotype correlation makes reporting novel *GNAS* variants and their associated clinical presentations valuable for understanding this complex locus. Here we report a novel variant with associated clinical findings.

CASE REPORT

A 32-year-old woman presented to the dermatology clinic with firm lesions behind her right knee

From the Department of Dermatology, Brigham and Women's Hospital, Boston^a; Department of Dermatology, Massachusetts General Hospital, Boston^b; Department of Dermatology, Beth Israel Deaconess Medical Center, Boston^c; Dermatology Program, Boston Children's Hospital^d; Harvard Medical School, Boston^e; Department of Genetics, Brigham and Women's Hospital, Boston^f; Division of Genetics and Genomics, Boston Children's Hospital^g; and Department of Internal Medicine, King Saud University Medical City, Riyadh.^h

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Correspondence to: Joel B. Krier, MD, Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA. E-mail: jkrier@partners.org.

Joseph F. Merola, MD, MMSc, Brigham and Women's Hospital, 41 Avenue Louis Pasteur, Room 319, Boston, MA 02115. E-mail: jfmerola@bwh.harvard.edu.

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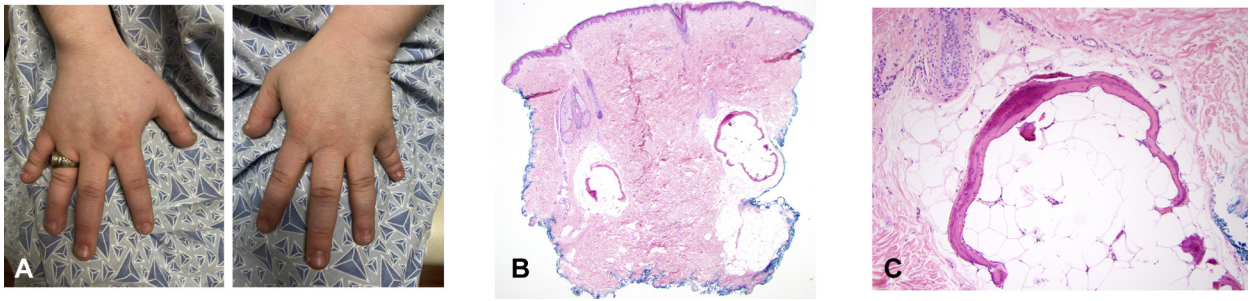


Fig 1. Key clinical and pathologic findings of Albright hereditary osteodystrophy. **A**, Brachydactyly. Punch biopsy of the lower back demonstrating osteoma cutis at **(B)** low power and **(C)** high power.

and on her lower back. The lesions had first appeared 10 years previously and had slowly progressed to affect ambulation, cause pain, and become cosmetically disfiguring. Computed tomography of the right lower extremity demonstrated soft tissue calcification along the fascial planes of the posterior right thigh, initially raising concern for dermatomyositis. Creatine phosphokinase, calcium, phosphorus, vitamin D, PTH, glomerular filtration rate, and complete blood count were within normal limits. An antinuclear antibody test was reactive at 1:160 with diffuse patterning; antibodies to extractable nuclear antigens were negative, interpreted as nonspecific and without immediate clinical relevance. She was well aside from the progressively debilitating lesions on her back and right thigh, as well as hypothyroidism diagnosed at age 16. Review of systems was negative for muscle weakness, joint pain, dysphagia, shortness of breath, chest pain, oral or genital ulcers, and symptoms of Raynaud phenomenon.

On examination, her height was relatively short at 152 cm. Her weight was 76.2 kg, yielding a body mass index of 33. She had truncal obesity. Her face was rounded, with mild facial hirsutism. Hand examination revealed brachydactyly, most prominently of the bilateral fifth fingers (Fig 1, A). She also had brachytelephalanges of both thumbs. The shortness of the fifth fingers was mostly accounted for by the significantly short middle phalanges but also by the proximal and distal phalanges, as radiographically confirmed. Other phalanges appeared short to variable degrees, more notably on the fourth fingers. Examination of the feet revealed short toes and toenails. She had extensive subcutaneous, firm, immobile, lesions on her posterior right thigh extending to the popliteal region and throughout her lower back. No epidermal changes were seen. The results of a strength examination were normal. Written informed consent for a skin biopsy was obtained. A punch biopsy of the lower back revealed

osteoma cutis (Fig 1, B and C). The patient had hypothyroidism but normal serum levels of PTH, calcium, phosphate, growth hormone, insulin-like growth factor 1, luteinizing hormone, and follicle-stimulating hormone.

Based on the findings suggestive of AHO, the patient was referred to genetics. She underwent next-generation sequencing and insertion and deletion analysis of the *GNAS* and *STX16* loci. DNA was extracted from peripheral blood leukocytes and randomly fragmented according to Illumina sequencing-by-synthesis technology. The human reference genome GRCh37/hg19 was used for mapping of the reads. One *GNAS* allele was found to carry a c.43G>T variant in the first exon of the *Gαs* transcript.

DISCUSSION

The *GNAS* c.43G>T variant has not been previously described and is predicted to introduce a Glu15X premature stop codon to the *Gαs* transcript. Since the wild-type *Gαs* protein is 394 amino acids in length, this novel variant is presumed to be pathogenic as a result of producing severely truncated peptides or producing no protein due to messenger RNA decay. The patient had no measured hormone abnormalities aside from being treated for hypothyroidism, which is relatively prevalent in the female population. Given the high penetrance in childhood of multihormonal resistance in PHP,⁵ this patient's hypothyroidism was judged to be unrelated to her underlying genetic variant and she was given a diagnosis of AHO-associated pseudopseudohypoparathyroidism. The observed variant is expected to have been inherited or arisen de novo on the paternally inherited allele. The patient's mother and father, who did not have similar symptoms, underwent *GNAS* allele sequencing. Both parents were wild-type, confirming a de novo origin.

Although short fourth and fifth metacarpals are typically seen in cases of AHO,⁶ the metacarpals of

this patient did not appear overly disproportionate. The finding of hypoplastic fourth and fifth phalanges was unexpected, since the AHO phenotype, to our knowledge, is classically associated with brachydactyly type E, which is associated with shortened metacarpals but not with shortened phalanges.⁷ This finding may expand the skeletal phenotype of AHO to include prominent hypoplastic phalanges other than the first distal phalanx. If the patient bears children carrying the same *GNAS* variant, their phenotype will be expected to be that of PHP with endocrinopathies and AHO, as opposed to the more limited AHO phenotype of the patient. This shift in offspring phenotype is due to the maternal origin of the variant and the imprinting properties of the *GNAS* locus.

In summary, we present a novel *GNAS* variant leading to AHO-associated pseudopseudohypoparathyroidism and describe how this condition can initially present to a dermatologist. This case further adds to our understanding of the *GNAS* locus.

Conflicts of interest

Dr Merola is a consultant and/or investigator for Merck, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Sorono, Avotres, and Leo Pharma. Drs Smith,

Aldeeri, Elman, and Krier have no conflicts of interest to declare.

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