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REVIEW

Progressive osseous heteroplasia: diagnosis, treatment, and prognosis

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Abstract: Progressive osseous heteroplasia (POH) is an ultrarare genetic condition of progressive ectopic ossification. Most cases of POH are caused by heterozygous inactivating mutations of *GNAS*, the gene encoding the alpha subunit of the G-stimulatory protein of adenylyl cyclase. POH is part of a spectrum of related genetic disorders, including Albright hereditary osteodystrophy, pseudohypoparathyroidism, and primary osteoma cutis, that share common features of superficial ossification and association with inactivating mutations of *GNAS*. The genetics, diagnostic criteria, supporting clinical features, current management, and prognosis of POH are reviewed here, and emerging therapeutic strategies are discussed.

Keywords: progressive osseous heteroplasia, GNAS, heterotopic ossification

Introduction

Progressive osseous heteroplasia (POH) is an ultrarare genetic condition of progressive extraskeletal bone formation (Online Mendelian Inheritance in Man 166350).[1] POH is clinically suspected by cutaneous ossification, usually presenting in early life, that involves subcutaneous and then subsequently deep connective tissues, including muscle and fascia. Most cases of POH are caused by heterozygous inactivating mutations of *GNAS*, the gene encoding the alpha subunit of the G-stimulatory protein of adenylyl cyclase (Gsα).[2] POH is among a number of related genetic disorders, including Albright hereditary dystrophy (AHO), pseudohypoparathyroidism (PHP), and primary osteoma cutis (OC), that share common features of superficial heterotopic ossification (HO) in association with inactivating mutations of *GNAS*.[3–5] Although there are similarities among these conditions, POH is distinguished clinically from these related disorders by the deep and progressive nature of the heterotopic bone that forms in POH.[6] Clinically, POH overlap syndromes are recognized in which both POH-like HO and features of AHO or PHP are present. Most cases of POH, PHP1a (pseudohypoparathyroidism type 1a), and AHO are associated with heterozygous inactivating mutations of the *GNAS* gene, which is transcriptionally regulated through multiple promoters and the production of several transcripts, both protein-coding and noncoding RNAs.[7,8] The major product of the locus is the G-protein subunit Gsα. Additional regulatory complexity of the *GNAS* locus results from genomic imprinting, which causes allele-specific regulation of transcript expression that influences the spectrum of clinical phenotypes of the *GNAS* inactivation disorders.[2,9–31]

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GNAS function, genetics, regulation, and signaling

G-protein repertoire and signaling

Guanine nucleotide-binding proteins (G-proteins) are ubiquitous and mediate key extracellular signals that transmit autocrine, paracrine, and endocrine signals. G-proteins are heterotrimeric complexes of α, β, and γ subunits. At this time, 21 Gα subunits encoded by 16 genes are classified into four families on the basis of their α-subunit component: G_s, $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$. In addition, six Gβ subunits encoded by five genes and twelve Gγ subunits are recognized. Ligands, including hormones (eg, parathyroid [PTH]), neurotransmitters (eg, acetylcholine), and chemokines (eg, CXC chemokines), activate seven-transmembrane domain G-protein coupled receptors (GPCRs; such as the PTH receptor and the β-adrenergic receptor); more than 1,000 GPCRs have been identified in the mammalian genome.[32–34]

A given GPCR binds and interacts with only a subset of G-protein α-subunits, with specificity conferred by different structural motifs of both the receptor and the G-protein.[33,35] On ligand binding, activated GPCRs function as guanine nucleotide exchange factors, causing the release of guanosine diphosphate (GDP) and binding of guanosine triphosphate (GTP) to the Gα subunit. This GDP–GTP switch leads to a conformational change in the G-protein α-subunit and promotes the release of Gα and Gβγ subunits from the heterotrimeric complex. Gsα-GTP activates adenylyl cyclase to convert adenosine triphosphate to cyclic adenosine monophosphate (cAMP), an important secondary messenger that regulates multiple cellular processes. The inherent GTPase activity of the Gα subunit subsequently stimulates GTP hydrolysis and GDP binding, followed by reassociation of the α subunit with the βγ subunits and by return to the basal state.

The duration of G-protein activation and signaling is regulated by the GTPase activity intrinsic to the Gα subunit. The GTPase reaction is catalyzed by a family of proteins called "regulators of G-protein signaling" (RGS). RGS proteins bind to Gα subunits to stabilize the transition state of and to accelerate GTP hydrolysis. RGS proteins serve as scaffolding proteins that coordinate components of GPCR signaling to orchestrate their rapid activation and termination.[36] Thirty-seven RGS proteins, clustered into ten subfamilies, are currently known. Although various RGS proteins have been demonstrated to play roles in a broad range of metabolic processes, including lipolysis and cellular differentiation, some of them directly affect Gsα and downstream cAMP signaling. Specifically, RGS2 and RGS-Px1 have been identified to downregulate Gsα-mediated cAMP signaling, whereas RGS4 impedes Gi- and Gq-mediated cAMP synthesis.[37–39]

GNAS locus organization and genomic imprinting

The *GNAS* gene is a highly complex locus that synthesizes several transcripts (Figure 1), the most abundant and best

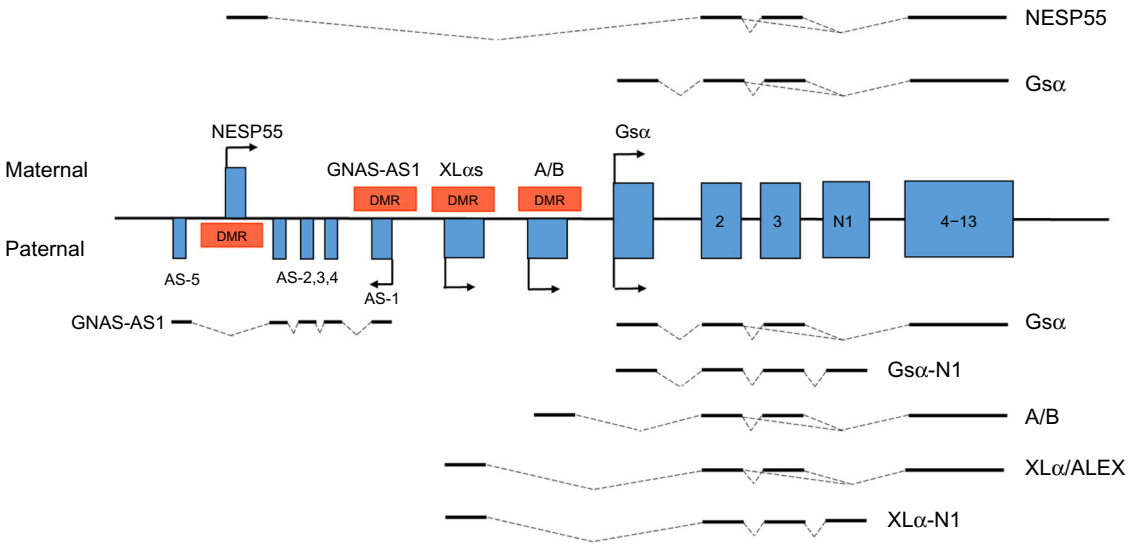

Figure 1 Schematic diagram of multiple transcripts from the *GNAS* locus.

Notes: Gsα, XLαs, and NESP55 are the primary transcripts that produce proteins from the *GNAS* locus. GNAS-AS1 is transcribed in the antisense direction. All transcripts have distinct first exons that splice to common exons 2–13. Gsα is biallelic in most tissues. XLαs, A/B, and GNAS-AS1 are restricted to expression from the paternal allele, whereas NESP55 is only expressed maternally. Imprinting is regulated by differentially methylated regions (DMR) in the promoters. Alternative splicing leads to neuronal-specific transcripts Gsα-N1 and XLαs-N1, whereas a second open reading frame of XLαs leads to a protein called ALEX. Transcripts from maternal and paternal alleles are shown above and below, respectively. Bold lines indicate exons, and dashed lines indicate introns.

characterized of which encodes the ubiquitously expressed α-subunit of the stimulatory G protein (Gsα). Other protein-coding transcripts produce XLαs, the extra-large variant of Gsα (Gnasxl in mice), and NESP55, a neuroendocrine secretory protein (mouse Nesp).[3,40,41] Each of the GNAS transcripts are initiated at unique promoters and first exons but share common downstream exons (exons 2–13 in humans and 2–12 in mice) of the *GNAS* locus (Figure 1). Alternative splicing of exon 3 generates short and long forms of both Gsα and XLαs, and neuronal-specific splicing to include exon N1, which resides between exons 3 and 4, leads to the Gsα-N1 and XLαs-N1 transcripts that have a truncated C terminus. A second open reading frame of XLαs mRNA produces a protein called ALEX that is unrelated to G-proteins. In addition, the transcripts A/B (mouse exon 1A) and GNAS antisense (human GNAS-AS1 or mouse *Nespas*) appear to be non-protein-coding transcripts, although translation of A/B is predicted to start at an in-frame ATG start site within exon 2 and to produce a truncated Gsα isoform.[3,40–43]

The *GNAS* locus also exhibits genomic imprinting, adding yet another level of regulatory complexity.[3,40,41,44,45] Allele-specific expression of GNAS transcripts is dependent on parent of origin, resulting in transcript expression from only one allele. The effects of preferential expression of one of the two *GNAS* alleles are reflected in the different disease phenotypes that result from *GNAS* inactivation of paternally versus maternally inherited genes. For example, PHP1a is primarily caused by maternally inherited heterozygous mutations in *GNAS* locus, whereas POH is correlated with inactivating mutations in the paternally inherited allele.

XLαs and A/B transcripts are expressed only from the paternally inherited *GNAS* gene copy, whereas NESP55 is synthesized only from the maternally inherited allele. In contrast, Gsα is expressed biallelically in most tissues, including bone and white adipose tissue. However, Gsα transcription is regulated by tissue-specific imprinting and is restricted to expression from the maternal allele in tissues including renal proximal tubules, thyroid, pituitary, and gonads.[3,40,41,44,45]

Various functions have been attributed to *GNAS* transcripts on the basis of phenotypes in mice with specific deletions. Mice that are null for Gsα are embryonic lethal, whereas heterozygotes show different metabolic and tissue-specific phenotypes according to parent of origin of the mutation. Similar to PHP patients, mice with maternal inheritance of exon 1 mutations that decrease Gsα and cAMP levels exhibit resistance to PTH and thyroid stimulating hormone.[46,47] Turan et al found that paternal silencing of Gsα in renal proximal tubules does not occur until after the early postnatal period, which could explain the development of PTH resistance and hypocalcemia only after infancy.[48] Maternal allele *GNAS* inactivation is also expected to affect NESP55 expression. Plagge et al generated mice that are deficient in Nesp, which showed enhanced reactivity to novel environments appropriate for the protein's predominant expression in the central nervous system.[49] XLαs, which shares sequence and functional similarity with Gsα at a protein level, forms heterotrimers with Gβγ subunits and activates adenylyl cyclase in specific cell types, similar to Gsα.[3,40] In addition, based on phenotypic observations from mouse models and data from newborn children, XLαs has been known to play important functions during perinatal and early postnatal development.[50] A summary of other mouse models that resemble human conditions of *GNAS* mutations has been provided elsewhere.[8]

GNAS regulation of cellular differentiation via cAMP/protein kinase A (PKA) activation

Gsα activation, through coupling to various receptors and ligands (PTH, adrenaline, glucagon, adenosine, etc) governs multiple important cellular processes to maintain physiologic functions and development in a variety of tissues. Gsα has been implicated in stem cell renewal[51] and differentiation pathways, including osteogenesis,[52,53] myogenesis,[54] adipogenesis,[55,56] chondrongenesis,[57] and neurogenesis.[58] In the context of POH, in which ossifications occur within subcutaneous fat, a role of Gsα may be to maintain the balance in adipogenesis/osteogenesis in the mesenchymal stem cell (MSC) lineage. Although the molecular pathology of POH remains incompletely understood, substantial evidence shows that paternally inherited loss of Gsα function leads to subcutaneous HO and significant leaner phenotype in mice.[55,59] Consistent with these observations, in vitro assays have shown that a paternally inherited Gsα-inactivating mutation impairs adipogenesis and enhances osteogenesis in MSCs.[52,53,55]

In addition to the PTH receptor, other G protein-coupled receptors play roles in regulating the adipogenesis/osteogenesis balance in MSCs, including the adenosine, β-adrenergic, and purinergic receptors. Studies using mouse preosteoblasts and rat bone marrow MSCs demonstrate that adenosine A_{2A} receptors support adipogenic differentiation, whereas A_1 receptors play a role in the lipogenic activity of adipocytes. Conversely, A_{2B} receptors inhibit adipogenesis and activate osteogenesis, illustrating the differential effects of adenosine receptors on MSC differentiation.[60,61] The roles of beta-adrenergic receptors (β-AR) in lipolysis and

thermogenesis are well documented in vitro and in vivo.[62] Moreover, studies have described β2- and β3-AR as playing a part in regulating adipogenesis/osteogenesis partly via the cAMP/PKA pathway. Results from these studies indicate that antagonists of adrenergic receptors induce both adipogenesis and osteogenesis of mouse bone marrow MSCs. Similar to adenosine receptors, mRNA and protein expression of both β2- and β3-AR are elevated during adipogenesis and osteogenesis in bone marrow-derived MSCs. Interestingly, β3-AR and β2-AR were found to be the dominant receptors in adipogenesis and osteogenesis, respectively.[63,64] The purinergic receptor P2Y family also stimulates adenylyl cyclase activation and cAMP production[65] and, additionally, have been implicated in white adipocyte physiology, including leptin secretion and lipolysis.[66]

Signal transduction pathways downstream of GNAS and cAMP/PKA

In POH, HO initiates within subcutaneous fat before progressing to deep tissue, suggesting abnormal osteogenesis of mesenchymal precursor in adipose tissues. In fact, paternal inactivation of Gsα in adipose stromal cells (ASCs) enhances osteogenesis in vitro and promotes intramembranous HO in subcutaneous fat in vivo.[52] Conversely, paternal-inactivation of Gsα in ASCs severely limits adipogenesis in vitro.[55] Importantly, this defect can be rescued by an adenylyl cyclase activator (forskolin),[55] indicating that Gsα-cAMP signals regulate the bipotential adipogenic-osteogenic lineage cell fate switch.

Gsα expression is tightly regulated under physiologic and developmental conditions. Although Gsα signaling is ubiquitous, various cell types are expected to respond to G-protein signaling and cAMP in cell and developmentally specific manners. Gsα appears to have crucial roles in maintaining balance in two key signaling pathways: Wnt/β-catenin and Hedgehog (Hh).[67] Gain-of-function mutation of Gsα leads to overactive Wnt/β-catenin signal and is associated with fibrous dysplasia,[68] whereas loss-of-function mutations of Gsα lead to increased Hh signaling and are associated with POH.[67]

Hh signaling controls numerous aspects of development, including proliferation, patterning, and morphogenesis. Three Hh proteins have been identified in vertebrates: Sonic (SHH), Indian, and Desert. Desert Hh expression is limited to the male reproductive tract, Indian Hh regulates chondrogenesis and endochondral bone formation, and SHH plays a critical role in the formation of the skeleton and in cell differentiation.[69] SHH signaling was also found to have antiadipogenic and pro-osteogenic effects in mouse ASCs (mASCs).[70] Hh signaling is activated when Hh protein binds to its receptor to relieve the protein smoothened (Smo) from its repressive state. Active Smo triggers a cascade of events that activates GLI transcription factors. Interestingly, SHH signaling enhances bone morphogenetic protein (BMP) 2 signaling (a known cytokine to be critical for osteogenesis) in mASCs. It is interesting to speculate that in POH, loss of function of Gsα leading to enhanced Hh signaling would increase BMP signaling and contribute to HO.

PKA (activated by cAMP) is known to negatively regulate Hh signaling by inhibiting GLI nuclear localization[71] and targeting GLI for proteosomal degradation/truncation.[72–74] Homozygous inactivation of *GNAS* in MSCs leads to overactivation of Hh signaling (observed in both in vitro and in vivo studies) and causes POH-like HO in mice.[67] Thus, elevation in Hh signaling in Gsα-deficient cells appears to be the upstream signal that contributes to HO in POH.

The BMP signal transduction pathway, a key regulator of osteoblast differentiation, serves to phosphorylate SMAD proteins and transcriptionally activate osteogenic genes.[75,76] The relationship between *GNAS* and BMP signaling is not clear. However, using forskolin to stimulate cAMP production in mouse embryonic stem cells at the earliest stages of osteogenesis, Zhang et al demonstrated that BMP signaling and osteogenic markers (Msx2, Osterix) are significantly reduced, whereas adipogenic markers (LPL, PPARg, EBP1, aP2) are elevated.[77] These findings provide further evidence that cAMP serves as a key regulator of osteoblast and adipocyte lineage commitment upstream of BMP signaling.[77]

GNAS mutation in POH patients

Heterozygous inactivating *GNAS* mutations occur in most patients with a definitive clinical diagnosis of POH (see following). All the POH-associated *GNAS* mutations identified in our cohort have mutations that cause a shift in the protein-coding reading frame: small deletions, insertions, duplications, or alteration of conserved splice site donor/acceptor dinucleotides (Table 1). Nonsense mutations leading to early protein termination have not been identified in this cohort. Although some patients diagnosed with AHO/PHP1a have mutations in exon 1,[78] as do patients diagnosed with PHP1a/POH, we have not identified exon 1 mutations in patients with a confirmed diagnosis of POH. Two POH patients with an exon 1 mutation have been reported;[79] however, the clinical descriptions are ambiguous, and thus these diagnoses are not confirmed (see following for further discussion). Any functional significance for the absence of exon 1 mutations is unclear and could reflect the small sample

Table 1 *GNAS* mutations in progressive osseous heteroplasia patients

GNAS location	Mutation site (cDNA)	Frameshift start (codon)
Exon 5	344–345insT	115
Exon 5	348delC;	116
Exon 5	348–349insC	117
Exon 5	355delC	119
Exon 7	565–68delGACT	189
Exon 9	679–80insC	227
Exon 10	725delC	242
Exon 10	835–39duplAACAG	280
Exon 11	860–61delTG	287
Exon 11	960insCT	321
Intron 12	IVS12+1G>C splice donor site	347
Intron12	IVS12-1G>C splice acceptor site	347
Exon 13	1053–77dupl25n	360
Exon 13	1107–08delTG	369–370
Exon 13	1162delC	388

size of POH patients. *GNAS* mutations in POH patients reduce Gsα protein levels and decrease cAMP signaling (our unpublished data).

Our unpublished data and other reports[80] support that POH is preferentially caused by *GNAS* mutations occurring on the paternally inherited copy of the gene. This suggests that the paternal and maternal *GNAS* alleles function differently to regulate osteoblast differentiation (see earlier sections: GNAS regulation of cellular differentiation via cAMP/protein kinase A (PKA) activation and Signal transduction pathways downstream of GNAS and cAMP/PKA).

Classic mosaicism, or the presence of at least two genotypically different cell populations derived from a single zygote, may explain the pattern of lesion distribution in POH that distinguishes it from other *GNAS*-based conditions in which HO does not progress to deeper tissues. For example, a germline mutation in *GNAS* may be followed by a second mutation in the other allele during development and both be retained by a finite number of progenitor cells in the postnatal state. Possible mechanisms include the presence of somatic mutations or random inactivation of the second *GNAS* allele in progenitor cells, a de novo mutation in a gene that normally functions in a *GNAS*-interacting pathway, or epigenetic changes in somatic cells. Depending on the location of resident progenitor cells or their predisposition toward certain migration patterns, HO formation with progression to deeper tissues may be favored in POH. Revertant mosaicism in uninvolved dermomyotomes, or in patients with *GNAS* mutations and no apparent or very limited disease, cannot be excluded.[81]

Most POH mutations appear to be de novo mutations in a family, with a given specific mutation found in only a single family.[6] However, a four-nucleotide deletion in exon 7 that was found to be a mutational hot spot for AHO/PHP1a is found as a recurring mutation in POH as well. Within a family, carriers with the mutation but no clinical manifestations have been identified.

Clinical features and diagnosis

As a disorder of extraskeletal bone formation, POH must first be differentiated from nonhereditary as well as other genetic conditions of HO to diagnose the condition (Table 2).

Table 2 Differential diagnosis of extraskeletal bone formation

- Genetic
  - Primary osteoma cutis
  - Fibrodysplasia ossificans progressiva
  - Progressive osseous heteroplasia
  - Albright hereditary osteodystrophy
  - Pseudohypoparathyroidism 1a/1c (PHP1a/1c)
  - Progressive osseous heteroplasia overlap syndromes (POH/PHP1a/1c)
- Nonhereditary
  - Injury
    - Traumatic head injury
    - Paraplegia/quadriplegia (spinal cord injury)
    - Poliomyelitis
    - Guillain–Barré syndrome
    - Muscle hematoma
    - Joint dislocation
    - After hip and knee arthroplasty
    - Surgical scars
    - Severe burns
    - Secondary osteoma cutis
    - Endovascular injury (atherosclerosis, valvular heart disease, cerebrovascular accident)
  - Arthropathy
    - Ankylosing spondylitis
    - Psoriatic arthritis
    - Seronegative arthropathies
    - Diffuse idiopathic skeletal hyperostosis
  - Aging
    - Postarthroplasty
    - Atherosclerosis
    - Cerebrovascular accident
    - Valvular heart disease
    - Atherosclerosis
    - Miliary osteoma (of the face)*
    - Pressure ulcers†‡
    - Urinary tract infections‡
  - Other
    - Metastatic osteosarcoma
    - Fibrosing lung disorders
    - Pulmonary venous hypertension
    - Conditions that increase calcium–phosphate product levels

Notes: *Occurs predominantly in middle-aged and older females. †At the site of reactive soft tissue ossification. ‡May be a predisposing factor or a secondary complication of nonhereditary heterotopic ossification.

Abbreviations: AHO, Albright hereditary osteo dystrophy; POH, progressive osseous heteroplasia; PHP, Pseudohypoparathyroidism.

Nonhereditary forms of HO are excluded on the basis of prior trauma or surgery, age, and known history or suspicion of arthropathy. POH is distinguished from fibrodysplasia ossificans progressiva (FOP), another rare autosomal dominant genetic condition of HO, by the presence of cutaneous ossification, the absence of congenital malformation of the first toes, and the absence of preosseous tumor-like inflammation or "flare-ups."[82,83] Other genetic causes of HO (Table 2) can be excluded on clinical grounds alone.

POH is among several related genetic disorders, including AHO, PHP, and OC, which share the common features of superficial ossification and association with inactivating mutations of *GNAS*.[4–6] AHO is characterized by variable subsets of features, in addition to superficial HO, including short adult stature, obesity, round faces, brachydactyly, and neurobehavioral problems (including mental retardation). PHP, or end-organ resistance to PTH, is subdivided into types 1a, 1b, and 1c.[4] Clinically, PHP1a and 1c are identical and can include AHO features, deficient responses to PTH, and multiple other hormone resistance. PHP1a is distinguished from PHP1c by the presence of inactivating *GNAS* mutations and/or reduced activity of Gsα, the major protein product encoded by the *GNAS* locus. Patients with PHP1b have hormone resistance, usually limited to PTH target tissues, but no AHO features or reduced Gsα activity. PHP1b is associated with a *GNAS* imprinting defect and caused by heterozygous deletions of a suspected imprinting control element in familial forms.[4,14,45,84,85] Pseudopseudo-hypoparathyroidism (PPHP) refers to the condition in patients with AHO who do not have PTH resistance. OC describes superficial HO without any hormone resistance or AHO features. A familial form of primary OC has been described.[86]

POH is diagnosed on the basis of three major criteria: superficial HO that progresses to deep connective tissue; two or fewer AHO features, excluding HO; and no PTH resistance (Table 3). Dermal involvement appears as hard maculopapular lesions (Figure 2A and B). Over time, these lesions coalesce into plaques with spread into deeper connective tissues including fascia, skeletal muscle, tendon, and ligament (Figure 2C). Small spicules of dermal bone may occasionally extrude through the epidermis, although bone formation does not originate in the epidermis. Extensive ossification of the deep connective tissues can result in ankylosis of affected joints and growth retardation of involved limbs (Figure 2C).[1,87–90] In addition to HO, some patients exhibit one or two AHO features, but never obesity or multiple AHO features.[6] Hormonal abnormalities are rarely associated with POH, and never PTH resistance.[6]

Table 3 Diagnostic criteria for progressive osseous heteroplasia

Criteria
Major criteria
Superficial and deep heterotopic ossification
Two or fewer features of Albright hereditary dystrophy, not including heterotopic ossification
No parathyroid hormone resistance
Supporting clinical findings
GNAS mutation
Evidence for paternal inheritance
Radiographic evidence for reticular pattern of ossification
Exclusive intramembraneous ossification or both intramembraneous and endochondral ossification
Lateralization in a dermomyotomal pattern
History of intrauterine growth retardation
Leanness
Age of onset younger than 1 year

In addition to these key diagnostic criteria, there are several clinical findings that support the diagnosis of POH (Table 3).[6] Although some individuals can present with a later age of onset, most POH patients have an average age of onset earlier than 1 year. Almost two-thirds of POH patients have mutations in *GNAS*. However, those without detectable mutations are clinically indistinguishable from those with mutations. Maternally inherited mutations in *GNAS* cause PHP1a, whereas paternally inherited mutations are associated with POH and are supportive of the diagnosis, especially with delayed onset of more extensive ossification. Although maternally inherited mutations are more often found with AHO, paternally inherited mutations can also be associated with AHO and lead to PPHP. POH-like HO associated with the overlap syndromes can be inherited through the maternal as well as the paternal allele. Although exon 1 mutations have been reported in individuals with subcutaneous ossifications (including those close to muscle),[79] it is unclear whether these individuals meet the POH criterion of deep HO. In a large series of POH patients, diagnosed on the basis of key criteria described here only, exon 1 mutations were not found.[6]

Birth weight tends to be very low in patients with POH, usually at or below the fifth percentile compared with sex-matched normative data.[55] In fact, heterozygous *GNAS* mutations on either parental allele were found to be associated with intrauterine growth retardation, and when these mutations were located on the paternal *GNAS* allele, intrauterine growth retardation was considerably more pronounced compared with mutations on the maternal allele.[50] At any age, POH patients with paternally inherited inactivating *GNAS* mutations were always found to have a lean phenotype.[6,91] There is also a striking lateralization of lesions in a dermatomyotomal

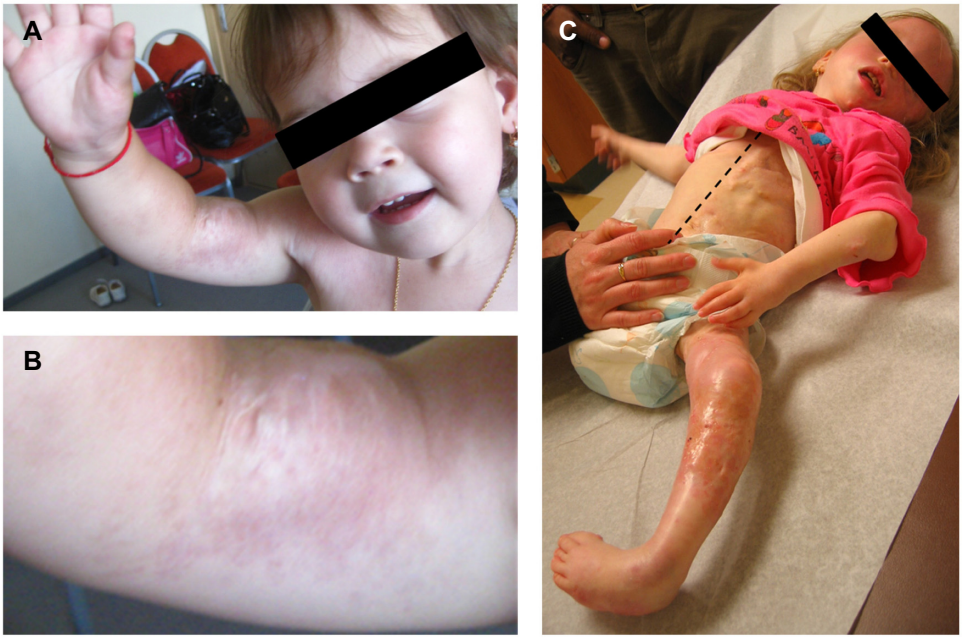

Figure 2 Appearance of heterotopic ossification in POH.
Notes: (**A** and **B**) Early clinical appearance of heterotopic ossification in POH. Note the maculopapular lesions that correspond to extensive dermal and subcutaneous ossification. (**C**) Advanced heterotopic ossification in POH results in large coalesced bony plaques. Note the distinct lateralization of lesions that is observed in some patients, as well as contracture and ankyloses of the left lower extremity.
Abbreviation: POH, progressive osseous heteroplasia.

distribution (Figure 2C),[81] but this may be difficult to assess early in the presentation. Radiographic appearance of HO in POH shows a distinctive reticular pattern of web-like ectopic bone involving soft connective tissues from the dermis down to skeletal muscle (Figure 3). Half of lesional biopsies taken in patients ultimately confirmed to have POH demonstrated intramembraneous ossification (Figure 4), with 20% showing endochondral ossification and 30% both types.[6]

POH occasionally presents as an overlap syndrome with additional features associated with other *GNAS*-based disorders of HO. Two cases in which patients exhibited progressive HO together with characteristics of AHO (short stature, round face, and brachydactyly) and reduced levels of Gsα protein were reported by Eddy et al;[92] one of the two cases had a heterozygous *GNAS* mutation. Another patient with progressive HO had severe plate-like OC and also possessed a mutation in the *GNAS* gene.[93,94] These cases are consistent with POH being part of a clinical spectrum of HO disorders caused by inactivating *GNAS* mutations.

POH, other disorders associated with inactivating mutations of *GNAS*, and POH overlap syndromes are distinguished solely by clinical criteria (Figure 5). *GNAS*-based disorders of HO can be divided into those presenting with stable superficial bony lesions and those in which superficial lesions progress into deep connective tissue. Among the nonprogressive forms are OC, AHO/PPHP, and PHP1a/c. Those without AHO features have OC. Those with AHO features and no hormone resistance have AHO/PPHP, and those with hormone resistance have PHP (Figure 5). The progressive types are POH and the POH-related syndromes. Patients with POH present with superficial HO that progresses to deeper tissues in the absence of multiple other AHO features and without hormone resistance (Figure 5). A small subset of patients has progressive HO with more extensive AHO features (POH/AHO) or with both AHO features and hormone resistance (POH/PHP1a/1c). It is possible that individuals without progressive HO could be too young at the time of initial diagnosis to have yet developed progressive disease. Similarly, individuals with POH could be too young at the time of diagnosis to have yet developed other features of AHO. Nevertheless, POH and progressive HO syndromes can be distinguished from other *GNAS*-based disorders by one clinical parameter alone: the extension of HO from superficial to deep tissue. *GNAS* inactivating mutations, either by presence alone or by mutation pattern within *GNAS*, do not predict a specific disorder, variability of phenotype, or severity of progression within this spectrum.

Current management and prognosis

In POH, the degree of morbidity depends on the location and extent of HO, and in some cases, the condition

Figure 3 Radiographic appearance of severe heterotopic ossification in POH.
Notes: (**A**) Anterior view roentgenogram of the lower extremities of a child with POH shows progressive heterotopic ossification on the left side. Note the web-like pattern of ossification. (**B**) Cross-sectional, midfemur view by computerized tomography demonstrates extensive ossification of soft tissues in the superficial and deep posterior compartments of the leg.
Abbreviation: POH, progressive osseous heteroplasia.

results in severe disability.[1,93–95] Growth retardation may be associated with limited movement of extremities caused by joint ankyloses and bone pain, and secondary osteoporosis may ensue.[1,93–95]

Because of the ultrarare nature of POH, we have limited information about prognosis. There are no distinguishing forms of POH based on progression; however, we did observe that HO in the dermis shows a seemingly random distribution

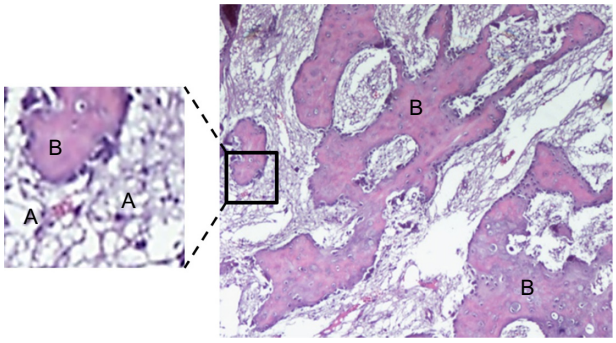

Figure 4 Photomicrograph of a POH lesional section shows intramembranous ossification.
Notes: Note that deposits of bone are surrounded by adipose tissue (inset). Hematoxylin and eosin staining; original magnification, 200×.
Abbreviation: A, adipose tissue; B, bone; POH, progressive osseous heteroplasia.

of affected areas and that this mosaic distribution of lesions lateralized in a distinct dermomyotomal pattern present in very few conditions.[81] In some patients, dermomyotomal distribution was partial, which may suggest that lesion progression was incomplete or delayed at the time of presentation. Often it is only later in the course of the condition that one can clinically determine areas of severe involvement.

At this time, there are no effective treatments or prevention for POH. Surgical resection of diffuse lesions usually leads to recurrences or complications;[1,2,82,87] however, areas of well-circumscribed HO can often be removed, with successful long-term results.[94] Successful functional repositioning of a joint after the development of a contracture from HO was reported in the case of one child.[88] Unfortunately, amputations are sometimes needed in the setting of severe growth retardation and functional ankylosis.[89]

A single case report on the use of the bisphosphonate pamidronate in POH suggested stabilization of the

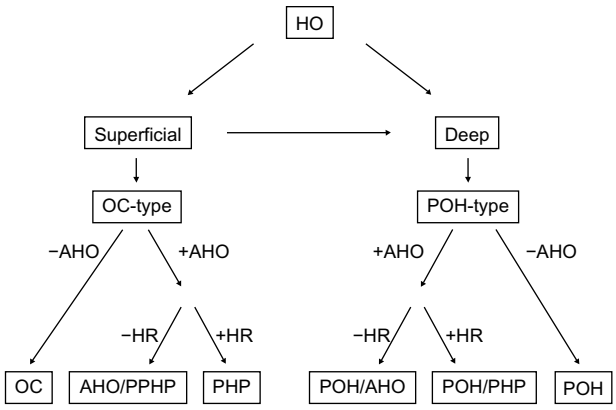

Figure 5 Diagnostic algorithm for distinguishing among *GNAS*-based conditions of heterotopic ossification.
Abbreviations: HO, heterotopic ossification; OC, osteoma cutis; POH, progressive osseous heteroplasia; AHO, Albright hereditary dystrophy; HR, hormone resistance; PPHP, pseudopseudo-hypoparathyroidism; PHP, pseudohypoparathyroidism.

condition,[96] but it is unclear how generally applicable this finding may be to prevention of new skin lesions. Treatment with bisphosphonate is unlikely to resolve preexisting bone formation in POH.

Physical therapy and meticulous skin care are important conservative approaches to preserving movement and preventing cutaneous breakdown, respectively.[90,95]

Emerging therapeutic strategies

Regard et al showed that Gsα restricts bone formation to the normotopic skeleton by inhibiting Hh signaling in mesenchymal progenitor cells, whereas genetically mediated exogenous Hh signaling is sufficient to induce POH-like HO.[67] Furthermore, inhibition of this signaling pathway by genetic or pharmacological methods reduced the severity of ectopic bone formation.[67] Therefore, Hh inhibitors currently used for other conditions, such as cancer, may be potential candidate drugs for treating HO caused by *GNAS* inactivation.[97]

Endochondral ossification is present singly or in combination with intramembranous ossification in 50% of POH lesional biopsies,[6] and so known inhibitors of endochondral ossification are potential therapies. For example, retinoic acid receptor γ agonists were shown to be highly effective at inhibiting HO in mouse models.[98] In fact, a marked increase in Gsα expression at the transcriptional level is induced by retinoic acid, suggesting that the same retinoic acid receptor γ agonists may be used to increase production of Gsα protein from the normal allele and minimize the effects of *GNAS* inactivation.[99]

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Disclosure

The authors report no conflicts of interest in this work.

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