

Perspective

Progressive Osseous Heteroplasia

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ABSTRACT

Progressive osseous heteroplasia (POH) is a recently described genetic disorder of mesenchymal differentiation characterized by dermal ossification during infancy and progressive heterotopic ossification of cutaneous, subcutaneous, and deep connective tissues during childhood. The disorder can be distinguished from fibrodysplasia ossificans progressiva (FOP) by the presence of cutaneous ossification, the absence of congenital malformations of the skeleton, the absence of inflammatory tumorlike swellings, the asymmetric mosaic distribution of lesions, the absence of predictable regional patterns of heterotopic ossification, and the predominance of intramembranous rather than endochondral ossification. POH can be distinguished from Albright hereditary osteodystrophy (AHO) by the progression of heterotopic ossification from skin and subcutaneous tissue into skeletal muscle, the presence of normal endocrine function, and the absence of a distinctive habitus associated with AHO. Although the genetic basis of POH is unknown, inactivating mutations of the *GNAS1* gene are associated with AHO. The report in this issue of the *JBMR* of 2 patients with combined features of POH and AHO—one with classic AHO, severe POH-like features, and reduced levels of $G_s\alpha$ protein and one with mild AHO, severe POH-like features, reduced levels of $G_s\alpha$ protein, and a mutation in *GNAS1*—suggests that classic POH also could be caused by *GNAS1* mutations. This possibility is further supported by the identification of a patient with atypical but severe platelike osteoma cutis (POC) and a mutation in *GNAS1*, indicating that inactivating mutations in *GNAS1* may lead to severe progressive heterotopic ossification of skeletal muscle and deep connective tissue independently of AHO characteristics. These observations suggest that POH may lie at one end of a clinical spectrum of ossification disorders mediated by abnormalities in *GNAS1* expression and impaired activation of adenylyl cyclase. Analysis of patients with classic POH (with no AHO features) is necessary to determine whether the molecular basis of POH is caused by inactivating mutations in the *GNAS1* gene. (*J Bone Miner Res* 2000;15:2084–2094)

Key words: progressive osseous heteroplasia, fibrodysplasia ossificans progressiva, Albright hereditary osteodystrophy, heterotopic ossification, *GNAS1*

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HOW WAS POH DISCOVERED?

IN AN ARTICLE in *Science*, 1996, Claire O'Brien wrote, "New diseases do not suddenly present themselves, ready labeled, in a new patient. They emerge slowly from the collection and interpretation of clinical observations and physiological measurements."⁽¹⁾ Such is the case with progressive osseous heteroplasia (POH), which was first described in 1994.⁽²⁾

Before describing exactly what POH is, it will be helpful to understand what it is not. The recognition of POH as a distinct disorder of heterotopic ossification arose over a 5-year period (1989–1994) during which time one of us (F.S.K.) evaluated more than 125 patients with fibrodysplasia ossificans progressiva (FOP), a rare and devastating genetic disorder of progressive heterotopic ossification, recently associated with overexpression of bone morphogenetic protein 4 (BMP-4).^(3–10) The classic phenotype of FOP includes a diagnostic triad: congenital malformation of the great toes; progressive heterotopic ossification of skeletal muscles, tendons, ligaments, and fascia through an endochondral process; and progression of disease activity in characteristic anatomic patterns (dorsal to ventral, axial to appendicular, cranial to caudal, and proximal to distal) (Figs. 1–3). Although the timing, severity, and rate of progression of postnatal heterotopic ossification varies considerably among affected individuals, the classic triad of disease activity is nearly inviolate.^(11–18)

Among the children examined at our center with a preliminary diagnosis of FOP by the referring physician were those with a clinical phenotype distinct from FOP. Although these children suffered from progressive heterotopic ossification, they clearly were afflicted with something other than FOP (Table 1). How could we be so certain? First, none of the children had malformations of the great toes, a nearly ubiquitous feature in FOP. Although many had digital deformities in the feet, all of the deformities had developed secondary to progressive ossification of soft tissues and none were congenital.^(2,19) By contrast, congenital malformations of the great toes are characteristic of FOP.^(12,18) Second, all of the children had ossification of the skin in infancy, a feature not seen in FOP (Fig. 1A). Third, none of the children developed proosseous tumorlike swellings, a nearly universal finding in FOP (Fig. 1B). Fourth, all of the affected children suffered from progression of heterotopic ossification into deep connective tissues, including fascia and skeletal muscle, in a process of ossification that was primarily intramembranous rather than endochondral as had been described in FOP (Fig. 2).⁽⁴⁾ Fifth, the evolving radiographic pattern of heterotopic ossification in the children we evaluated was clearly different from anything previously described in FOP. Radiographs in children with this distinctive form of progressive heterotopic ossification revealed a cocoonlike web of heterotopic bone entangling the soft connective tissues from the dermis down through the skeletal muscle in a manner completely reckless to the fidelity of tissue planes (Figs. 3A–3C).⁽²⁾ By contrast, radiographs in children with FOP showed distinct well-circumscribed areas of deep heterotopic ossifications that often corresponded to a distinct skeletal muscle (Fig. 3D).⁽²⁰⁾

Cutaneous and subcutaneous ossification is a well-recognized, although variable, feature of Albright hereditary osteodystrophy (AHO),^(21,22) but the children we evaluated had no other morphological manifestations of AHO or any evidence of hypocalcemia, pseudohypoparathyroidism, hypothyroidism, or hormone resistance.^(23–29) Moreover, no family member of an affected child suffered from AHO or pseudohypoparathyroidism. Could the ossification in the skin have been a secondary manifestation of a focal dermatological disorder, a soft tissue injury, a vascular malformation, or an underlying arthropathy, conditions all known to predispose to dermal ossification?^(14,30–33) None of those clinical considerations seemed to be germane in the children we evaluated, because the ossification process was not limited to the skin but progressed into subcutaneous fat and deep connective tissues.

Primary dermal ossification is rarely seen in childhood,^(33–37) and primary dermal ossification during childhood with progressive involvement of deep connective tissue is exceedingly rare. In fact, we were able to find only five case reports in the English language medical literature of the 20th century.^(38–42) Among these few case reports, the following diagnoses had been made: disseminated congenital osteomas,⁽³⁸⁾ localized tissue malformation or heterotopia,⁽³⁹⁾ dysplastic cutaneous osteomatosis,⁽⁴²⁾ limited dermal ossification,⁽⁴⁰⁾ and familial ectopic ossification.⁽⁴¹⁾ In addition, there were several incomplete or ambiguous reports and many that implicated secondary causes of ossification. Many reported cases of primary cutaneous ossification were actually mild variants of AHO.

After conducting a review of the literature, we attempted to contact as many of the original patients as possible to confirm the diagnosis and to provide follow-up.⁽²⁾ Although all of the patients in this original series were female, several more discovered recently have been male,^(19,43) and the female gender bias seems less prominent than it did originally.⁽²⁾ The diagnostic description of POH in 1994 was made on the basis of the unique clinical, roentgenographic, and histopathological findings and on the basis of the natural history encountered in the children we evaluated. The unique constellation of clinical, pathological, and roentgenographic features that characterized POH justified its consideration as a distinct developmental disorder of mesenchymal differentiation and heterotopic ossification in humans.

WHAT IS POH?

POH is a developmental disorder of mesenchymal differentiation characterized by dermal ossification during infancy and by progressive heterotopic ossification of cutaneous, subcutaneous, and deep connective tissue during childhood (Table 1).⁽²⁾ The disorder can be distinguished from FOP by the presence of cutaneous ossification, by the absence of congenital skeletal malformations, by the asymmetric mosaic distribution of lesions, by the absence of predictable regional patterns of heterotopic ossification, and by the predominance of intramembranous rather than endochondral ossification (Table 1).⁽¹⁴⁾



FIG. 1. Early clinical appearance of severe heterotopic ossification in POH and FOP. (A) Posterior aspect of the left leg and popliteal fossa of a 5-year-old child with POH. Note the severe maculopapular lesions that correspond to extensive dermal and subcutaneous ossification. (Reprinted with permission from Kaplan FS, Hahn GV, Zasloff MA, 1994.⁽¹⁴⁾) (B) Back of a 4-year-old child with FOP. Note the characteristic subfascial nodules that correspond to preosseous fibroproliferative lesions and heterotopic ossification evolving through an endochondral process. (Reprinted with permission from Kaplan FS, Tabas JA, Gannon FH et al., 1993.⁽⁴⁾)

POH can be distinguished from AHO by the progression of heterotopic ossification from skin and subcutaneous tissue into skeletal muscle, by the absence of morphological features associated with AHO, and by the presence of normal endocrine function (Table 1). As with many newly described and extremely rare conditions, POH probably is underdiagnosed. Careful consideration of clinical and radiographic signs usually is enough to recognize the disorder and to differentiate it from FOP and AHO. There have been 16 case reports of POH: 13 in females and 3 in males.^(2,19,43-48) At present, we are aware of an additional 13 patients of both genders (4 females and 9 males).

The first sign of POH occurs during infancy with the appearance of islands of heterotopic bone in the reticular dermis and subcutaneous fat. Over time, the islands of heterotopic bone coalesce into plaques with subsequent involvement of the deeper connective tissues including fascia, skeletal muscle, tendon, and ligament. Extensive ossification of the deep connective tissues results in ankylosis of affected joints and focal growth retardation of involved limbs.^(2,19,43,44) At times, small spicules of dermal bone can protrude through the epidermis, although bone formation does not originate in the epidermis. Occasionally, involvement of the subcutaneous fat and deep connective tissues

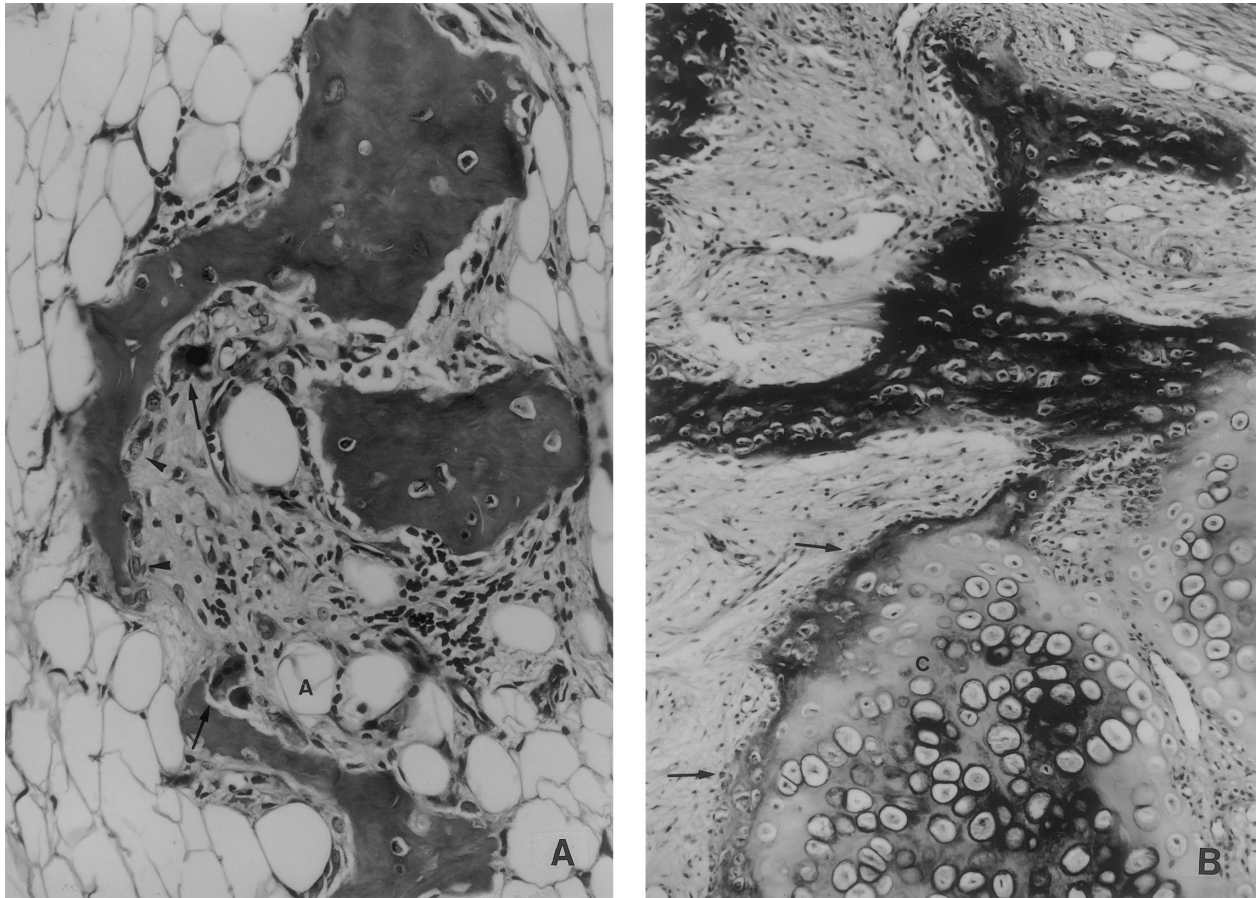


FIG. 2. Histopathology of predominant pathways of heterotopic ossification in POH and FOP. (A) Medium-power photomicrograph of a POH lesion shows intramembranous ossification arising from subcutaneous fat. Note the irregular deposits of woven and lamellar bone surrounded by adipose tissue. Arrows indicate osteoclasts; arrowheads indicate osteoblasts (hematoxylin-eosin; original magnification, $\times 200$). (B) Medium-power photomicrograph of an intermediate-stage FOP lesion shows endochondral ossification. Arrows indicate osteoblasts; C, cartilage (hematoxylin-eosin; original magnification, $\times 125$; A and B reprinted with permission from Kaplan FS, Hahn GV, Zasloff MA, 1994.⁽¹⁴⁾)

may precede dermal involvement. Rarely, there may be deeper involvement without any cutaneous or subcutaneous involvement at a particular site.

Some cases of POH appear sporadic, whereas some are familial.⁽²⁾ Offspring of affected individuals can inherit the disease in an autosomal dominant manner with widely variable expression.^(2,43) The absence of large multigenerational families impedes gene identification by linkage analysis and positional cloning, but linkage exclusion analysis and mutational analysis with promising candidate genes is certainly possible. The etiology and pathogenesis of POH remain unknown.

WHAT IS THE PATHOLOGY OF POH?

Heterotopic ossification in POH occurs predominantly through an intramembranous pathway (Fig. 2; Table 2).^(2,19,43,44,46) Two reports of POH describe islands of endochondral ossification in the deep connective tissue with the sporadic appearance of marrow elements.^(45,47) Hetero-

topic ossification through an endochondral pathway also has been described in POH after unsuccessful attempts at surgical ablation of deep heterotopic ossification.⁽²⁾

The results of routine laboratory studies in POH usually are normal, although elevated levels of serum alkaline phosphatase have been observed during phases of progressive heterotopic osteogenesis. Typically, serum levels of calcium, inorganic phosphate, parathyroid hormone (PTH), and vitamin D metabolites are normal, although transient abnormalities have been noted in rare instances.⁽⁴⁷⁾ Elevated serum levels of lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) have been observed and may reflect bone deposition in skin and skeletal muscle.^(46,47)

WHAT IS THE DEVELOPMENTAL BIOLOGY OF POH?

The anatomic distribution of lesions in POH suggests that the pathogenesis may involve the presence of a mutant gene



FIG. 3. Radiographic appearance of severe heterotopic ossification in POH and FOP. (A–C) Lateral serial roentgenograms of the leg of a child with POH show progressive heterotopic ossification of the soft tissues when the child was (A) 18 months old and (B) 30 months old. Lateral roentgenogram of the amputation specimen (C) shows extensive ossification of the soft tissues of the superficial and deep posterior compartments of the leg. There is severe disuse osteopenia and anterior bowing of the tibia. (A–C reprinted with permission from Kaplan FS, Craver R, MacEwen GD et al., 1994.⁽²⁾) D. Lateral radiograph of the knee in a patient with FOP shows well-developed heterotopic bone in the popliteal fossa with distinct cortical features. The heterotopic bone appears to have formed a pseudoarticulation, but the patient progressed to form complete bony ankylosis over the next year during a subsequent flare-up of disease activity. (Reprinted with permission from Kaplan FS, Strear CM, Zasloff MA, 1994.⁽²⁰⁾)

in mesenchymal stem cells destined for widespread distribution.⁽²⁾ Observations in patients with POH suggest that such mesenchymal stem cells or more committed osteogenic precursor cells are present in skin, subcutaneous fat,

muscle, tendon, and ligament tissue. Also, the intramembranous bone formation that occurs in subcutaneous fat in patients with POH provides evidence for a close relationship between adipogenesis and osteogenesis in peripheral

TABLE 1. CLINICAL FEATURES OF HETEROTOPIC OSSIFICATION IN POH, FOP, AND AHO

<i>Feature</i>	<i>POH</i>	<i>FOP</i>	<i>AHO</i>
Sex distribution	Female = male	Female = male	Female = male
Genetic transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant
Congenital malformation of great toes	–	+	–
Congenital papular rash	+	–	–
Cutaneous ossification	+	–	±
Subcutaneous ossification	+	–	±
Muscle ossification	+	+	–
Superficial to deep progression of ossification	+	–	–
Severe limitation of mobility	+	+	–
Severe flare-ups of disease	–	+	–
Ectopic ossification after intramuscular injections	–	+	–
Ectopic ossification after trauma	±	+	–
Regional patterns of progression	–	+	–
Definitive treatment available	–	–	–

TABLE 2. PATHOLOGICAL AND LABORATORY FEATURES OF POH, FOP, AND AHO

<i>Feature</i>	<i>POH</i>	<i>FOP</i>	<i>AHO</i>
Predominant mechanism of ossification	Intramembranous	Endochondral	Intramembranous
Inflammatory perivascular and muscle infiltrate	–	+	–
Hematopoietic marrow in ectopic bone	±	+	–
PTH resistance	–	–	+
Hypocalcemia and hyperphosphatemia	–	–	+
Pathogenesis	Unknown	Associated with increased expression of BMP-4	Unknown
Genetic mutations	Unknown	Unknown	Inactivating mutation of α -subunit of G-stimulatory protein of adenylyl cyclase

tissues, a phenomenon well documented in bone marrow stromal cells^(49–54) and in immortalized mesodermal progenitor cells.⁽⁵⁵⁾

Many animals (living and extinct) have been known to form primary dermal ossification as part of a normal developmental defense mechanism.⁽⁵⁶⁾ However, we are unaware of any naturally occurring animal models of progressive heterotopic ossification that specifically recapitulate the natural history and pathology of POH.

WHAT IS THE PROGNOSIS AND TREATMENT FOR PATIENTS WHO HAVE POH?

Presently, there are no effective treatments or preventions for POH. Areas of well-circumscribed heterotopic ossification often can be removed successfully without recurrence. However, the extensive coalescence of ossified skin plaques and the slow relentless progression of deep heterotopic ossification pose perplexing therapeutic dilemmas. One child successfully underwent functional

repositioning of a joint after the development of a joint contracture from heterotopic ossification.⁽¹⁹⁾ Two other children underwent amputations (one of a lower limb⁽²⁾ and another of a nondominant index finger⁽⁴⁴⁾) as a result of severe growth retardation and complete loss of function of the affected part.

The surgical removal of POH tissue has led to recurrence in most patients, notably when the heterotopic ossification is diffuse and weblike rather than focal. One patient⁽⁴⁵⁾ encountered extensive bleeding during an unsuccessful attempt to remove recurrent heterotopic bone and subsequently died from complications arising from the surgery (Dr. Roger Smith, personal communication, 1998).

It is important for geneticists, dermatologists, pediatricians, pathologists, and orthopedic surgeons to be aware of POH so that unnecessary treatments can be avoided, and proper counseling can be offered.⁽⁵⁷⁾ The long-term prognosis of POH is uncertain because only a few patients have been followed beyond adolescence, but in these few patients, the disease has followed a course of slower progression during adulthood.

DO AHO AND G PROTEINS HOLD A CLUE TO THE PATHOGENESIS OF POH?

AHO is an autosomal dominant disorder of the skin, skeletal, and endocrine systems, with variable features that may include pseudohypoparathyroidism, multiple hormone resistance, obesity, brachydactyly (especially fourth and fifth metacarpals), short stature, round facies, and cutaneous and subcutaneous ossification (Table 1).^(22–26,28,58–70) Although patients with POH do not show the developmental dysmorphologies and hormone resistance that commonly are associated with AHO, cutaneous and subcutaneous ossification of the skin in childhood is rare, and therefore the possibility that the heterotopic ossification in these two conditions might involve the same cellular pathways is a reasonable consideration.

In most patients with AHO, the disease is caused by heterozygous mutations in *GNAS1*,^(26,59–61,63–72) a gene on human chromosome 20 encoding the α -subunit of the stimulatory G protein of adenylyl cyclase ($G_s\alpha$). Patients with AHO have a 50% reduction in the expression (both the long and short forms of $G_s\alpha$ are equally reduced⁽⁵⁹⁾) or activity of $G_s\alpha$ in plasma membranes of multiple cell types.⁽⁶⁵⁾ This genetic defect leads to the impaired activation of adenylyl cyclase and impaired cyclic adenosine monophosphate (AMP)-mediated signal transduction.

Functional inactivation of $G_s\alpha$ leads to the multiple organ hormone resistance and variable phenotypic features in patients who have AHO (Table 2).^(26,59–61,63–72) Family members of patients with pseudohypoparathyroidism who have a body habitus of AHO but who lack hormone resistance are described as having pseudopseudohypoparathyroidism.⁽⁷³⁾ The remarkable complexity of allele-specific imprinting of the *GNAS1* gene in selective tissues may, at least in some cases, underlie the often dramatic phenotypic variability, such as the presence or absence of hormone resistance, among family members who may harbor the identical mutation.^(65,74–82)

PTH and PTH-related protein (PTHrP) use a common cell membrane receptor linked to $G_s\alpha$.^(83–86) The normal physiological roles of the common receptor include not only calcium homeostasis but also embryonic bone and cartilage development^(83,85,87–92) and osteoblast regulation.^(85,93,94) Inactivating mutations in the *GNAS1* gene could disrupt embryonic signal transduction of PTHrP and plausibly contribute to the short stature, brachydactyly, and subcutaneous ossification seen in patients who have AHO.⁽⁷²⁾ However, the exact molecular pathophysiology by which inactivating mutations in the *GNAS1* gene lead to heterotopic ossification of the dermis and subcutaneous fat in patients with AHO is unknown.

IS THERE A CONNECTION BETWEEN AHO AND SEVERE POH-LIKE HETEROTOPIC OSSIFICATION?

Cutaneous and subcutaneous ossification occur commonly in patients who have AHO and POH, but progressive

ossification of deep connective tissues is not known to occur in patients who have AHO. However, a report in this issue of the Journal⁽⁹⁵⁾ describes two unusual cases of children who have both AHO and severe POH-like heterotopic ossification. One child, with classic AHO and severe POH-like features, has 50% activity of the $G_s\alpha$ protein without any detected mutation in *GNAS1*, while the other, with mild AHO and POH-like features, has 50% activity of the $G_s\alpha$ protein with an inactivating mutation in *GNAS1*, providing an explanation for the AHO features that are expressed in these children. Although it is possible that the AHO- and POH-like phenotypes of these children are caused by mutations in different genes, the presence of deep and progressive heterotopic ossification in children with variable features of AHO suggests that a common molecular mechanism may be responsible for their heterotopic ossification.

Further evidence for a connection between *GNAS1* and heterotopic ossification has been found in a child who has no evidence of AHO or hormone resistance but who has severe atypical congenital platelike osteoma cutis (POC) and a *GNAS1* mutation.⁽⁹⁶⁾ Although this POC patient shows a substantially different distribution and extent of heterotopic bone formation compared with classic POH, this case shows that an inactivating mutation in *GNAS1* can lead to heterotopic ossification in the absence of expression of AHO features. Interestingly, the mutation identified in this POC patient is identical to a mutation that previously has been found in AHO.^(70,97,98)

The three reported cases of atypical severe dermal ossification described in this issue of the Journal indicate that inactivating mutations of *GNAS1* are present in patients with progressive heterotopic ossification. Further analysis of a wide sample of patients with classic POH (i.e., with no AHO features) is necessary to determine whether the molecular basis of POH is caused by inactivating mutations of the *GNAS1* gene, and those studies are underway.

WHAT ARE THE LESSONS OF A RARE DISEASE LIKE POH?

These three atypical cases^(95,96) suggest that inactivating mutations in *GNAS1* can lead not only to cutaneous and subcutaneous heterotopic ossification in AHO, but also to a phenotype of severe progressive heterotopic ossification within skeletal muscle and deep connective tissue. The exact mechanism by which an inactivating mutation in the $G_s\alpha$ gene may lead to progressive heterotopic ossification of deep connective tissues remains elusive, as it does for the cutaneous and subcutaneous ossification seen characteristically in AHO. Such a mutation could plausibly lead to altered regulation of cyclic AMP-mediated signal transduction in mesenchymal stem cells (Table 3). However, it is of interest to note that a mouse model of AHO that contains a heterozygous knockout of the *GNAS1* gene shows no evidence of heterotopic ossification.^(80,99)

Somatic activating mutations of *GNAS1* in patients with the McCune-Albright Syndrome and germ line inactivating mutations of *GNAS1* in patients with AHO affect mesenchymal cells of both mesodermal and ectodermal origin.⁽⁸¹⁾

TABLE 3. POH AND VARIANTS: CLINICAL, PATHOLOGICAL, AND MOLECULAR FEATURES

<i>Feature</i>	<i>PHPIa</i>	<i>PPHP</i>	<i>Patient 1</i> <i>(Eddy et al, 2000)⁽⁹⁵⁾</i>	<i>Patient 2</i> <i>(Eddy et al, 2000)⁽⁹⁵⁾</i>	<i>Patient 3</i> <i>(Yeh et al, 2000)⁽⁹⁶⁾</i>	<i>POH</i>
PTH resistance	+	-	-	+	-	-
AHO body habitus	+	+	±	+	-	-
Short stature						
Round face						
Brachydactyly						
Cutaneous and subcutaneous heterotopic ossification	+	+	+	+	+	+
Heterotopic ossification in skeletal muscle and deep connective tissue	-	-	+	+	+	+
Heterozygous loss of function or expression of $G_s\alpha$	+	+	+	+	+	?

PHPIa, pseudohypoparathyroidism Ia; PPHP, pseudopseudohypoparathyroidism.

Early developmental arrest of osteogenesis in affected bones in the McCune-Albright Syndrome involves lineage specification of mesenchymal precursor cells of ectodermal and mesodermal origin under the influence of activating mutations of GNAS1. By contrast, inactivating mutations of GNAS1 lead to down-regulation of adenylyl cyclase catalyzed pathways and to the apparent inappropriate recruitment to an osteogenic lineage from pluripotent mesenchymal cells. In the context of bone development, GNAS1 may encode a negative regulator of the osteogenic lineage.

One hypothesis is that expression of the obligate bone-specific transcription factor Cbfa1⁽¹⁰⁰⁻¹⁰⁶⁾ in dermal fibroblasts or in mesenchymal stem cells residing in the skin could result in dermal ossification. Inactivating GNAS1 mutations may induce alterations in the Cbfa1 pathway in dermal fibroblasts; however, this link needs to be established.

The importance and implications of understanding the cause of POH are unassailable for the children who have the condition. However, the importance of POH to medical science is far greater than its extreme rarity might indicate. POH is, in fact, an important disorder for specialists in numerous fields, including the basic sciences of developmental biology, cell biology, and molecular biology as well as the clinical sciences of neonatal medicine, pediatrics, dermatology, orthopedics, internal medicine, rheumatology, and physical medicine and rehabilitation. By unraveling the complex pathogenesis of POH and by more thoroughly deciphering the molecular basis of gene expression involved in directing the transformation of skin, fat, and muscle precursor cells into bone, there is great hope that more common disorders of osteogenesis will become understandable and treatable.

William Harvey, the discoverer of the circulation of the blood, stated the following in 1657 in a letter to a fellow physician: "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path, nor is there any better method to advance the proper practice of medicine than to give our minds to the discovery of the

usual law of nature by careful investigation of cases of rarer forms of disease. For it has been found in almost all things that what they contain that is useful or applicable is hardly perceived unless we are deprived of them, or they become deranged in some ways."⁽¹⁰⁷⁾

WHAT SUPPORT GROUPS ARE AVAILABLE FOR PATIENTS WITH POH?

During the past decade, two dedicated support groups, one for FOP and one for POH, have been established for patients and families.

The International Fibrodysplasia Ossificans Progressiva Association (IFOPA) is a nonprofit organization that supports research and education for patients with FOP and served as a model organization for members of the POH community. The IFOPA was founded in 1988 by Jeannie Peeper, an adult with FOP, in order to end the social isolation imposed by this rare and debilitating disease. Today, the IFOPA has nearly 200 members in over 25 countries. The IFOPA's home page on the Worldwide Web contains information about FOP, the IFOPA, and the international collaborative research project. "What is FOP? A Guidebook For Families" is also available on the website. The address for the site is <http://www.IFOPA.org>. Those using email can contact the IFOPA at ifopa@vol.com. The address of the IFOPA is Ms. Jeannie Peeper, President, IFOPA, P.O. Box 196217, Winter Springs, FL 32719-6217.

The Progressive Osseous Heteroplasia Association (POHA) is a nonprofit organization that supports research and education for patients with POH. The POHA was founded in 1995 by Fred Gardner, the grandfather of a child with POH. Today, the POHA has approximately 25 members. The POH Collaborative Research Project is an international group of physicians and scientists who work together on all clinical and basic aspects of the POH project. The focus of the research is to identify the cause and to find a cure for POH. Currently, the POHA does not have its own newsletter but participates in *The FOP Connection*, pub-

lished quarterly by the IFOPA. "What Is POH? A Guidebook for Families" (Kaplan, Wagman et al., 1997) is available through the POHA. The address of the POHA is Fred Gardner, Executive Director, POHA, 33 Stonehearth Square, Indian Head Park, IL 60525.

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