Illustrative Disorders of Ectopic Skeletal Morphogenesis: A Childhood Parallax for Studies in Gravitational and Space Biology
Frederick S. Kaplan, M.D.\textsuperscript{1,2} and Eileen M. Shore, Ph.D.\textsuperscript{1,3}

Departments of\textsuperscript{1} Orthopaedic Surgery, \textsuperscript{2}Medicine, and \textsuperscript{3}Genetics, The University of Pennsylvania School of Medicine, Philadelphia, PA 19104

ABSTRACT
Heterotopic ossification is a key feature of at least three distinct genetic disorders of osteogenesis in humans: fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, and Albright's hereditary osteodystrophy. All three conditions are genetic disorders of childhood, but the pathobiology of osteogenic induction, the histopathology of osteogenesis, the anatomic distribution of heterotopic lesions, and the developmental patterns of disease progression differ among the three conditions. The phenotypic distinction of these disorders is critically important in counselling patients and families as well as in advancing research to define the molecular pathophysiology of heterotopic osteogenesis in these disabling genetic disorders. Genetic disorders of tissue modeling and morphogenesis provide an important parallax to disturbances of tissue re-modeling that are of paramount importance to gravitational and space biologists as humans begin to explore and live in environments beyond the planet on which they evolved. Disorders of osteogenesis are of particular concern to space biologists due to the dramatic changes in skeletal biology in altered gravitational fields.

INTRODUCTION
Genetic disorders of heterotopic ossification are rare conditions that lead to progressive and catastrophic disability beginning in childhood. The most severe genetic condition of heterotopic ossification, fibrodysplasia ossificans progressiva, has been known as a distinct disorder for more than three centuries. Progressive osseous heteroplasia, first described in 1994, is another distinct genetic disorder of heterotopic ossification and shares several non-endocrine features with Albright's hereditary osteodystrophy, the only one of the three disorders in which a genetic mutation has been identified. These three disorders of heterotopic ossification provide a unique opportunity to identify genetic pathways involved in osteogenic induction. Detailed knowledge of genetic pathways of heterotopic osteogenesis will be invaluable in designing better treatments for these enigmatic and disabling disorders. In this article, we will outline knowledge and research on these disorders, and compare and contrast clinical and pathophysiologic features that will promote better clinical identification and care of children who have these disorders. These conditions may also be interesting to space biologists who study perturbances of osteogenesis and bone remodeling in extraterrestrial environments.

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA
Fibrodysplasia ossificans progressiva is a rare genetic disorder of connective tissue characterized by congenital malformation of the great toes and by progressive heterotopic endochondral osteogenesis in predictable anatomic patterns (Table I). Congenital malformation of the great toes is the earliest phenotypic feature of fibrodysplasia ossificans progressiva and is present in nearly all affected individuals (Connor et al., 1982; Kaplan et al., 1994b; Smith et al., 1996). Congenital malformations of the cervical spine may also occur, and most commonly manifest as defects in segmentation (Smith, 1998). Progressive heterotopic ossification begins early in life with the first involvement typically occurring along the neck and upper back (Cohen et al., 1993; Rocke et al., 1994). Impending heterotopic ossification is heralded by the appearance of large, variably painful tumors of highly vascular fibroproliferative tissue (Gannon et al., 1997; Kaplan et al., 1993b) involving tendons, ligaments, fascia, and skeletal muscle (Kaplan et al., 1994c). These lesions mature through an endochondral pathway and form normal lamellar bone. The anatomic progression of heterotopic ossification in fibrodysplasia ossificans progressiva occurs in specific patterns (or gradients) over time (Cohen et al., 1993). Involvement is typically seen earliest in dorsal, axial, cranial, and proximal regions of the body and later in ventral, appendicular, caudal, and distal regions (Cohen et al., 1993). These developmental patterns are similar to the patterns and progression of embryonic skeletal formation, although the exact cause of this precise pattern of heterotopic ossification is unknown.

Progressive episodes of heterotopic ossification lead typically to ankylosis of all major joints of the axial and appendicular skeleton, including the jaw, rendering movement impossible. Although the rate of disease progression is variable (Janoff et al., 1995), most patients are confined to a wheelchair by the second or third decade of life and require lifelong assistance in performing activities of daily living (Shah et al., 1994). Severe scoliosis may develop due to asymmetric heterotopic ossification of the paravertebral soft tissues. People with fibrodysplasia ossificans progressiva have markedly reduced reproductive fitness (Connor et al., 1982). Surgical trauma associated with the resection of heterotopic bone, injections for dental work, routine immunizations, and falls lead to exacerbation of local ossification (Glaser et al., 1998; Lanchoney et al., 1995; Luchetti et al., 1996). At present, there is no effective prevention or treatment.

Fibrodysplasia ossificans progressiva is an autosomal dominant disorder, and most cases are due to spontaneous mutations (Delatycki et al., 1998). The genetic defect and pathophysiology of the disorder are not known, although the bone morphogenetic protein (BMP) genes and other genes in the BMP pathway have been implicated as plausible candidate genes (Connor, 1995; Kaplan et al., 1990; Shafriz et al., 1996; Smith et al., 1986). Studies to identify the cause of fibrodysplasia ossificans progressiva are currently focused on the candidate gene pathway approach since karyotypic abnormalities have not been detected in patients with the disorder and lesional tissue is
**Table I. Clinical Features of Fibrodysplasia Ossificans Progressiva, Progressive Osseus Heteroplasia, and Albright's Hereditary Osteodystrophy**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Fibrodysplasia Ossificans Progressiva</th>
<th>Progressive Osseus Heteroplasia</th>
<th>Albright's Hereditary Osteodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex distribution</td>
<td>female = male autosomal dominant</td>
<td>female &gt; male autosomal dominant</td>
<td>female &gt; male autosomal dominant</td>
</tr>
<tr>
<td>Genetic transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital malformation of great toes</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Congenital papular rash</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Cutaneous ossification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle ossification</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Superficial to deep progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe limitation of mobility</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Severe flare-ups of disease</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ectopic ossification following IM injections</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ectopic ossification following trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional patterns of progression</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Definitive treatment available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

not readily available for study (Kaplan et al., 1996). Definitive linkage analysis and positional cloning is not possible, since only a few small families with inheritance of fibrodysplasia ossificans progressiva have been identified worldwide (Connor et al., 1993; Delatycki et al., 1998; Janoff et al., 1996; Janoff et al., 1995; Kaplan et al., 1993a), providing insufficient statistical power to perform such an analysis.

**PATHOLOGY OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA**

Failure to recognize the phenotypic features of fibrodysplasia ossificans progressiva frequently has led to biopsy of the acute lesion. Such biopsies are the only source of FOP lesions, since biopsies are contraindicated following diagnosis.

Histologic examination of early fibrodysplasia ossificans progressiva lesions reveals an intense perivascular lymphocytic infiltration followed by lymphocytic invasion into muscle, and robust development of fibroproliferative tissue with extensive neovascularity (Gannon et al., 1998). Tissue from fibrodysplasia ossificans progressiva lesions at a later stage of maturation shows characteristic features of endochondral ossification including chondrocyte hypertrophy, calcification of cartilage, and formation of woven bone with marrow elements. Traumatic fractures through heterotopic bone appear to heal normally (Einhorn et al., 1994).

A role for hematopoietic cells in the induction of heterotopic osteogenesis has been suggested (Buring, 1975). Immunohistochemical evaluation of lymphocyte markers in the early lesions of fibrodysplasia ossificans progressiva revealed a mixed population of perivascular B-lymphocytes and T-lymphocytes. A population of predominantly T-lymphocytes weakly positive for bone morphogenetic protein-4 was detected invading the skeletal muscle (Gannon et al., 1998). Whether the early lymphocytic infiltrate is part of an inductive cascade, a reaction to it, or both, cannot be determined from the observations in this small sample of patients. The intermediate lesions of fibrodysplasia ossificans progressiva are histologically indistinguishable from those of aggressive juvenile fibromatosis, a highly vascular fibroproliferative condition which does not progress to form bone (Gannon et al., 1997). Recent studies document the expression of BMP-4 in cultured fibroproliferative cells and in intact tissue specimens from pre-osseous lesions in patients with fibrodysplasia ossificans progressiva (Shafriz et al., 1996), but not from tissue specimens from patients with aggressive juvenile fibromatosis (Gannon et al., 1997).

Levels of basic fibroblast growth factor (bFGF), an extremely potent angiogenic peptide, are markedly elevated in the urine of patients with fibrodysplasia ossificans progressiva during times of disease flare-up (Kaplan et al., 1998). Elevation of urinary bFGF correlates with the appearance of an early vascular fibroproliferative lesion.
MOLECULAR GENETICS OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

The usual approach of identifying the genetic basis of a disease by performing genetic linkage analysis and positional cloning is presently unfeasible for fibrodysplasia ossificans progressiva due to the small number of affected individuals and lack of multi-generational families showing inheritance of the disease. The candidate gene approach has been pursued as an alternative indirect method of attempting to identify the mutant gene.

Among known genes, those that seem to best fit these criteria for FOP candidate genes are the bone morphogenetic protein (BMP) genes. Several members of the BMP gene family have been identified and cloned, and based on similarity of protein structure, the BMPs are members of the transforming growth factor beta (TGF-β) super-family of peptides (Hogan, 1996; Kaplan et al., 1990; Kingsley, 1994; Reddi et al., 1993; Urist, 1997; Vainio et al., 1993; Winnier et al., 1995; Wozney et al., 1988). BMP has the capability to induce the complete pathway of endochondral bone and bone marrow formation (Reddi et al., 1993; Urist, 1965; Wozney et al., 1988).

In addition, mutations in the genes of two members of the BMP family which result in skeletal abnormalities during embryogenesis have been identified in the mouse. Homozygous deletions of the BMP-5 gene cause malformations of the axial skeleton and abnormal fracture repair (Kingsley et al., 1992). Homozygous mutations of Gdf-5 (growth-differentiation factor-5) result in malformations of the appendicular skeleton (Storm et al., 1994). A mutation in the human homologue of the Gdf-5 gene, CDMP-1 (cartilage-derived morphogenetic protein 1), is associated with a recessive human chondrodysplasia, acromesomelic chondrodysplasia, Hunter-Thompson type (Thomas et al., 1996). Thus, naturally occurring mutations in BMP genes provide evidence for a direct role of at least some of the BMPs in embryonic and post-natal bone formation (Hogan, 1996; Kingsley, 1994).

BMP-2 and BMP-4 play critical roles in early embryogenesis and in skeletal formation, important criteria in considering them as candidate genes for fibrodysplasia ossificans progressiva. The BMP-2 and BMP-4 genes, which produce proteins that are about 90% similar to each other, are homologous to the Drosophila decapentaplegic (dpp) gene (Hogan, 1996; Kaplan et al., 1990; Kingsley, 1994), and BMP-4 and DPP are secreted peptides and appear to function by directing cell fate in a gradient-dependent manner (Jones et al., 1991; Kaplan et al., 1990). Several additional members of the TGF-β super-family have been shown experimentally, at least in certain developmental contexts, to act as morphogen-like molecules that influence cell fate by a concentration dependent mechanism (Francis et al., 1994; Katagiri et al., 1994; Zecca et al., 1995). The absence of BMP-4 in a transgenic knockout mouse is lethal early in embryogenesis, showing little or no mesodermal differentiation, and no hematopoiesis (Johansson et al., 1995; Winnier et al., 1995). BMP-4 has also been implicated in patterning of the developing mouse limb. Over-expression of BMP-4 in the chick embryonic limb bud is associated with polarizing defects in limb formation (Francis-West et al., 1996).

Recent studies have examined the expression of many of the BMPs in cells from fibrodysplasia ossificans progressiva patients (Gannon et al., 1997; Kaplan et al., 1990; Shafritz et al., 1996). Although early fibrodysplasia ossificans progressiva lesions are histologically indistinguishable from those of aggressive juvenile fibromatosis, these two disorders can be distinguished by BMP-2/4 expression (Gannon et al., 1997). While tissue from aggressive juvenile fibromatosis lesions (which does not progress to form bone) shows no binding to an antibody for BMP2/4, fibrodysplasia ossificans progressiva lesional tissue binds the antibody, indicating the presence of BMP proteins within early stage lesions that will progress to endochondral ossification. Although the antibody used for these experiments cannot distinguish between BMP-2 and BMP-4, the activity of these two BMP genes can be distinguished by examining specific mRNA expression (Gannon et al., 1997).

Northern analysis and ribonuclease protection assays were used to specifically examine the expression of BMP-2 and BMP-4 mRNAs in cells from fibrodysplasia ossificans progressiva patients. Cells derived from a pre-ossesous fibrodysplasia ossificans progressiva lesion and from approximately 80% of immortalized lymphoblastoid cell lines established from fibrodysplasia ossificans progressiva patients showed increased expression of BMP-4 but not BMP-2 compared to controls. Correlation of BMP-4 expression with fibrodysplasia ossificans progressiva was also observed in a family showing inheritance of fibrodysplasia ossificans progressiva: the affected father and three affected children over-expressed BMP-4, while the unaffected mother did not (Shafritz et al., 1996). Further studies have verified that BMP-4 protein is over-expressed in cells from patients who have fibrodysplasia ossificans progressiva (Lanchoney et al., 1998; Olmsted et al., 1996). Recent results have indicated that the increased levels of BMP-4 mRNA in fibrodysplasia ossificans progressiva cells are due to an increased rate of transcription of the BMP-4 gene (Olmsted et al., 1996).

The appearance of large aggregates of T-lymphocytes in the intramuscular and perivascular spaces of the earliest detectable lesions of fibrodysplasia ossificans progressiva suggest that lymphocytes and perivascular cells are involved in the induction of osteogenesis (Gannon et al., 1998). These findings suggest a mechanism to explain the pathophysiology of heterotopic bone formation in this disorder. We hypothesize that lymphocytes capable of expressing BMP-4 circulate in the peripheral blood of patients with fibrodysplasia ossificans progressiva, and are recruited to connective tissue sites after soft-tissue injury (Shafritz et al., 1996). Alternatively, an event at a soft-tissue site may cause an immune-like response and recruitment of lymphocytes, with cells within the soft tissue induced to produce BMP-4. Type IV collagen, a primary
Figure 1. Conserved BMP Signaling Pathways Involved in the Regulation of Skeletal Morphogenesis. This composite schematic depicts experimentally-determined features of BMP signaling identified in numerous in vitro and in vivo model systems including *Drosophila*, *Xenopus*, chicken, mouse, and humans. Each component of this pathway may not be active in every model system or in every cell type within a model system. Arrows = activating pathways; blunt-ended lines = inhibitory pathways. PTHrp: parathyroid hormone related protein; PTH: parathyroid hormone; IHH: Indian hedgehog; SHH: sonic hedgehog; PTC, ptc: patched; SMO: smoothened; GLI: glioblastoma-derived oncogene family; BMP: bone morphogenetic protein; Wnt: vertebrate wingless family; FGFR: fibroblast growth factor receptor; BMPR: receptors for BMP-2 and 4; Hox: vertebrate homeobox family; Fos and Jun: members of the AP1 family of transcription factors; PAX-3 and MyoD: transcription factors in muscle development; Osf2/Cbfa1: obligate osteogenic transcription factor; SMADs: transcription factors in BMP pathway; Noggin and Chordin: BMP inhibitors; NF-κB and Twist: transcription factors in inflammatory and morphogenetic pathways.
constituent of the basement membrane of endothelial cells, muscle cells, and myoblast-like satellite cells, avidly binds BMP-4, and could result in increased local concentrations of BMP-4. (Reddi et al., 1993). At high concentrations, BMP-4 acts as a morphogen capable of upregulating its own expression (Vainio et al., 1993). Such an autoregulatory cascade could lead to the development of pre-osseous lesions around muscle satellite cells or pericytes (Brighton et al., 1992) capable of transducing the BMP signal. To test the hypothesis that lymphocyte-mediated BMP expression can result in fibrodyplasia ossificans progressiva lesions, transgenic animal models are being developed to over-express BMP-4 in B-lymphocytes and T-lymphocytes. The expression of BMPs and BMP receptors in hematopoietic stem cells is also being investigated.

The stringent temporal and spatial patterns of post-natal heterotopic ossification in patients with fibrodyplasia ossificans progressiva are reminiscent of patterns of mesenchymal cell condensation during skeletal embryogenesis and suggest a common molecular basis for pre-natal and post-natal osteogenesis. Post-natal osteogenesis in humans most commonly occurs during fracture healing. Fracture callus and heterotopic bone formation in fibrodyplasia ossificans progressiva form by endochondral pathways and both involve increased BMP-4 expression (Bostrom et al., 1995; Nakase et al., 1994). BMP-4 over-expression at connective tissue sites leads to focal osteogen-esis at those sites (Shimizu et al, 1994; Takaoka et al., 1994).

Presently, a direct link between fibrodyplasia ossificans progressiva and the BMP-4 gene has not been proven and remains circumstantial. The genetic mutation(s) in fibrodyplasia ossificans progressiva could plausibly reside anywhere in the BMP-4 signaling pathway, such as the NF-κB (Bushid et al., 1998; Kanega et al., 1998; Tickle, 1998) or SMAD genes (Heldin et al., 1997), or in other molecular pathways that affect the level of BMP-4 expression (Roush, 1996) (Figure 1).

PROGRESSIVE OSSEOUS HETEROPLASIA

Progressive osseous heteroplasia is a distinct genetic disorder of osteogenesis characterized by dermal ossification during infancy and by progressive heterotopic ossification of subcutaneous and deep connective tissue during childhood (Table I) (Kaplan et al., 1994a). The disorder can be distinguished from fibrodyplasia ossificans progressiva 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 (Kaplan et al., 1994b). There have been 13 classic case reports of progressive osseous heteroplasia, 11 in females, and 2 in males (Athanasou et al., 1994; Kaplan et al., 1994a; Miller et al., 1996; Rosenfeld et al., 1995; Schmidt et al., 1994).

The first signs of the disease are the appearance of cutaneous plaques of intramembranous ossification during infancy. Over time, the plaques coalesce and progress to invade the deeper connective tissues. Extensive ossification of the deep tissues results in ankylosis of affected joints and focal growth retardation of involved limbs. Patients with progressive osseous heteroplasia have normal intelligence, normal developmental milestones, and lack sustained biochemical or endocrine abnormalities.

The long-term prognosis for patients who have progressive osseous heteroplasia is uncertain, as only several cases have been followed beyond adolescence. At present, there is no definitive prevention of treatment available for children with progressive osseous heteroplasia. The extensive coalescence of ossified skin plaques and the progressive ossification of deep tissues pose perplexing therapeutic dilemmas.

PATHOLOGY OF PROGRESSIVE OSSEOUS HETEROPLASIA

The heterotopic ossification of progressive osseous heteroplasia occurs predominantly by an intramembranous pathway (Table II) (Kaplan et al., 1994a). Although the osteogenesis seen in progressive osseous heteroplasia is similar to that observed in Albright’s hereditary osteodystrophy, the lesions in Albright’s hereditary osteodystrophy are limited to the skin and subcutaneous tissues, whereas those in progressive osseous heteroplasia may also involve the deep mesenchymal tissues of the limbs (Kaplan et al., 1994b). Recent reports of progressive osseous heteroplasia describe islands of endochondral ossification in the deeper connective tissue with the sporadic appearance of marrow elements (Rodriguez-Jurado et al., 1995).

MOLECULAR GENETICS OF PROGRESSIVE OSSEOUS HETEROPLASIA

Some cases of progressive osseous heteroplasia are sporadic, while some are familial. (Kaplan et al., 1994a) Once the disease appears, it is inherited in an autosomal dominant Mendelian manner with mosaic distribution in affected individuals and variable expressivity between individuals (Kaplan et al., 1994a). The etiology and pathogenesis of the disease are unknown.

The anatomic distribution of lesions in progressive osseous heteroplasia suggests that the pathogenesis may involve variable expression of the mutant gene in mesenchymal stem cells destined for widespread mosaic distribution (Bernards et al., 1994). Although dermal fibroblasts and internal limb structures arise embryonically from limb bud mesenchyme, the fate map of the blastoderm mammalian embryo suggests that specific cell types, such as muscle or bone, are polyclonal in origin. Conversely, in the mature organism, a single cell such as a hematopoietic stem cell or connective tissue stem cell can, under various conditions, generate a wide variety of cell types. At present, little is known about the molecular mechanisms of the signal and response system of mesodermal induction.

A recently discovered promising candidate gene for progressive osseous heteroplasia is Osf2/Cbfal. Osf2/Cbfal is an obligate transcriptional activator of osteoblast differentiation. Osf2/Cbfal binds to the OSE-element in the promoter of numerous bone-associated genes
HETEROPTIC OSSIFICATION

Table II. Pathologic Features of Fibrodysplasia Ossificans Progressiva, Progressive Osseus Heteroplasia, and Albright’s Hereditary Osteodystrophy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Fibrodysplasia Ossificans Progressiva</th>
<th>Progressive Osseus Heteroplasia</th>
<th>Albright’s Hereditary Osteodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant mechanism of ossification</td>
<td>endochondral</td>
<td>intramembranous</td>
<td>intramembranous</td>
</tr>
<tr>
<td>Inflammatory perivascular and muscle infiltrate</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hematopoietic marrow in ectopic bone</td>
<td>+</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Parathyroid hormone resistance</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Hypocalcemia, hyperphosphatemia</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Involves increased expression of BMP4</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Genetic mutations</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Inactivating mutation of a subunit of G protein of adenyl cyclase</td>
</tr>
</tbody>
</table>

...to regulate the expression of the osteogenic phenotype. The spurious expression of Osf2/Cbfa1 in pluripotent mesenchymal cells and in mouse skin fibroblasts induces a mature osteoblast-specific phenotype. Osf2/Cbfa1 is positively regulated by at least several of the BMPs (Figure 1) and inhibited by 1,25-dihydroxyvitamin D in the mouse (Ducy et al., 1997; Komori et al., 1997). Homozygous knockout of the Osf2/Cbfa1 gene in the mouse leads to complete lack of bone formation by both the endochondral and intramembranous pathways due to a failure of osteoblastic differentiation (Komori et al., 1997). In mice and humans, heterozygotes for mutations in Osf2/Cbfa1 exhibit the skeletal disorders cleidocranial dysplasia (Mundlos et al., 1997; Otto et al., 1997). These and other findings raise the critically important questions: "What is the relationship of Osf2/Cbfa1 to osteoblast commitment and to sustained phenotype expression; and how is the expression of Osf2/Cbfa1 regulated?" (Rodan et al., 1997) Could the misexpression of Osf2/Cbfa1 in pluripotent mesenchymal cells derived from embryonic somites plausibly lead to the progressive osseous heteroplasia phenotype? Linkage exclusion analysis using polymorphic microsatellite markers closely linked to the Osf2/Cbfa1 gene on human chromosome 6q21 in multigenerational families with progressive osseous heteroplasia may be revealing.

ALBRIGHT’S HEREDITARY OSTEODYSTROPHY AND G PROTEINS

Albright’s hereditary osteodystrophy is an autosomal dominant disorder that involves the dermatologic, skeletal, and endocrine systems, with variable features including cutaneous and subcutaneous ossification, pseudohypoparathyroidism, hypoparathyroidism, gonadotropin resistance, obesity, brachydactyly, short metacarpals, and plethoric round facies (Table I) (Albright et al., 1942; Barranco, 1971; Brook et al., 1971; Carter et al., 1987; Clapham, 1993; Eyre et al., 1971; Farfel et al., 1980; Izraeli et al., 1992; Kidd et al., 1980; Lefkowitz, 1995; Levine et al., 1988; Levine et al., 1986; Patten et al., 1990a; Patten et al., 1990b; Piesowicz, 1965; Spiegel, 1990; Spiegel et al., 1993; Weinstein et al., 1992; Weinstein et al., 1990).

In contrast to the activating mutations of the GNAS-1 gene in McCune-Albright Syndrome that lead to increased activity of the stimulatory G protein, a functional inactivation of the stimulatory G protein leads to the multiple organ resistance of patients who have Albright’s hereditary osteodystrophy (pseudohypoparathyroidism type 1A) (Table II) (Carter et al., 1987; Clapham, 1993; Farfel et al., 1980; Izraeli et al., 1992; Lefkowitz, 1995; Levine et al., 1988; Levine et al., 1986; Patten et al., 1990a; Patten et al., 1990b; Spiegel, 1990; Spiegel et al., 1993; Weinstein et al., 1992; Weinstein et al., 1990). In most patients with Albright’s hereditary osteodystrophy (pseudohypoparathyroidism type 1A), the disease is caused by an inherited single-base mutation in the GNAS-1 gene (Carter et al., 1987; Clapham, 1993; Farfel et al., 1980; Izraeli et al., 1992; Lefkowitz, 1995; Levine et al., 1988; Levine et al., 1986; Patten et al., 1990a; Patten et al., 1990b; Spiegel, 1990; Spiegel et al., 1993; Weinstein et al., 1992; Weinstein et al., 1990). Patients with Albright’s hereditary osteodystrophy (pseudohypoparathyroidism type 1A) have a 50% reduction in the activity of the stimulatory G protein of adenylate cyclase in plasma membranes of multiple cell types (Levine et al., 1986), leading to an
increased intracellular accumulation of ATP. In Albright's hereditary osteodystrophy, the steady-state content of both the long and short forms of the α-subunit of the stimulatory G protein are equally reduced (Carter et al., 1987).

Recent studies have shown that parathyroid hormone (PTH) and PTH-related protein use a common cell membrane receptor linked to the α-subunit of the stimulatory G protein (Jupner et al., 1991). The normal physiologic roles of PTH-related protein include not only calcium homeostasis but also embryonic bone and cartilage development (Ish-Shalom et al., 1996; Jupner et al., 1991; Karaplis et al., 1994). Germline homozgyous mutations in the gene for PTH-related protein are fatal and lead to gross malformations of the skeleton (Karaplis et al., 1994). Heterozygous mutations in the GNAS-1 gene disrupt embryonic signal transduction of PTH-related protein and may contribute to the short stature, brachydactyly, and cutaneous ossification seen in patients who have Albright's hereditary osteodystrophy. However, the exact molecular pathophysiology by which inactivating mutations in the GNAS-1 gene lead to heterotopic ossification of the dermis and subdermal tissue is unknown.

ALBRIGHT'S HEREDITARY OSTEODYSTROPHY AND PROGRESSIVE OSSEOUS HETEROPLASIA

While cutaneous and subcutaneous ossification occur commonly in patients who have Albright's hereditary osteodystrophy and progressive osseous heteroplasia, progressive ossification of deep connective tissues is not known to occur in patients who have Albright's hereditary osteodystrophy. Similarly, patients with progressive osseous heteroplasia have not been noted to have primary endocrine dysfunction. However, recent clinical observations have identified two children from different families who have prominent features of both Albright's hereditary osteodystrophy and progressive osseous heteroplasia (Kaplan, 1996). The occurrence in the same patients of 2 distinct disorders of heterotopic ossification is intriguing and suggests that a common molecular mechanism may be responsible for the unique phenotypic features of Albright's hereditary osteodystrophy and progressive osseous heteroplasia in these two patients.

The exact mechanism by which an inactivating mutation in the α-subunit of the stimulatory G protein of adenylate cyclase may lead to progressive osseous heteroplasia remains elusive, as it does for the cutaneous and subcutaneous ossification seen classically in Albright's hereditary osteodystrophy. It is plausible that the molecular basis of at least one form of progressive osseous heteroplasia consists of an as yet undiscovered mutation in the α-subunit of the stimulatory G protein of adenylate cyclase or in a related signaling pathway plausibly involving the common G-linked protein receptor for PTH and PTH-related protein.

PATIENT SUPPORT GROUPS

During the past decade, two dedicated support groups, one for fibrodysplasia ossificans progressiva and the other for progressive osseous heteroplasia, have been established for patients and families.

The International Fibrodysplasia Ossificans Progressiva Association (IFOPA) is a nonprofit organization which supports research, education, and clinical care for patients with FOP. The IFOPA was founded in 1988 by Jeannie Peeper, an adult with FOP, to end the social isolation imposed by this rare and debilitating disease. Today the IFOPA has nearly 200 members in over 15 countries. The IFOPA's home page on the World Wide Web contains information about the disease, the IFOPA and the international research project. "What is FOP? A Guidebook for Families" is available on the web or through the IFOPA. The address for the site is http://www.vol.com/~skant. Those using email can contact the IFOPA at ifopa@vol.com. The address of the IFOPA is Jeannie Peeper, President, IFOPA, P.O. Box 3578, Winter Springs, Florida 32708.

The Progressive Osseous Heteroplasia Association (POHA) is a nonprofit organization which supports research, education, and clinical care 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, scientists and technicians who work together on all clinical and basic aspects of the POH project. In 1996, their commitment helped to establish a laboratory which is exclusively devoted to the research of POH and related disorders. 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, published quarterly by the IFOPA (International Fibrodysplasia Ossificans Progressiva Association). "What is POH? A Guidebook for Families" is available through the POHA. The address of the POHA is: Fred Gardner, Secretat-Treasurer, POHA, 33 Stonehearth Square, Indian Head Park, Illinois 60525.

SUMMARY

Fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, and Albright's hereditary osteodystrophy are three extremely rare and disabling genetic disorders of heterotopic ossification in humans. These disorders have the enormous potential to illuminate molecular and genetic pathways of osteogenic induction. Knowledge gained from the study of these rare disorders will be useful in designing more effective therapies for these devastating and crippling disorders of childhood, and may also propel discoveries for more common disorders of osteogenesis.

Beyond consideration of these rare genetic disorders lurks larger questions relevant to the evolution of life on earth and to the existence and survival of life in extra-terrestrial environments. To what extent does the regulation of embryonic morphogenesis dictate the regulation of postnatal tissue remodeling? How do mechanical factors affect embryonic morphogenesis and
postnatal tissue remodeling? To what extent is the gravitational imperative of earth-based life modeled into the genetic structure of the organism? To what extent might organisms that exist in altered gravitational fields or altered biomechanical environments (the ocean floor, for example) display genetic drift in genes that regulate morphogenesis? To what extent do mutations that affect morphogenesis also affect postnatal remodeling, tissue repair and regeneration?

Disorders of morphogenesis could provide a startling perspective for understanding the physical forces that lead to the emergence and remodeling of form that may be critical for long term extra-terrestrial activity. Furthermore, longer-term studies of morphogenesis in zero gravity may provide important insights for understanding the pathogenesis and treatment of devastating childhood diseases of ectopic osteogenesis.

REFERENCES


HETEROPTIC OSSIFICATION


