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Fibrous Dysplasia/McCune-Albright Syndrome: Clinical and Translational Perspectives

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Abstract Fibrous dysplasia (FD) is an uncommon and debilitating skeletal disorder resulting in fractures, deformity, functional impairment, and pain. It arises from post-zygotic somatic activating mutations in *GNAS*, in the cAMP-regulating transcript α-subunit, $G_s\alpha$. Constitutive G_s signaling results in activation of adenylyl cyclase and dysregulated cAMP production. In the skeleton, this leads to the development of FD lesions with abnormal bone matrix, trabeculae, and collagen, produced by undifferentiated mesenchymal cells. FD may occur in isolation or in combination with extraskeletal manifestations, including hyperfunctioning endocrinopathies and café-au-lait macules, termed McCune-Albright syndrome (MAS). This review summarizes current clinical and translational perspectives in FD/MAS, with an emphasis on FD pathogenesis, natural history, pre-clinical and clinical investigation, and future directions.

Keywords Fibrous dysplasia · McCune-Albright syndrome · *GNAS* gene · $G_s\alpha$ · FGF23

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Introduction

Fibrous dysplasia (FD; OMIM 174800) is an uncommon skeletal disorder resulting in fractures, deformity, pain, and functional impairment. First described by Lichtenstein in 1938, FD is an example of somatic mosaicism occurring along a broad clinical spectrum [1]. Disease may affect one bone (monostotic) or multiple (polyostotic) and may occur in isolation or in combination with café-au-lait spots and hyperfunctioning endocrinopathies, termed McCune-Albright syndrome (MAS) [2]. Any part or combination of features is possible, giving rise to a phenotype that is complex and striking in its diversity.

GNAS Gene

FD/MAS is caused by somatic activating mutations in *GNAS*, located on the q arm of chromosome 20 at position 13.3. The *GNAS* locus is a complex, imprinted gene that uses several promoters to produce assorted gene products, including the ubiquitously expressed α-subunit of the G_s stimulatory protein ($G_s\alpha$) [2]. The primary role of $G_s\alpha$ is to couple hormones and certain seven-transmembrane receptors to adenylyl cyclase, facilitating production of intracellular cyclic AMP [3]. $G_s\alpha$ is comprised, in part, by an intrinsic GTPase domain, which binds guanine nucleotide and interacts with specific receptors and effectors. The intrinsic GTPase activity of $G_s\alpha$ inactivates receptor signaling by hydrolyzing bound GTP to GDP [2, 4].

In FD/MAS, activating missense mutations in $G_s\alpha$ have been identified in two amino acid residues: Arg^{201} (>95 % mutations, divided evenly between R201C and R201H) or Gln^{227} (<5 %) [5]. R201 is an essential regulator of GTPase, and mutations in this domain result in disruption of GTPase activity and constitutive $G_s\alpha$ activation [2]. Intracellularly,

this results in dysregulated production of cyclic AMP and other downstream messengers [6]. Constitutive receptor activation results in overproduction of hormones, manifesting clinically as hyperfunctioning endocrinopathies and increased skin pigmentation. The effects of $G_s\alpha$ activation on bone are complex and are discussed in detail below.

Mosaicism in FD/MAS

FD/MAS arises sporadically, and there are no confirmed cases of vertical transmission. This has led to the unproven but generally accepted model of FD pathogenesis where postzygotic *GNAS* mutations acquired early in embryogenesis lead to a somatic mosaic disease state [7]. Under this model, the lack of vertical transmission presumably reflects early lethality in germline mutations. This concept is also supported by reports of discordance of FD/MAS between monozygotic twins [8–10].

Mosaicism is apparent in the clinical features of FD/MAS, including patchy bone disease occurring along a broad spectrum of distribution, which can range from an isolated, trivial lesion to severe disease involving nearly the entire skeleton (Fig. 1a, b). Skin lesions additionally have characteristic jagged borders and reflect along the midline of the body, following patterns of embryonic cell migration (Fig. 1c, d). Under this model, the phenotype in FD/MAS is determined by a combination of factors, including the point in development in which the mutation occurs, the locations to which the mutated progeny cell migrates, and the specific effects of constitutive $G_s\alpha$ in the affected tissues. In cases where tissues originating from all three germ layers are involved (i.e., ectoderm, mesoderm, and endoderm, comprising portions of the skin, endocrine, and skeletal systems), it can be postulated that the mutation arose in a single pluripotent cell at the inner cell mass stage, prior to the derivation of the germ layers.

Animal studies provide further support for a mosaic model of FD. Bianco et al. observed that cells with both normal and disease-associated genotype are found within an individual FD lesion [11]. In this study, transplantation of clonal populations of mutant cells into immunocompromised mice led to loss of transplanted cells, while transplantation of a mixture of normal and mutant cells resulted in formation of abnormal ectopic ossicles with histologic features consistent with human FD [11]. These findings suggest that somatic mosaicism at the tissue level is characteristic of FD, and the presence of both mutant and normal cells is required for the formation of dysplastic lesions.

Cellular and Histologic Features of Fibrous Dysplasia

FD is a disease of post-natal skeletal stem cells. In bone, constitutive $G_s\alpha$ activation gives rise to bone marrow stromal cells (BMSCs) with impaired capacity to differentiate toward mature osteoblasts, adipocytes, and hematopoiesis-supporting stroma. Bone and bone marrow are thus replaced by proliferating BMSCs, resulting in fibro-osseous tissue typically

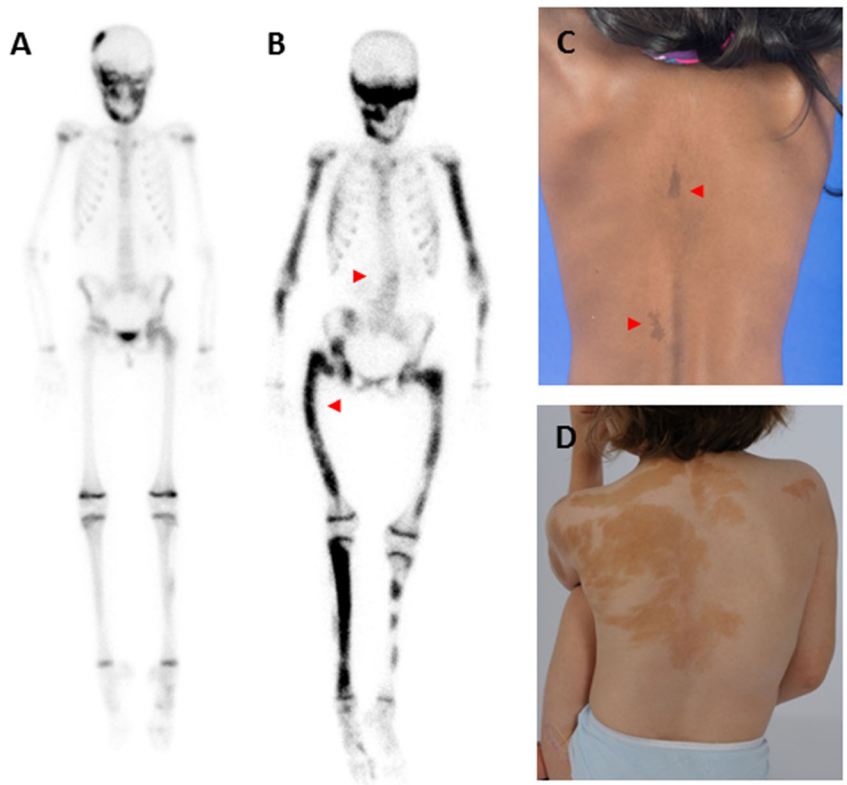

Fig. 1 Mosaicism in fibrous dysplasia/McCune-Albright syndrome. **a**, **b** ^{99}Technetium bone scintigraphy studies. Note physiologic bilateral tracer uptake in growth plates in the extremities and ribs. Additional areas of tracer uptake correspond to FD lesions, which range from mild (**a** limited to the skull and left femur) to severe (**b** involving the majority of the skeleton). Note the presence of scoliosis and a right-sided coxa vara ("shepherd's crook") deformity in **b** (*red arrowheads*). **c**, **d** Typical café-au-lait macules, which tend to have jagged borders and reflect along the midline of the body, following patterns of embryonic cell migration. Macules occur along a broad spectrum, which may range from small subtle lesions (**c**, *red arrowheads*) to large areas of pigmentation with extensive truncal involvement (**d**)

devoid of hematopoietic marrow [5]. The changes in the properties of skeletal progenitors mediate the pathological effect of mutant $G_s\alpha$ on bone.

FD is characterized by complex site-specific histologic changes falling broadly into three categories [12] (Fig. 2). In this classic form, low to moderately cellular fibrous stroma surround irregular, curvilinear trabeculae of woven bone, arranged in a discontinuous pattern commonly referred to as a "Chinese writing pattern." The sclerotic/pagetoid histologic type is typically associated with cranial bones and characterized by dense, sclerotic trabecular bone with complex systems of arrest/reversal (cement) lines. The sclerotic/hypercellular type is characteristically associated with gnathic and skull base bones and includes discontinuous bony trabeculae distributed in an ordered, often parallel pattern. At all sites, subtle recurrent features can generally distinguish FD from other fibro-osseous lesions, including stellate-shaped osteoblasts, Sharpey fibers, and excess osteoid indicative of undermineralization [12, 13].

Clinical Features of FD/MAS

FD/MAS has a broad phenotypic spectrum, with disease potentially involving any part or combination of the skin, bone, and endocrine systems. Café-au-lait skin macules are typically the first manifestation and are apparent at or shortly after birth. These lesions characteristically reflect along the midline of the body and include jagged, irregular borders said to resemble the "coast of Maine," in contrast to the smooth-bordered "coast of California" macules seen in neurofibromatosis (Fig. 1c, d).

FD lesions are typically not apparent at birth and begin to manifest clinically during the first few years of life [14]. In the appendicular skeleton, fractures and bowing are common, in particular, the proximal femur, which may develop the classic "shepherd's crook" coxa vara deformity [15, 16] (Fig. 1b). Scoliosis resulting from spinal FD occurs commonly [17] (Fig. 1b) and, in rare cases, can be severe and progressive, leading to respiratory compromise and even death [17, 18•]. FD in the craniofacial region may cause facial deformity and rarely functional deficits, including vision and hearing loss [19••, 20].

Precocious puberty is frequently the presenting symptom in girls with FD/MAS, affecting nearly 80 % of patients [21]. Recurrent ovarian cysts result in episodic estrogen production and intermittent vaginal bleeding, which may ultimately lead to bone age advancement and reduced adult height. Testicular involvement is common in boys; however, precocious puberty

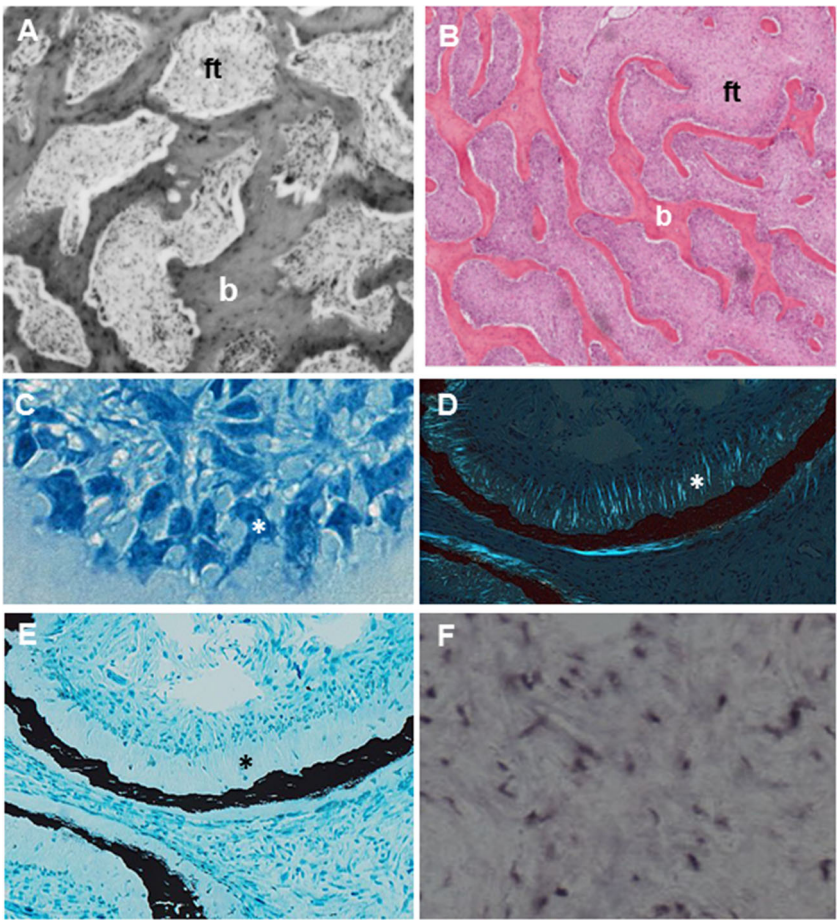

Fig. 2 Representative histologic features of fibrous dysplasia (FD). **a** FD lesions in the calvarium demonstrate typical complexes of bone trabeculae (*b*) embedded in areas of fibrous tissue (*ft*). **b** Bone trabeculae (*b*) within areas of fibrous tissue (*ft*) demonstrate a typical discontinuous and parallel pattern. **c** Morphologically atypical osteoblasts located along bone surfaces (*asterisk*). **d** Collagen fibers perpendicularly oriented along forming bone surfaces, also termed Sharpey fibers (*asterisk*). **e** Severe undermineralization of FD bone, as evidenced by excess osteoid (*asterisk*). **f** In situ hybridization demonstrates FGF23 production by activated FD osteogenic cells

develops only rarely [22]. Thyroid abnormalities affect approximately two thirds of patients, half of which are associated with frank hyperthyroidism [23]. Growth hormone excess occurs less commonly, affecting 15–20 % of patients [21]. Fibroblast growth factor-23 (FGF23) is overproduced by FD cells, which may lead to frank hypophosphatemia and rickets/osteomalacia in patients with high skeletal disease burden [24]. Hypercortisolism is the rarest endocrinopathy associated with MAS and occurs exclusively during the neonatal period due to cortisol overproduction from the fetal adrenal gland [25]. Endocrinopathies typically develop during infancy or early childhood and persist into adulthood. Exceptions include neonatal hypercortisolism, which may undergo spontaneous resolution after involution of the fetal adrenal gland, and FGF23-mediated hypophosphatemia, which may wax and wane along with disease activity (discussed below).

Evaluation and treatment of endocrinopathies are an important component of management in FD/MAS, because endocrine dysfunction can exacerbate skeletal disease. In particular, growth hormone excess is associated with expansion of craniofacial FD, leading to macrocephaly and increased risk of vision loss [26••]. Hypophosphatemia has been associated with increased risk of fractures and bone pain [27].

Activating *GNAS* mutations in FD/MAS are considered weak oncogenes and may infer a small increased risk of malignant transformation in affected tissues. Cancers reported in association with FD/MAS include bone [28], thyroid [29], breast [30, 31], and testicular [22]. Activating *GNAS* mutations have also been identified as early driver mutations for pancreatic intraductal papillary mucinous neoplasms (IPMNs) [32], and these lesions along with rare cases of pancreatic cancer have been identified in patients with FD/MAS [33, 34].

Fibrous Dysplasia and FGF23 Processing

Studies of the role of FGF23 in FD/MAS have been informative in advancing understanding of mineral metabolism. The recognition that hypophosphatemia in FD/MAS results from overproduction of FGF23 by abnormal skeletal progenitor cells led to the observation that under physiologic conditions, normal bone is the tissue source of FGF23 [35]. While urinary phosphate wasting is one of the most common extraskeletal features of FD/MAS, frank hypophosphatemia occurs infrequently. Serum levels of FGF23 correlate with disease activity [35], and significant hypophosphatemia is typically seen only in patients with substantial FD burden. Hypophosphatemia is one of the few endocrinopathies that may wax and wane; it may be "unmasked" during periods of rapid linear growth and may improve or resolve with age as disease activity declines [21, 24, 36].

The infrequency of hypophosphatemia in FD/MAS patients despite high levels of FGF23 production appears to be explained by alterations in FGF23 processing [37]. Under physiologic conditions, biologically active intact FGF23 is glycosylated by ppGalNAcT3 and cleaved by furin into inactive N- and C-terminal fragments. Total FGF23 levels are elevated in the serum of patients with FD/MAS; however, there is a proportionally greater elevation in levels of the C-terminal fragment relative to intact FGF23 [24, 37]. An analysis of normal and mutation-bearing bone marrow stromal cells (BMSCs) demonstrated that cells harboring the causative $G_s\alpha$ mutation had higher cAMP levels, lower ppGalNAcT3, and higher furin activity [37]. These findings support a model where a cAMP-mediated decrease in glycosylation by ppGalNAcT3 results in enhanced FGF23 cleavage by furin, suggesting that regulation of FGF23 processing controls overall FGF23 activity in patients with FD/MAS. Clinically, hypophosphatemia is associated with early-onset and more frequent fractures, necessitating prompt identification and treatment [16].

Age-Related Changes in Fibrous Dysplasia

FD lesions are characterized by age-related histologic, radiographic, and clinical changes. Kuznetsov et al. observed a decline in the number of mutated BMSCs and high levels of apoptosis in FD specimens from older individuals [36]. Lesions in older patients also demonstrated fewer histologic features characteristic of FD and, in some cases, appeared to demonstrate normal bone and marrow histology, complete with restoration of hematopoiesis [36]. This suggests a model where, over time, mutation-bearing skeletal stem cells in the BMSC population fail to self-renew and are ultimately consumed by apoptosis, while co-existent normal skeletal stem cells survive and enable formation of normal marrow structures.

These findings are mirrored radiographically. In young children (<2 years of age), FD lesions often appear heterogeneous on radiographs and lack the classic "ground glass" appearance [38] (Fig. 3a). In later childhood, lesions typically develop a homogeneous ground glass radiographic density and with aging appear denser and more sclerotic [38] (Fig. 3b, c). Craniofacial lesions in older individuals typically become less homogeneous on computed tomography, developing discrete radiolucent, "cystic" appearing areas over time [13] (Fig. 3d, e).

The natural history of FD also supports a model of age-related changes in disease activity. Skeletal development appears to occur normally in utero, and FD lesions are typically not evident at birth. FD becomes apparent in early childhood, with the majority of skeletal lesions and their associated disability manifesting within the first decade of life [14]. In a retrospective series of 103 patients, 90 % of craniofacial lesions were present by age 3.4 years, 90 % of extremity lesions by 13.7 years, and 90 % of axial lesions by 15.5 years [14]. Functional impairment was also established relatively early,

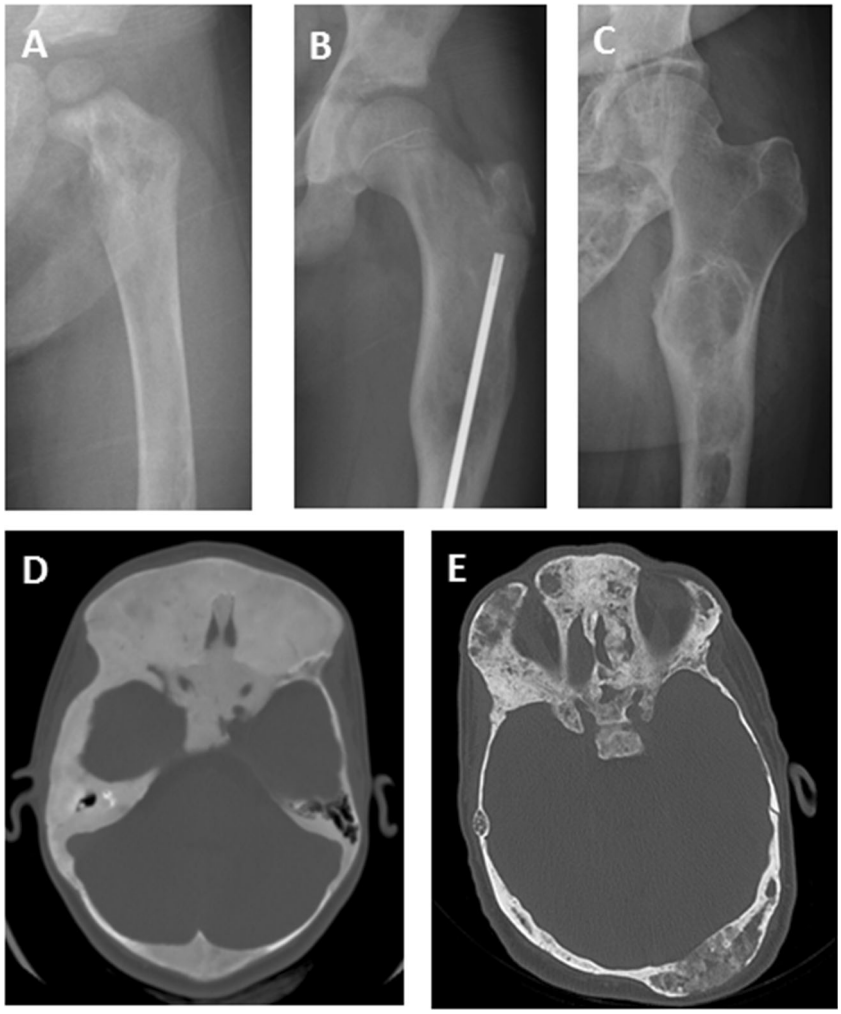

Fig. 3 Age-related radiographic features of fibrous dysplasia (FD). **a** Radiograph from a 2 year old demonstrates a typical heterogeneous-appearing FD lesion in the proximal femur. **b** Radiograph from an 11 year old shows a characteristic "ground glass" lesion, which appears homogeneous and radiolucent. **c** Radiograph from a 57 year old demonstrates the tendency of FD to become more heterogenous and sclerotic over time. **d** Head computed tomography from an 11 year old shows diffuse FD involvement with homogenous "ground glass" appearance. **e** Head computed tomography from a 54 year old demonstrates the tendency for FD to become more heterogeneous, with focal areas of lucency throughout

with 92 % of subjects who ultimately lost independent ambulation receiving ambulatory aids prior to age 17 [14]. Fracture rates in FD similarly peak relatively early in life, with the highest prevalence between ages 6 and 10 years and declining thereafter [16].

Taken together, these studies suggest an age-related pattern of disease activity, where skeletal lesions develop in the postnatal period, progress during childhood, and remain static or potentially improved in later adulthood. Therapeutic interventions for skeletal disease should therefore be tailored individually, with consideration given to the expected course and natural history of the disease.

Clinical Management

Management in FD/MAS should be individualized and is best accomplished through the input of a multidisciplinary team. Treatment for FD lesions is mainly palliative, with an emphasis on optimizing function and minimizing morbidity related to deformities and fractures. There are no medications capable of altering the disease course. Optimizing conservative techniques is an important component of management, including controlling underlying endocrinopathies, physical therapy to maintain strength and range of motion, orthoses to correct limb length discrepancies and misalignment, and avoidance of prolonged non-weight bearing [39].

Surgical management is challenging, and there is little data to inform appropriate indications and techniques. Approaches such as curettage, grafting, plates and screws and other external fixation devices are frequently ineffective and should generally be avoided [40••, 41]. A retrospective analysis of a large cohort of patients who received femoral bone grafts showed a high rate of graft resorption, particularly in patients less than 18 years of age [40••]. Intramedullary devices are generally preferred for management of fractures and deformity in the lower extremities [38, 41], and progressive scoliosis can generally be managed with standard instrumentation and fusion techniques [17, 41, 42]. Surgical management in the craniofacial skeleton is complicated by frequent post-operative FD regrowth and should focus on correction of functional deformities [43, 44]. Optic nerve decompression may be required for patients with objective vision loss; however, prophylactic

decompression increases the risk of vision loss and is contraindicated [19••, 45].

Antiresorptive therapy with bisphosphonates has been advocated due to high levels of bone resorption frequently seen in FD tissue [12, 46•]. Early, uncontrolled series reported improvements in bone pain, with variable effects on FD radiographic appearance [47–49]. A 2-year randomized, placebo-controlled trial of alendronate did not demonstrate an improvement in FD-related bone pain, radiographic appearance, or skeletal disease burden [46•]. Given the data thus far, bisphosphonates are not likely to be effective in altering the disease course in FD; however, more potent intravenous formulations may have a role in treating FD-related bone pain.

Pain is common in FD and can significantly impact mobility and quality of life [50]. Interestingly, there is no association between the extent or location of the disease and the likelihood of having pain; patients with mild FD may have debilitating pain and patients with extensive disease may be pain-free [38]. FD pain is more common in adults; however, it may be underreported and undertreated in children [50]. Patients with FD pain should first be evaluated for underlying metabolic, functional, and orthopedic complications. In particular, pain may be the presenting symptom in patients with untreated hypophosphatemia, leg-length discrepancies, and acute or impending fracture. When other causes have been excluded, intrinsic FD pain is generally treated with conservative measures and non-opioid analgesics. Intravenous bisphosphonates may be helpful for persistent, moderate to severe pain, given at the lowest dose and frequency needed [18•].

Endocrinopathies are generally managed medically. Growth hormone excess responds to somatostatin analogues or pegvisomant in most cases [18•, 51]. Precocious puberty in girls is managed by the aromatase inhibitor letrozole, which may be used in combination with leuprolide in patients with comorbid central puberty [18•]. Precocious puberty in boys may be managed with a combination of an aromatase inhibitor and a testosterone receptor antagonist [22]. Similar to other disorders of FGF23 excess, hypophosphatemia is managed with oral phosphorus and calcitriol. Hyperthyroidism is effectively managed by methimazole, with total thyroidectomy as a potential option for long-term management [52].

In summary, clinical management in FD/MAS is complex and highly individualized depending upon the extent and severity of each patient's presentation. A comprehensive compilation of evidence-based and expert opinion-based treatment for all aspects of FD/MAS is available in [18•].

Animal Models of Fibrous Dysplasia

The development of representative animal models in FD/MAS has been challenging. The first successful animal studies were reported by Bianco et al., where immunocompromised mice were given transplants of both normal and mutant BMSCs leading to the production of a human-like fibrous dysplastic ossicle [11]. This model provided valuable insights into FD pathogenesis by suggesting the necessity of both mutant and wild-type BMSCs to support formation of FD lesions. Limitations included the need for repeated transplantations and the inability to replicate the age-related changes seen in human disease.

Hsiao et al. developed a mouse model with constitutive G_s signaling induced by expression of an engineered receptor, Rs1, in cells of the osteoblastic lineage [53]. Mice developed dramatic increases in bone volume, with histologic features reminiscent of FD [54]. Interestingly, the phenotype was substantially attenuated when expression of the Rs1 receptor was delayed past the post-natal period and was largely reversed when Rs1 signaling was suppressed in adult mice [53, 54]. While this model did not replicate the mosaic nature of the human disease phenotype, it provided important evidence for an age-dependent effect of G_s signaling on bone formation and supported inhibition of G_s signaling as a potential therapeutic strategy to treat FD.

Saggio et al. developed the first inherited, histopathologically similar replica of human FD by generating multiple lines of mice with constitutive $G_s\alpha^{R201C}$ expression [55]. Similar to human disease, FD lesions in mice developed only in the post-natal period; however, the lesions developed through a sequence of three distinct histopathological stages, which do not appear to be characteristic of human disease. This included a primary phase of excess bone formation, followed by a secondary phase of excess remodeling with marked narrowing of the marrow cavity. The tertiary phase, which most resembled human FD, was not established in these mice until well into adulthood at age ≥1 year. This is notably different than the human phenotype, where lesions develop in early childhood. While animal studies have provided valuable insights into FD pathogenesis, further work is needed to develop a model that replicates key features of human disease, including mosaic gene expression and early post-natal lesion development.

Future Directions

There is a critical need to develop medical therapies to treat FD. Several lines of investigation are ongoing. Skeletal stem cells are an intuitive potential intervention, given that skeletal progenitors are the disease-causing cells in FD. These multipotential cells are self-renewing and when transplanted in vivo have the ability to generate a miniature bone organ with appropriate histology, architecture, and hematopoietic microenvironment [56]. Preclinical studies have demonstrated that when used in conjunction with appropriate carriers, in vivo transplantation of skeletal stem cell/BMSCs may promote skeletal regeneration; however, the quality of regeneration is greatly affected by the ability of transplanted cells [57, 58]. In contrast, skeletal stem cell transfusion has been studied in a

diversity of skeletal and immune-mediated disorders in an effort to harness purported paracrine, immunomodulatory, and immunosuppressive effects of these cells, and results have been generally disappointing [59]. While it continues to hold promise as a potential therapeutic intervention, at present, the clinical applicability of skeletal stem cells remains limited by knowledge gaps in their precise nature, function, and optimal handling and delivery [56, 59].

Another potential therapeutic strategy is to alter the activity of the mutant $G_s\alpha$. Because greater than 90 % of mutations in FD/MAS occur at the R201 position, this provides the opportunity to develop therapies that specifically target this mutated protein and modify its GTPase activity. In an ongoing project at the NIH, a small molecule library of >350,000 compounds was screened to identify modulators of $G_s\alpha$ activity [60]. Both inhibitors and activators were evaluated, based upon age-related changes that suggest that further activation of the mutated $G_s\alpha$ might promote apoptosis of mutant BMSCs. Compounds have been subjected to secondary screens and are currently undergoing further investigation, with future studies including testing in preclinical in vivo models and early-phase clinical studies.

Interest has recently emerged regarding a potential role for the receptor activator of nuclear kappa B ligand (RANKL) pathway in treatment of FD. RANKL is a cell surface protein involved in many cellular processes, including osteoclastogenesis [61]. Denosumab is a humanized monoclonal antibody against RANKL, approved for treatment of osteoporosis and prevention of skeletal-related events from bone metastases [62, 63]. Denosumab interrupts the cycle of RANKL binding to osteoprotegerin and prevents the formation and function of osteoclasts [64]. Evidence suggests that denosumab may be effective for treatment of giant cell tumors of the bone, another disorder of BMSCs which is histologically similar to FD [65, 66]. RANKL is also reported to be overexpressed in a model of FD-like bone cells [6] and in FD tissue [67], suggesting that this pathway may play a role in FD pathogenesis.

There are several reports of denosumab treatment in FD patients [68, 69], including a 9-year-old boy treated for a rapidly expanding femoral lesion [69]. In this patient, denosumab treatment was associated with improved pain and decreased femoral expansion; however, the patient developed hypophosphatemia and hypocalcemia while on treatment. Upon denosumab discontinuation, there was a marked rebound in bone turnover accompanied by life-threatening hypercalcemia, requiring hospitalization and bisphosphonate treatment [69]. Rebound hypercalcemia upon denosumab discontinuation has subsequently been reported in other disorders of high bone turnover, including giant cell tumor and juvenile Paget's disease [70–72]. These findings suggest that denosumab may hold promise as a potential treatment for FD; however, given these safety concerns, its use should be limited to research protocols.

Conclusions

Clinical and translational studies in FD/MAS have greatly advanced our understanding of the pathogenesis and natural history of this complex disorder. The development of therapeutic interventions has been relatively less robust, and current treatments are inadequate. There is a critical need to develop novel interventions capable of altering disease activity in FD, as well as pre-clinical and animal models in which to study them.

Compliance with Ethical Standards

Conflict of Interest Cemre Robinson, Michael T Collins, and Alison M Boyce declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human subjects performed by any of the authors.

With regard to the authors' research cited in this paper, all institutional and national guidelines for the care and use of laboratory animals were followed.

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- •• Of major importance

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