Fibrous dysplasia/McCune-Albright syndrome: pathogenesis, clinical description and management

Irene Falsetti [1], Gaia Palmini [2], Cinzia Aurilia [1], Simone Donati [1], Teresa Iantomasi [1], Maria Luisa Brandi [2]

[1] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [2] F.I.R.M.O Italian Foundation for the Research on Bone Diseases, Florence, Italy

ABSTRACT

Fibrous dysplasia (FD) is a rare non-hereditary skeletal disease in which abnormal fibrous tissue replaces bone tissue. It is due to a mutation in the GNAS gene that alters the differentiation of skeletal stem cells into mature osteoblasts. Osteoclastogenesis is also strongly activated, due to the presence of numerous cytokines and factors that promote this process. The resulting bone is poorly mineralized, with an excess of extracellular matrix, and predisposed to fractures and deformities. Lesions can affect only one bone, several bones, or occur in association with hyperfunctioning endocrinopathies and hyperpigmentation of the skin, which may already be present at birth and in severe cases can lead to death (FD/McCune-Albright syndrome [MAS]). The clinical spectrum is extremely complex. To date, there is no pharmacological treatment to prevent the appearance of FD lesions or slow their course. Therefore, the purpose of this concise review is to provide a general overview of current knowledge about FD/MAS and its clinical manifestations, in order to find new molecules useful for the future development of drugs.

KEYWORDS

Fibrous dysplasia, McCune-Albright syndrome, rare disease, bone disorders.

Definition

First described in 1891 by Von Recklinghausen, fibrous dysplasia (FD) was only defined as such by Lichtenstein and Jaffe in 1938 [1,2]. FD is a skeletal disease that consists of the replacement of characteristic bone structure with abnormal fibrous connective tissue. This makes the skeleton weak, predisposing it to fractures, pain and deformities. FD can occur in a single bone (monostotic FD) or in multiple bones (polyostotic FD). Monostotic FD is the most common form (80%) and in 25% of cases it occurs at craniofacial level, in the mandible and maxilla. FD can occur as a disease in its own right, but also in association with extraskeletal diseases, such as hyperpigmentation of the skin or hyperfunctional endocrinopathies. In the latter case, it is called FD/McCune-Albright syndrome (MAS).

The purpose of this concise review is to provide an updated overview of current knowledge about FD/MAS and its clinical manifestations in order to find new molecular targets useful for the future development of drugs to treat this rare disease.

Prevalence and epidemiology

FD is a rare disease with an incidence of one in 5000-10000 people and it appears to be equally distributed between males and females. It accounts for 2% of all bone tumours and 5-7% of benign bone tumours. However, due to its rarity, but also to instances of underdiagnosis and overdiagnosis [3], the available epidemiological data on it cannot be considered accurate. In fact, many asymptomatic patients may never be diagnosed with FD, or diagnosed only incidentally, while in a patient with monostotic FD the presence of polyostotic lesions or MAS cannot be studied. The onset of FD is early because it coincides with the skeletal growth phase. The monostotic form is generally diagnosed at between 10 and 30 years of age, while the polyostotic form can manifest itself before 10 years of age [4].

Article history
Received 7 Jun 2024 – Accepted 8 Oct 2024

Contact
Gaia Palmini; gaia.palmini@unifi.it
F.I.R.M.O Italian Foundation for the Research on Bone Diseases, Florence, Italy

Genetic aetiology

FD is caused by a gain-of-function post-zygotic mutation in the *GNAS* gene, located on chromosome 20q13.3 and encoding the α subunit of the Gs protein. Gα proteins have an intrinsic GTPasic activity, which is inhibited by the mutation in FD. This results in ligand-independent activation of adenylyl cyclase, unbalanced cyclic AMP production, and thus prolonged downstream signalling [5].

Most FD-associated mutations occur in exon 8. The most common are point substitutions of arginine 201 with histidine (R201H) or cysteine (R201C) in codon 201, occurring with a frequency of 80.5% and 19.5%, respectively. Rarer mutations involve substitution of glutamine with lysine (Q227K) in co-

don 227 of exon 9 or impairment of other codons [6]. All these mutations are non-hereditary.

Clinical manifestations and the number of tissues affected by the disease depend on the embryonic stage of development in which the mutation occurred [7]. If the mutation develops in the early stages of embryonic development, tissues from all three germ layers (endoderm, mesoderm, ectoderm) will be compromised; accordingly, the symptomatology of FD will be more severe because the mutation will be expressed in different cell types (such as osteoblasts, endocrine cells and melanocytes). Conversely, if the mutation occurs in later stages of development (before gastrulation), the number of cell types with mutation that derive from two germ layers will be lower. In general, the appearance of the mutation at later stages of development is linked to polyostotic FD [8].

Overall, the stage of embryonic development in which the mutation happens, the number and type of tissues involved, and the action of the Gs protein in these tissues are the factors determining the enormous variability of the FD clinical manifestations (cases range from asymptomatic to affected by highly disabling disease).

Pathogenesis

The mutation, when present in the osteoprogenitor cells, compromises their differentiation into mature osteoblasts and osteocytes, but also causes excessive production of the extracellular matrix (ECM), resulting in the formation of a poor-quality bone matrix.

In fact, in FD lesions, bone mesenchymal stem cells (BMSCs) express high levels of the *Runt-related transcription factor 2* (*RUNX2*), *alkaline phosphatase* (*ALPL*) and *collagen type 1* (*COL1*) genes. This results in overproduction of ECM, excessive deposition of collagen, and altered differentiation into osteoblasts, which remain immature [6]. The excessive synthesis of ECM and the high number of immature osteoblasts also contribute to the high production of transforming growth factor-β, which is present in fibroblastic cells of FD lesions [9].

The maturation phase of osteoblasts is hampered by lower expression of the *osteopontin* (*OPN*) and increased expression of *osteonectin* (*OCN*) genes, present in the intermediate and late stages of differentiation of osteoblasts, respectively [6]. The defect in the mineralization process is further aggravated by low or absent expression of the *sialoprotein bone* (*BSP*), *osteocalcin* (*OC*) and *sclerostin* (*SOST*) genes [10-12]. This downregulation of the expression of *BSP*, *OC* and *SOST* also seems to be due to hyperactivation of the Wingless/Int-1/β-catenin signalling pathway [13].

In addition to the presence of immature osteoblasts, FD lesions are characterized by the presence of Sharpey fibres (poorly mineralized fibres of the connective tissue), and by strong bundles of collagen fibres, mainly type 1. Lee et al. showed an increase in mRNA levels of *COL1a1, COL4a1, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2* and *lysyl oxidase* (all involved in collagen formation) in cells obtained from FD lesions [14].

Osteoclastogenesis is also particularly active. This appears to be due to the presence of cytokines and factors that promote osteoclastogenesis and lead to loss of bone microstructure through autocrine and paracrine mechanisms of action [6,15]. In fact, the expression of numerous chemokines, interferons (IFNs) (i.e., IFNA2, IFNA17) and interleukins (ILs) (i.e., IL1B, IL6, IL7, IL13) appears to be upregulated in FD [16-18]. Riminucci et al. highlighted the existence of a direct link between *GNAS* mutation and the synthesis of IL6 in FD, demonstrating that mutated stromal cells synthesize a greater (around threefold greater) amount of IL6, and do so at a faster rate than wild-type cells [19].

Overall, the bone is poorly mineralized, lacks normal microarchitecture, and shows an abnormal presence of fibrotic tissue in place of hematopoietic tissue [20]. Figure 1 summarizes the pathogenesis of FD.

Clinical description of FD

The clinical manifestations of FD depend on the localization and extent of the skeletal lesions, and they can differ greatly between patients. In fact, some FD lesions can remain silent and be recognized only incidentally, while others can be more serious and impair the functionality of the areas involved (resulting in auditory and visual impairments, for example) [21,22]. The expansion of lesions has been reported to decrease in adults, and this has been linked to senescence or death induced by apoptosis of mutated BMSCs [20].

Over the years, the appearance of lesions on imaging can change. In fact, while in newborns and children they are heterogeneous, during adolescence and in adulthood they show a "ground glass" appearance, before again appearing more heterogeneous in the elderly [5].

FD lesions in the appendicular skeleton cause pain, bone fragility and fractures, resulting in lameness and problems with walking. Patients often have differences in limb length and show the coxa vara or "shepherd's crook" deformity of the femoral neck [23].

One of the most affected areas is the craniofacial region. Lesions in this area develop by 3 years of age. They have a slow onset but can result in pain, asymmetry, impaired auditory, nasal and visual function, dental problems, aesthetic deformities and potentially fatal skull base involvement [21]. Hearing and vision loss can occur as a result of damage to the external auditory channels and the optic nerve, respectively. However, these are rare occurrences, generally seen in patients with an excess of growth hormone (GH) [24,25].

In 30-50% of patients with the polyostotic form, FD can affect the spine and lead to the onset of scoliosis, which is progressive and if left untreated can lead to deformities, but is rarely fatal [26,27].

Regardless of the location and extent of the skeletal injury, FD involves bone pain, which leads to a deterioration in patients' quality of life, and in severe cases is highly disabling. Bone pain is widespread among patients and is not yet well understood [28]. The appearance of night pain or pain with acute onset may be a symptom of an imminent fracture or bleeding of a cyst [29]. Bone pain seems to be related to age and its inten-

sity is greater in adults and the elderly. It can be assessed using Wong Baker Faces (in children) and VAS 0-10 and Brief Pain Inventory (in adults) [30,31].

Another clinical manifestation of FD/MAS is increased synthesis of fibroblast growth factor 23 (FGF23). This appears to be due to the presence of the mutation in immature osteocytes in bone lesions, and it leads to phosphate loss [32]. Severe hypophosphataemia is rare and generally occurs in patients with severe FD; indeed, overproduction of FGF23 is directly related to the severity of the disease [17,33]. Unlike other clinical manifestations of FD, overproduction of FGF23 can increase or decrease over time and is generally more severe during childhood and adolescence (two phases in which there is greater demand for phosphate), subsequently becoming less complex with age. Hypophosphataemia complicates the skeletal morbidity of FD and is associated with abnormalities in the skull base, a greater number of fractures, pain and worsening of scoliosis [27,34].

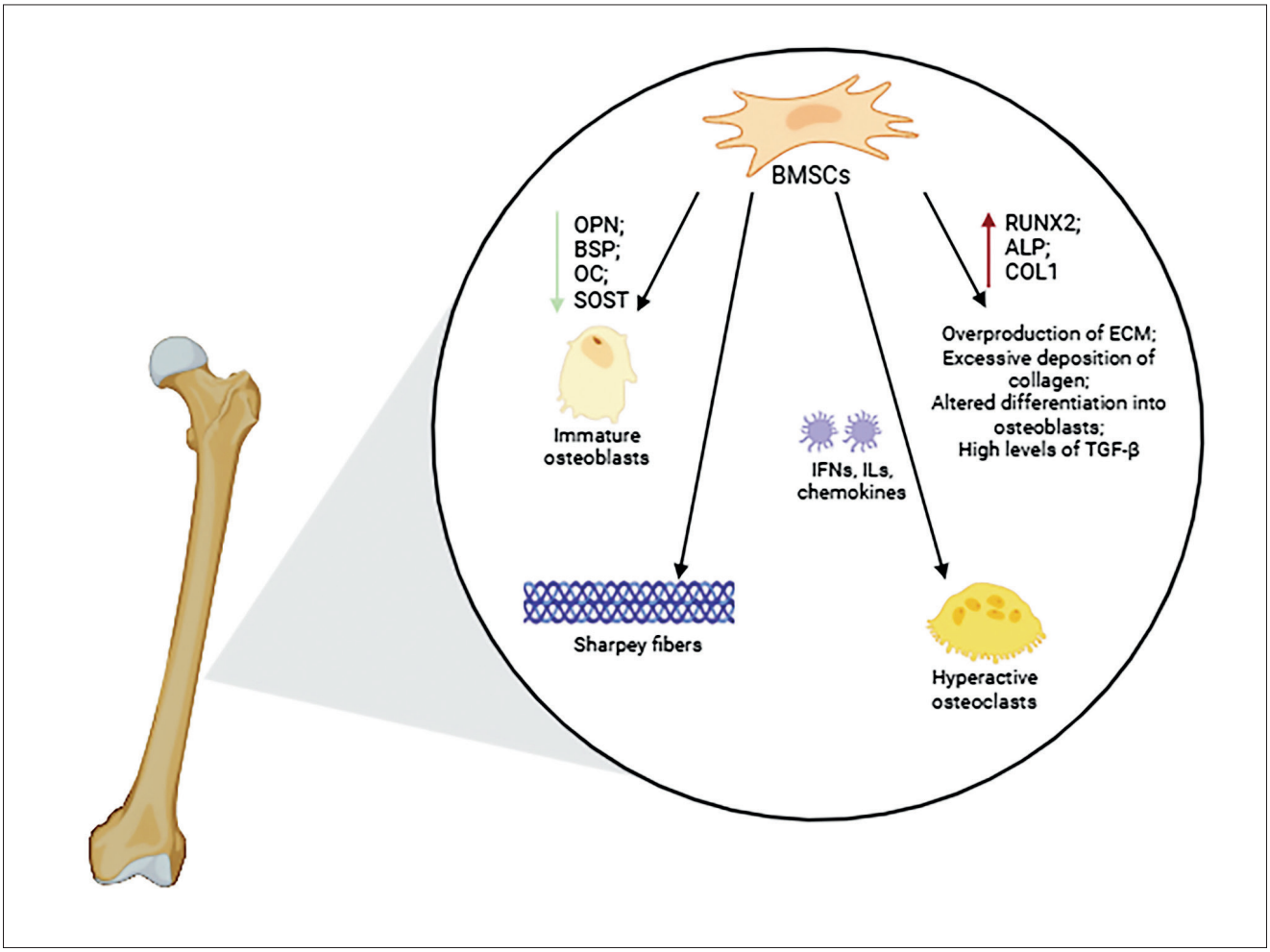
Although the malignant transformation of FD lesions into bone tumours is a rare occurrence (whose incidence is difficult to determine accurately due to the lack of precise epidemiological studies), chondrosarcoma, osteosarcoma, fibrohistiocytoma and fibrosarcoma can all arise in these patients [35]. Warning signs are acute expansion of a new injury and the appearance of pain. The predisposing factors for the development of bone cancer in FD are excess GH and therapeutic external radiotherapy (albeit now an obsolete practice) [36,37].

The presence of café-au-lait macules, which affect about 2/3 of patients, is a typical clinical manifestation of FD/MAS. In patients with this manifestation, they are usually present at birth or develop shortly afterwards, and can therefore be an alarm bell allowing early diagnosis [38]. In the affected areas an increase in melanin synthesis occurs due to cutaneous activation of Gα and constitutive melanocyte-stimulating hormone receptor signalling [39]. These macules have jagged edges and develop along the midline of the body, as a result of the migration of the first embryonic cells. The localization of pigmented macules shows no direct correlation with bone lesions or with the severity of FD [7].

The following are extraskeletal manifestations that can arise in FD/MAS:

- Production of gonadotropin-independent sex steroids. This affects about 85% of girls and women, who develop recurrent cysts with intermittent estrogen production [38]. In girls this

Figure 1 Pathogenesis of FD. The figure schematizes the pathogenetic mechanisms underlying FD (this image was created with BioRender software).
*Abbreviations: **BMSCs**: bone mesenchymal stem cells; **OPN**: osteopontin; **BSP**: sialoprotein bone; **OC**: osteocalcin; **SOST**: sclerostin; **RUNX2**: Runt-related transcription factor 2; **ALP**: alkaline phosphatase; **COL1**: collagen type 1; **ECM**: extracellular matrix; **TGF-β**: transforming growth factor-β; **IFNs**: interferons; **ILs**: interleukins.*



leads to acceleration of growth, vaginal bleeding and rapid breast development, while in adult women it causes irregularities in the menstrual cycle.

- Testicular lesions. About 85% of boys and men with FD/MAS suffer from testicular lesions (hyperplasia of Leydig and Sertoli cells), which manifests as unilateral or bilateral macro-orchidism. Early puberty in boys, which is uncommon (about 15%), is due to autonomous production of testosterone resulting in androgenization [39].
- Thyroid lesions with or without non-autoimmune hyperthyroidism. About 2/3 of patients are affected, half of whom develop hyperthyroidism, with tachycardia and sleep disorders [40]. In thyroid tissue, the *GNAS* mutation results in ligand-independent activation of the TSH/G protein/cAMP pathway (which can cause both hyperplasia and hyperfunction) and increased thyroxine (T4) to triiodothyronine (T3) conversion (which accounts for the T3-dominant biochemical phenotype of MAS patients with hyperthyroidism) [41,42]. If hyperthyroidism is neglected, it can manifest itself with fractures, advancing bone age and high bone turnover.
- Excess GH levels. This feature, recorded in 15% of patients with FD/MAS, is due to the presence of *GNAS* mutations in the anterior pituitary. It leads to acceleration of linear growth and acromegaly [37,38]. If untreated, it is associated with craniofacial FD expansion with an increased risk of vision and hearing loss [25,43,44].
- Neonatal hypercortisolism. Hypercortisolism, due to autonomous hypersecretion by the adrenal gland, is the rarest extraskeletal manifestation. It develops exclusively in the first year of life, and if not recognized and treated promptly it can even lead to death. However, if infants survive, spontaneous remission may occur [45,46].

Diagnosis and management

The clinical diagnosis of FD/MAS is made following careful evaluation of skeletal, dermatological, endocrine and soft tissue manifestations [47,48]. On conventional radiography FD/MAS presents with a ground-glass appearance; radiolucent, cystic and sclerotic or only sclerotic lesions; expanded lesions; defined margins [29]. For the diagnosis of FD, the presence of two lesions in association with extraskeletal manifestations of MAS is sufficient. However, molecular testing is suggested when a diagnosis cannot be made on the basis of clinical, radiological and histological analyses, as in the case of monostotic lesions without extraskeletal manifestations. Diagnostic biopsy is performed on fresh material, even frozen, or paraffin-embedded specimens (although this carries an increased likelihood of false negatives) [49]. The use of the latest generation of sequencing, as opposed to Sanger sequencing, makes it possible to reduce the number of false negatives and distinguish osteosarcomas from FD/MAS, and to date no false positives have been recorded [50].

To date, there is no approved cure and treatment for FD. For this reason, patients should be informed about the disease and urged to follow a lifestyle aimed at ensuring good bone health (25-OH vitamin D levels, adequate calcium intake, weight control, regular physical activity, dental checkups, and possible psychological support or intervention by a social worker) [29].

In the early stages, drug treatment involves addressing vitamin D deficiency and hypophosphataemia (due to FGF23-stimulated phosphate loss in the kidney) through supplementation with active metabolite or a vitamin D analogue.

For pain management, the first-line drugs are acetaminophen/acetomiphene. For moderate to severe persistent pain, bisphosphonates are recommended. However, there is no evidence either that bisphosphonates reduce the size or progression of FD lesions, or that they increase the bone density of lesioned areas [29].

In FD the use of denosumab is suggested only within specialist facilities because of the lack of data on dosage, efficacy and safety [51,52].

FD/MAS endocrinopathies should be appropriately treated. In girls, the first-line treatment of precocious puberty is letrozole and, if necessary, tamoxifen or fulvestrant as adjuvants [53]. In boys, treatment of precocious puberty involves combining a testosterone receptor blocker with an aromatase inhibitor. Annual testing of testicular lesions is strongly recommended, especially in cases with palpable lesions [40].

Hyperthyroidism is treated with methimazole or carbimazole; alternatively, thyroidectomy or radioablation may be used in patients with hyperthyroidism for more than 5 years [54].

Excess GH is treated with somatostatin analogues, while total hypophysectomy is used in treatment-resistant patients [29].

The first-line drug for hypercortisolism is metirapone, but bilateral adrenectomy is necessary in most cases [29].

The pharmacological treatment of FD/MAS is very complex and requires the intervention of a multidisciplinary team.

Conclusions

FD is a rare disease caused by a post-zygotic mutation in the *GNAS* gene. In FD, normal bone structure is replaced by abnormal fibrous tissue, which predisposes the bone to fractures and deformities. The presence of the mutation in osteoprogenitor cells alters their differentiation. In addition to skeletal lesions, FD can be accompanied by debilitating and in some cases fatal extraskeletal manifestations.

To date, however, no treatment has been approved for the pharmacological management of FD lesions. Given the many gaps in our understanding of FD, scientific research has an extremely important role to play in increasing our knowledge so that we might identify new therapeutic targets useful for the development of new drugs.

References

1. Lichtenstein L. Polyostotic fibrous dysplasia. Arch Surg. 1938;36(5):874-98.
2. Von Recklinghausen. Interrelationship between fibrous dysplasia or osteitis deformans, osteomalacia and osteoblastic metastasis. Festschrift Rudolf Virchow zum 13. Berlin, Germany: Georg Reimer Verlag; 1891.

3. Pai B, Ferdinand D. Fibrous dysplasia causing safeguarding concerns. Arch Dis Child. 2013;98(12):1003.
4. El-Mofty SK. Fibro-osseous lesions of the craniofacial skeleton: an update. Head Neck Pathol. 2014;8(4):432-44.
5. Hartley I, Zhadina M, Collins MT, Boyce AM. Fibrous dysplasia of bone and McCune-Albright syndrome: a bench to bedside review. Calcif Tissue Int. 2019;104(5):517-29.
6. Kim HY, Shim JH, Heo CY. A Rare skeletal disorder, fibrous dysplasia: a review of its pathogenesis and therapeutic prospects. Int J Mol Sci. 2023;24(21):15591.
7. Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet J Rare Dis. 2008;3:12.
8. Riminucci M, Saggio I, Robey PG, Bianco P. Fibrous dysplasia as a stem cell disease. J Bone Miner Res. 2006;21 Suppl 2:P125-31.
9. Maruyama Z, Yoshida CA, Furuichi T, et al. Runx2 determines bone maturity and turnover rate in postnatal bone development and is involved in bone loss in estrogen deficiency. Dev Dyn. 2007;236(7):1876-90.
10. Marie PJ, de Pollak C, Chanson P, Lomri A. Increased proliferation of osteoblastic cells expressing the activating Gs alpha mutation in monostotic and polyostotic fibrous dysplasia. Am J Pathol. 1997;150(3):1059-69.
11. Khan SK, Yadav PS, Elliott G, Hu DZ, Xu R, Yang Y. Induced GnasR201H expression from the endogenous Gnas locus causes fibrous dysplasia by up-regulating Wnt/β-catenin signaling. Proc Natl Acad Sci U S A. 2018;115(3):E418-27.
12. Meier ME, Hagelstein-Rotman M, Streefland TCM, Winter EM, Bravenboer N, Appelman-Dijkstra NM. Clinical value of RANKL, OPG, IL-6 and sclerostin as biomarkers for fibrous dysplasia/McCune-Albright syndrome. Bone. 2023;171:116744.
13. Komori T. Regulation of osteoblast differentiation by transcription factors. J Cell Biochem. 2006;99(5):1233-9.
14. Lee MO, You CH, Son MY, et al. Pro-fibrotic effects of PFKFB4-mediated glycolytic reprogramming in fibrous dysplasia. Biomaterials. 2016;107:61-73.
15. Piersanti S, Remoli C, Saggio I, et al. Transfer, analysis, and reversion of the fibrous dysplasia cellular phenotype in human skeletal progenitors. J Bone Miner Res. 2010;25(5):1103-16.
16. Persichetti A, Milanetti E, Palmisano B, et al. Nanostring technology on fibrous dysplasia bone biopsies. A pilot study suggesting different histology-related molecular profiles. Bone Rep. 2021;16:101156.
17. Riminucci M, Collins MT, Fedarko NS, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003; 112(5):683-92.
18. Raimondo D, Remoli C, Astrologo L, et al. Changes in gene expression in human skeletal stem cells transduced with constitutively active Gsα correlates with hallmark histopathological changes seen in fibrous dysplastic bone. PLoS One. 2020;15(1):e0227279.
19. Riminucci M, Kuznetsov SA, Cherman N, et al. Osteoclastogenesis in fibrous dysplasia of bone: in situ and in vitro analysis of IL-6 expression. Bone. 2003;33(3):434-42.
20. Kuznetsov SA, Cherman N, Riminucci M, Collins MT, Robey PG, Bianco P. Age-dependent demise of GNAS-mutated skeletal stem cells and "normalization" of fibrous dysplasia of bone. J Bone Miner Res. 2008;23(11):1731-40.
21. Hart ES, Kelly MH, Brillante B, et al. Onset, progression, and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. J Bone Miner Res. 2007;22(9):1468-74.
22. Szymczuk V, Taylor J, Michel Z, Sinaii N, Boyce AM. Skeletal disease acquisition in fibrous dysplasia: natural history and indicators of lesion progression in children. J Bone Miner Res. 2022;37(8):1473-8.
23. Ippolito E, Farsetti P, Boyce AM, Corsi A, De Maio F, Collins MT. Radiographic classification of coronal plane femoral deformities in polyostotic fibrous dysplasia. Clin Orthop Relat Res. 2014;472(5):1558-67.
24. Cutler CM, Lee JS, Butman JA, et al. Long-term outcome of optic nerve encasement and optic nerve decompression in patients with fibrous dysplasia: risk factors for blindness and safety of observation. Neurosurgery. 2006;59(5):1011-7.
25. Boyce AM, Brewer C, DeKlotz TR, et al. Association of hearing loss and otologic outcomes with fibrous dysplasia. JAMA Otolaryngol Head Neck Surg. 2018;144(2):102-7.
26. Mancini F, Corsi A, De Maio F, Riminucci M, Ippolito E. Scoliosis and spine involvement in fibrous dysplasia of bone. Eur Spine J. 2009;18(2):196-202.
27. Berglund JA, Tella SH, Tuthill KF, et al. Scoliosis in fibrous dysplasia/McCune-Albright syndrome: factors associated with curve progression and effects of bisphosphonates. J Bone Miner Res. 2018;33(9):1641-8.
28. Kelly MH, Brillante B, Collins MT. Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions. Osteoporos Int. 2008;19(1):57-63.
29. Javaid MK, Boyce A, Appelman-Dijkstra N, et al. Best practice management guidelines for fibrous dysplasia/McCune-Albright syndrome: a consensus statement from the FD/MAS international consortium. Orphanet J Rare Dis. 2019;14(1):139. Erratum in: Orphanet J Rare Dis. 2019;14(1):267.
30. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap. 1994;23(2):129-38.
31. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Okla Nurse. 1988;33(1):8.
32. Boyce AM, Bhattacharyya N, Collins MT. Fibrous dysplasia and fibroblast growth factor-23 regulation. Curr Osteoporos Rep. 2013; 11(2):65-71.
33. Collins MT, Chebli C, Jones J, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res. 2001;16(5):806-13.
34. Leet AI, Chebli C, Kushner H, et al. Fracture incidence in polyostotic fibrous dysplasia and the McCune-Albright syndrome. J Bone Miner Res. 2004;19(4):571-7.
35. Ruggieri P, Sim FH, Bond JR, Unni KK. Malignancies in fibrous dysplasia. Cancer. 1994;73(5):1411-24.
36. de Castro LF, Ovejero D, Boyce AM. Diagnosis of endocrine disease: mosaic disorders of FGF23 excess: fibrous dysplasia/McCune-Albright syndrome and cutaneous skeletal hypophosphatemia syndrome. Eur J Endocrinol. 2020;182(5):R83-99.
37. Salenave S, Boyce AM, Collins MT, Chanson P. Acromegaly and McCune-Albright syndrome. J Clin Endocrinol Metab. 2014;99(6):1955-69.
38. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the extraskeletal manifestations of fibrous dysplasia. Orphanet J Rare Dis. 2012;7 Suppl 1(Suppl 1):S4.
39. Boyce AM, Chong WH, Shawker TH, et al. Characterization and management of testicular pathology in McCune-Albright syndrome. J Clin Endocrinol Metab. 2012;97(9):E1782-90.
40. Boyce AM, Collins MT. Fibrous dysplasia/McCune-Albright syndrome: a rare, mosaic disease of Gαs activation. Endocr Rev. 2020; 41(2):345-70.
41. Celi FS, Coppotelli G, Chidakel A, et al. The role of type 1 and type 2 5'-deiodinase in the pathophysiology of the 3,5,3'-triiodothyronine toxicosis of McCune-Albright syndrome. J Clin Endocrinol Metab. 2008;93(6):2383-9.
42. Combest WL, Russell DH. Alteration in cyclic AMP-dependent protein kinases and polyamine biosynthetic enzymes during hypertrophy and hyperplasia of the thyroid in the rat. Mol Pharmacol. 1983;23(3):641-7.
43. Akintoye SO, Chebli C, Booher S, et al. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. J Clin Endocrinol Metab. 2002;87(11):5104-12.
44. Boyce AM, Burke A, Cutler Peck C, DuFresne CR, Lee JS, Collins MT. Surgical management of polyostotic craniofacial fibrous dysplasia: long-term outcomes and predictors for postoperative regrowth. Plast Reconstr Surg. 2016;137(6):1833-9.
45. Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab. 2010;95(4):1508-15.

46. Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011;35(9):1311-26.
47. Lumbroso S, Paris F, Sultan C; European Collaborative Study. Activating Gsalpha mutations: analysis of 113 patients with signs of McCune-Albright syndrome--a European Collaborative Study. J Clin Endocrinol Metab. 2004;89(5):2107-13.
48. Narumi S, Matsuo K, Ishii T, Tanahashi Y, Hasegawa T. Quantitative and sensitive detection of GNAS mutations causing McCune-Albright syndrome with next generation sequencing. PLoS One. 2013;8(3):e60525.
49. Idowu BD, Al-Adnani M, O'Donnell P, et al. A sensitive mutation-specific screening technique for GNAS1 mutations in cases of fibrous dysplasia: the first report of a codon 227 mutation in bone. Histopathology. 2007;50(6):691-704.
50. Jour G, Oultache A, Sadowska J, et al. GNAS mutations in fibrous dysplasia: a comparative study of standard sequencing and locked nucleic acid PCR sequencing on decalcified and nondecalcified formalin-fixed paraffin-embedded tissues. Appl Immunohistochem Mol Morphol. 2016;24(9):660-7.
51. Boyce AM, Chong WH, Yao J, et al. Denosumab treatment for fibrous dysplasia. J Bone Miner Res. 2012;27(7):1462-70.
52. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post-hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res. 2018;33(2):190-8.
53. Feuillan P, Calis K, Hill S, Shawker T, Robey PG, Collins MT. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. J Clin Endocrinol Metab. 2007;92(6):2100-6.
54. Tessaris D, Corrias A, Matarazzo P, et al. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. Horm Res Paediatr. 2012;78(3):151-7.

CoAuthor Contributions: *Each author contributed equally and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.*
Funding: *This research received no external funding.*
Institutional Review Board Statement: *Not applicable.*
Informed Consent Statement: *Not applicable.*
Data Availability Statement: *Not applicable.*
Acknowledgments: *This research was supported by F.I.R.M.O, Italian Foundation for the Research on Bone Diseases.*
Conflicts of Interest: *The authors declare no conflict of interest.*