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Osteochondromas in fibrodysplasia ossificans progressiva: a widespread trait with a streaking but overlooked appearance when arising at femoral bone end

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Abstract Metaphyseal bony outgrowths are a well-recognized feature of fibrodysplasia ossificans progressiva (FOP) phenotype, but its genuine frequency, topographic distribution, morphological aspect, and potential implications are not fully established. To better ascertain the frequency and characteristics of osteocartilaginous exostoses in FOP disease, we conducted a cross-sectional radiological study based on all the traceable cases identified in a previous comprehensive national research. Metaphyseal exostoses were present in all the 17 cases of FOP studied. Although most often arising from the distal femoral (where metaphyseal exostoses adopt a peculiar not yet reported appearance) and proximal tibial bones, we have found that they are not restricted to these areas, but rather can be seen scattered at a variety of other skeletal sites. Using nuclear

magnetic resonance imaging, we show that these exophytic outgrowths are true osteochondromas. As a whole, these results are in agreement with data coming from the literature review. Our study confirms the presence of metaphyseal osteochondromas as a very frequent trait of FOP phenotype and an outstanding feature of its anomalous skeletal developmental component. In line with recent evidences, this might imply that dysregulation of BMP signaling, in addition to promoting exuberant heterotopic ossification, could induce aberrant chondrogenesis and osteochondroma formation. Unveiling the molecular links between these physiopathological pathways could help to illuminate the mechanisms that govern bone morphogenesis.

Keywords Fibrodysplasia ossificans progressiva · FOP · Osteochondroma · Exostoses · Chondrogenesis

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Introduction

Fibrodysplasia ossificans progressiva (FOP; OMIM #135100) is an extremely rare genetic condition [2]—worldwide prevalence of approximately one in two million [1]—considered to be as the most severe and disabling disorder of ectopic ossification in humans [3, 4]. It is characterized by congenital skeletal malformations (especially great toe dysmorphologies [5]) and other early developmental skeletal defects [4], in association with postnatal progressive widespread endochondral osteogenesis at extra-skeletal sites [6], which occurs following predefined anatomic and temporal patterns [7]. Such abnormal formation of rigid bounds of mature heterotopic bone leads to ankylosis of major joints, thereby hampering and eventually preventing movement [3, 4]. However, phenotypic heterogeneity has been observed [8], and both genetic and environmental factors could affect the features of the disease. In this regard, results from a study carried out in monozygotic twins suggest that genetic determinants strongly influence disease phenotype during prenatal development, while environmental factors affect postnatal progression of heterotopic ossification [9]. Although people with FOP usually reach adult life [3, 4], lifespan is reduced mainly by cardiorespiratory complications secondary to severe restrictive disease of the chest wall [10] or by extreme nutritional disturbances due to jaw fixation [11].

Diagnostic errors are common in FOP [4]. Many patients are misdiagnosed before the appearance of heterotopic ossification plaques, causing them to undergo unnecessary procedures that alter the natural history of the disease, resulting in permanent harm [12, 13]. However, an accurate diagnosis of the disease can be made early in life on the basis of the clinical findings of tumor-like swellings in association with characteristic malformed great toes [13]. The recent discovery of a recurrent mutation in the gene encoding the activin A type I receptor/activin-like kinase-2 (*ACVR1/ALK2*), considered to be the cause of virtually all classically occurring inherited and sporadic cases of FOP [2], allows for a reliable confirmatory diagnosis before ectopic ossification appears, thus avoiding inappropriate medical interventions [4].

Nearly all patients that exhibit the “classic FOP” phenotype have the same recurrent c.617G>A (p.R206H) heterozygous missense mutation in the glycine–serine activation domain of the *ACVR1* gene [14], a bone morphogenetic protein (BMP) type I receptor. This single nucleotide point mutation renders the receptor and its downstream pathway hypersensitized. The *ALK2* receptor activation induces the expression of several protein ligands of BMPs pathway, thereby resulting in an auto-amplification loop that potently enhances the expression of osteogenic genes [15–17]. All this body of experimental facts, together with

the demonstration that *ACVR1/ALK2* receptor is expressed in tissues like skeletal muscle, blood vessels, and cartilage [14, 16, 17], illustrate the underlying cellular and molecular basis responsible for the distinctive features of “FOP phenotype” [18]. One of the consequences of BMP signaling perturbation is the induction of ectopic chondrogenesis [16, 17, 19]. Furthermore, involvement of BMP-2 has been related to the process of cap’s growth in osteochondroma [20]. Taken together these premises, we hypothesize that alteration of the BMP pathway in FOP results in increased chondrogenesis (in addition to inducing heterotopic ossification), thereby contributing to the development of osteochondromas as well as other early skeletal defects associated with the disease.

The presence of any kind of “metaphyseal abnormality” (referred as either “metaphyseal widening,” “spur formation,” “exostoses” or “osteochondroma”) was already mentioned in the very early reports of FOP disease [21–24]. Subsequently, other works provided more insights into the knowledge of these abnormalities [25–27]. Finally, isolated proven cases of “enchondroma” [27] and “synovial chondromatosis” [29, 30], as well as one patient with an osteochondroma located at an atypical skeletal site [31], were communicated. To date, the sole study specifically conducted to demonstrate an association between FOP and osteochondromas described a lesion located at proximal tibial metaphysis as a very common feature of FOP phenotype [32]. While its uniform appearance and elevated frequency preclude such association to be coincidental, given the scarcity of evidence further investigation is required for better characterizing such FOP metaphyseal anomalies improving the knowledge on its natural history, clinical consequences, and presumptive pathogenic inferences.

By studying a series of unselected patients using reliable radiological procedures, and by means of a comprehensive review of the literature, we seek to elucidate the clinical characteristics and plausible pathological meaning from this so far fairly neglected feature of FOP phenotype, in order to allow making inferences on its practical and pathogenic implications.

Methods

As a result of a national search recently performed in our country, we were able to confirm the diagnosis of FOP in 24 individuals [33]. From them, 17 were alive by the end of 2011 (two have died, and five other could not be traced), 15 of whom agreed to participate in this study. Thereafter, from April 2012 to July 2014, these patients were reevaluated seeking for the presence of bone metaphyseal abnormalities at any skeletal place. Since the proximal tibia has

been reported previously as the most frequent location for FOP osteochondroma, we particularly focused on this site.

The radiographic sample consisted of the complete stock of skeletal films yielded by the 15 aforementioned traceable patients, plus the available radiographs of two additional cases (both deceased prior to the initialization of this study). Most of these 17 patients have fairly good-quality plain X-rays, therefore allowing not just a complete evaluation of proximal part of the tibia, but a proper assessment of other relevant metaphyseal areas. Notwithstanding with this, in order to achieve a more accurate and complete appraisal of the lesions, new radiographs of hands, feet, and long bones were obtained in eight cases (Table 1). All the aforementioned plain radiographs were reviewed by two of us (A M-P and J B-C) and each knee (tibia or femoral) bone abnormality was classified as: i) normal, ii) metaphyseal widening, iii) spur formation, or iv) exostoses/osteochondroma. Any identified osteochondroma was measured in size and rated as i) sessile (when the dimension of the base of the tumor exceeds that of its length) or ii) pedunculated (the dimension of the length of the tumor exceeds that of its base). In addition, magnetic resonance imaging (MRI) of the knees was attempted in all cases in which both their medical condition and proximity to a hospital with proper technology made it possible.

In addition, we conducted a narrative review of the literature, but not a systematic search due to the relatively small number of studies investigating this issue. The articles included were primarily identified using “fibrodysplasia ossificans progressiva” OR myositis ossificans progressiva, with “metaphyseal widening,” “spur formation,” “exostoses,” “osteochondroma” as search terms. We also used “Fibrodysplasia ossificans progressiva” and “clinical review” as a strategy. As a result, we found 370 studies published since 1918 through 2014. After refining the search, we finally included 13 informative articles (Table 2) [3, 6, 21–27, 29–32]. The study was approved by the Ethical Committee of the Rare Disease Research Institute from Carlos III Institute of Health (Madrid, Spain).

Results

Details of the cases are listed in Table 1. At the end of the study, the mean age ($\pm$ SD) of the 15 patients alive was of 29.9 ± 12.8 years (limits 7–55) and the male/female ratio was 6/9. All individuals developed mature ossicles of heterotopic bone in typical patterns, ranging in number from 1 to 17 (9 ± 4). As previously shown [33], the vast majority (13 out of 15) had a classical FOP phenotype (with characteristic malformations of the big toe) and carried the canonical single point mutation c.617G>A in exon 4 of the *ACVRI* gene. The remaining two—both carrying

non-canonical *ACVRI* mutations—displayed non-specific minor abnormalities at great toe and presented with uncommon clinical features.

All the 17 patients showed at least one exophytic bone outgrowth compatible with osteochondroma. Distal femoral metaphysis was the most common affected area ($n = 14$; 82.4 %), appearing as the only lesion in eight patients (47.1 %) and in combination with proximal tibia osteochondroma in six (35.3 %). The majority was unilateral ($n = 9$; 64.3 %) and seemed to arise from the anterolateral aspect of the bone. In nine out of the fourteen cases (Fig. 1), this lesion showed an identical “horn-like” shape consisting in a wide base and a sharp-pointed ending (Fig. 2). In some instances, such lesion was associated with widened diaphysis and cortical thinning, resulting in an “Erlenmeyer flask-like” appearance [34] in one (Fig. 1; frame number 7). Tibial exostoses were seen in nine out of the 17 patients, and in three of them (17.6 %) they occurred as isolated lesions. In six cases they were unilateral (66.6 %), and in all but one (which forms a tibiofibular synostosis) they seem to arise from the medial aspect of bone. Regarding their morphology, four (44.4 %) could be classified as sessile, two adopted a pedunculated look, one form a synostosis, and the remaining two had an undefined morphology. We could confirm metaphyseal excrescences at different skeletal areas in at least nine out of the 17 patients. Four of these exostoses appear in metacarpal bones (two of them being of “synostoses type”), three in metatarsal head, three in the phalanges of the foot, two in distal radio, and one in the radio-ulnar and patellar areas.

Due to technical difficulties (mainly troublesome in patient positioning), MRI of the knees could only be performed in four patients. Nevertheless, in one case, using specially adapted devices, the images had enough quality to allow a reliable comparison with X-ray (Fig. 3). Thereby, on the medial aspect of the femoral metaphysis, an exophytic outgrowth could be identified that is consisting of both cortical and medullary bone tissues and shows continuity with the underlying parent bone cortex and medullary canal. The end of such bone excrescence is sharper and narrower than in conventional osteochondromas, and the overlying hyaline cartilaginous cap is not visible on either plain radiographs or MRI.

Exostoses were occasionally found in early childhood. They gradually increase in size until reaching the typical pattern of FOP-associated mature osteochondroma (Fig. 4). No foreseeable complications (i.e., compression of adjacent structures or sarcomatous degeneration) were seen. Two patients underwent surgery to excise a lesion deemed prior to surgery as exostosis. One was located in the proximal phalanx of the thumb, while the other arose from the proximal phalanx of the great toe. Histopathological evaluation confirmed the diagnosis, but no specimen is available

Table 1 Characteristics of 17 Spanish fibrodysplasia ossificans progressiva patients investigated

No. of X-ray case	study updated	Gender	Age (years)	No. of ectopic ossification plaques	Typical great toe malformation	ACVR1 c.617G>A mutation	Distal femoral exostoses (type)	Proximal tibial exostoses (type)	Other exostoses
1	Y	F	29	6	Y	Y	+ “Horn-shaped”	+ (synostosis)	Metacarpal bones Foot phalanges
2	Y	M	44	17	Y	Y	+ “Horn-shaped”	—	Patella
3	Y	M	7	12	Y	Y	+ (recent onset; undefined)	+ (undefined)	—
4	Y	M	26	13	Y	Y	+ “Horn-shaped”	—	—
5	Y	F	24	0	Y	Y	—	+ (sessile)	—
6	N	F	45	10	N	N	+ (sessile)	—	—
7	N	F	6	8	Y	Y	+ (unclear)	—	Metatarsal head Metatarsal head Foot phalanges
8	—	F	44 ^a	14	Y	—	+ “Horn-shaped”	—	—
9	—	F	46 ^a	15	Y	—	+ “Horn-shaped”	—	Radio-ulnar Foot phalanges
10	N	F	16	7	Y	Y	+ “Horn-shaped” (with Erlenmeyer)	—	—
11	N	F	43	9	Y	Y	+ “Horn-shaped”	+ (sessile)	Distal radio
12	N	M	32	4	N	N	+ (unclear)	—	Metacarpal bones
13	Y	M	16	1	Y	Y	+ “Horn-shaped”	+ (sessile)	Femoral head Metacarpal bones
14	Y	F	15	8	Y	Y	—	+ (sessile)	—
15	N	M	5	5	Y	Y	+ (unclear)	+ (unclear)	—
16	N	M	32	6	Y	Y	+ “Horn-shaped”	+ (pedunculated)	Foot phalanges
17	Y	M	29	9	Y	Y	—	+ (pedunculated)	Metatarsal head

^a Age at death

for reviewing. The result of the procedure was considered good, and neither had recurred at the site of operation.

Discussion

Traditionally, medial tibial exostoses have been recognized as one of the most frequent and defining developmental anomalies of FOP phenotype [3, 7, 21, 22, 24, 27, 32]. However, their actual characteristics have not been definitively established, and some uncertainty remains on its nature and significance. In fact, to our knowledge there is only one study in which tibial metaphyseal abnormalities were specifically investigated [32], so that in the present study we have extended the observation to other metaphyseal areas in order to have a more comprehensive and accurate view of this question. The cases on which our study lies derive from a national search based on different methods: personal follow-up, surveys obtained from patients associations, call to scientific societies, and comprehensive bibliographic search [33]. In our opinion, such combination of procedures makes the sample fair representative of the overall FOP morbidity in our country and minimizes the

risk of a potential selection bias. Therefore, considering that the number of cases is limited by the extreme rarity of the disease, we strongly believe that certain generalisations based on our findings seem possible.

While the presence of any kind of metaphyseal anomaly was mentioned from the early reports of FOP disease [21–24], determining the origin and relevance of these lesions has been somewhat controversial (Table 2). Thus, some authors describe these anomalies as: “bony extensions resulting in ossification of affected ligaments” [25], or as: “widened metaphyses and ossification of the tendinous insertions into the long bones” [27], concluding that in spite of the high frequency with which they are observed in FOP disease, they might be coincidental associations or just reactive exostosis-like bone outgrowths related to friction. In contrast, Connors and Evans report clear-cut bone exostoses in almost one-third of 34 patients personally evaluated [3]. And in the initial monographic work aimed to address this issue, “flaring and spiking at the end of the metaphyses” were shown, proposing that they represent a real feature of the disease [26]. The first histopathologically proven cases of osteochondroma [6] and enchondroma [28] associated with FOP disease were communicated in

Table 2 Review of metaphyseal abnormalities communicated in FOP studies

References	Features		Location	Appraisalment/implications (true exostosis/osteochondroma vs. reactive ossification, etc)
	Type of study, design, and size	Depiction/no. of affected (widening, spurs, exostosis/osteochondroma, etc.)		
Rosentirm [21]	Historical literature review (1692–1916)	The term exostoses appears in 22 of 120 cases* (many confirmed by autopsy); spurs in three cases	Most often: tibia; femur and phalanx of fingers	Not discussed
Fairbank [22]	Literature review and personal followed up cases reported ($n = 4$)	Bone outgrowths in one out of four personal cases. Exostoses in two of the reviewed ones	Femur (personal) and phalanx of fingers (review)	Similar to exostoses seen in diaphyseal aclasis
Lutwak [23]	Scientific report, literature review, and personal followed up cases reported ($n = 6$)	Not mention in 264 reviewed cases (out of scope). Exostoses in two of six personal cases	Tibias, femur, talus	Not discussed (out of scope)
Fletcher [24]	One case reported	Multiple exostoses in the only reported case	Metatarsal and metacarpal bones; phalanges	Not discussed
Connor [3]	General report; case series ($n = 34$)	Exostoses in 10 of 34 patients	Proximal tibia	Not discussed
Cremin [25]	Radiological analyses of personal series ($n = 9$)	Elongated exostoses or bony spurs, frequently present (n not specified)	Most frequent in tibia; also in humeral and femoral shafts	Pseudo-exostoses (ossification of ligaments)
O'Reilly [26]	Cases report ($n = 3$)	Metaphyseal widening and spur formation in all three reported cases	Proximal tibia; femoral bone; radio; ulna	Represent a constant feature of FOP but no explicit reasoning is proposed
Smith [27]	Personal follow-up of 28 cases (general report)	Exostoses, widened metaphyses, and ossification of tendinous insertions (n not specified)	Metatarsal bone (exostoses)	May be misinterpreted as diaphyseal aclasis
Kaplan [6]	Histopathological study (one case reported)	Exostoses excised	Tibia proximal	First time in which classic osteochondroma features (cartilage cap) were described
Connor [29]	Family description (five cases in three generations)	Bone spurs (two cases); synovial osteochondromatosis (hips)	Medial sides first metatarsals (heads)	No inferences were shown
Kalifa [30]	Cases report ($n = 2$)	Synovial chondromatosis in shoulder and hip (one case each), both confirmed by biopsy. Exostoses	Tibia; ulna	Association FOP-synovial chondromatosis was considered not coincidental
Chichareon [31]	One case reported	Osteochondroma (resected and confirmed by histological study)	Submandibular	Unusual and variable expression of FOP
Deirmengian [32]	Big case series (purpose designed)	90 % of 67 had proximal tibial osteochondroma (one confirmed by biopsy); 75 % pedunculated, 25 % had osteochondroma at other anatomic sites	Proximal part of tibia Distal femur, distal tibia, metacarpal bone	Very common FOP phenotypic feature; different implications than in other hereditary disorders (i.e., multiple hereditary exostoses)

* Only true exostoses were taken into account; other cases in which the term “exostoses” is more likely related to heterotopic bone plaques were missed



Fig. 1 Metaphyseal femoral osteochondroma observed in 9 out of the 14 patients. Although they differ in size, essentially share a common structure and morphology with a wide and well-delineated base and an elongated sharp spike end



Fig. 2 Bilateral femoral osteochondroma (*left side*) displaying a streaking morphological “horn-shaped” semblance. Continuity between the lesion and both the medullary space and the cortex of the underlying bone is observed

1993 by Fred Kaplan and his collaborators. More recently, Chichareon et al. [31] have reported one isolated case of osteochondroma (located at an atypical skeletal area) in a child with FOP. Finally, in a purpose-designed study in which ninety-six FOP patients were reviewed, proximal tibial osteochondromas were quoted as a very common feature of FOP phenotype present in up to 90 % of 96 new FOP cases [32]. Therefore, these results as a whole clearly point that these lesions are genuine osteochondromas and exclude such association to be coincidental.

Our investigation has confirmed that femoral and tibial osteochondromas—present in all but one of the seventeen patients included in the X-ray evaluation—are one of the most frequent skeletal anomalies associated with FOP disease. Strikingly, in nine out of the fourteen patients in which femoral osteochondroma was present, the lesion adopted an identical morphological aspect (Fig. 1) with a peculiar “horn-like” shape (Fig. 2) not previously recognized in FOP disease. Interestingly, this peculiar bone outgrowth appears to be unrelated to the ossification process

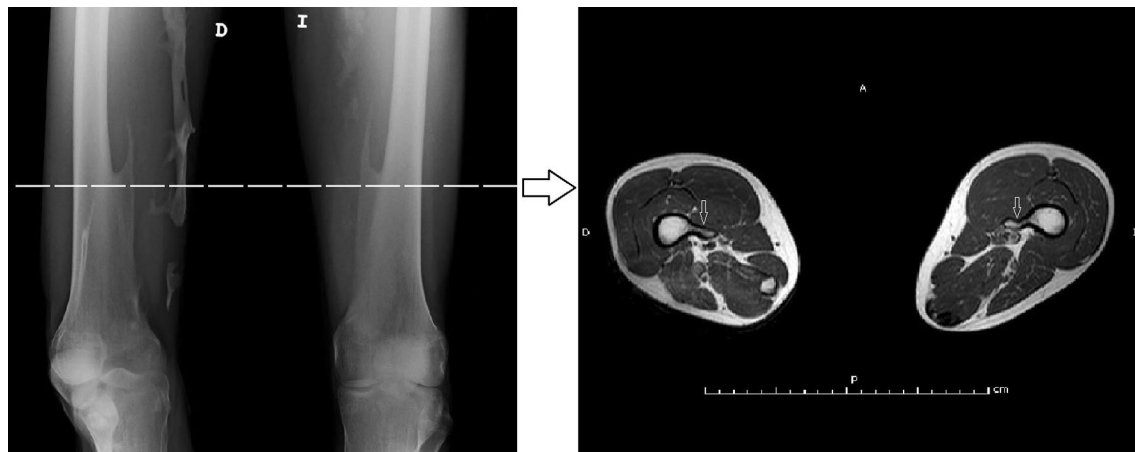


Fig. 3 NMI and X-ray composition images showing an exophytic bone outgrowth with well-defined cortical and medullary bone patterns. Whereas continuity with the underlying parent bone cortex and

medullary canal is apparent, the sharp morphology at the spike end of the lesion may interfere with the detection of the hyaline cartilaginous cap

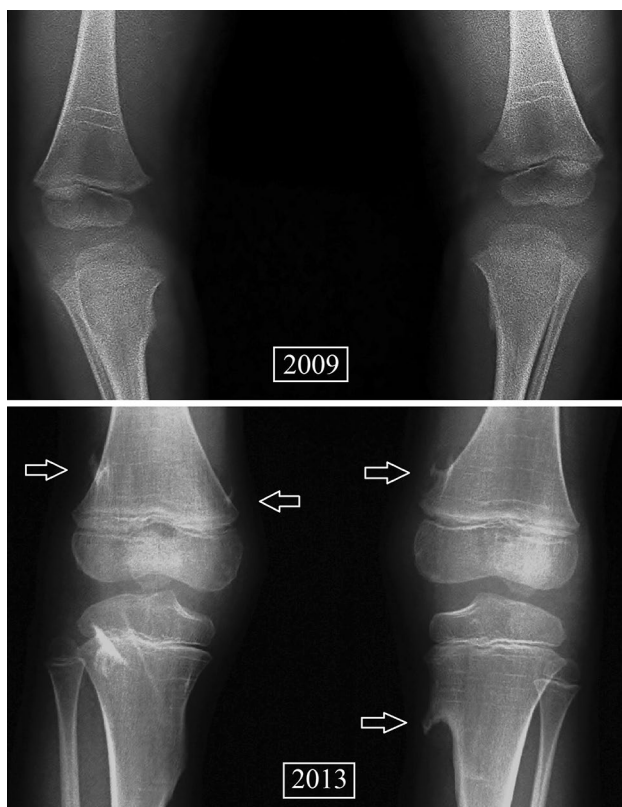


Fig. 4 Serial knee radiographs showing evolutionary changes at two different ages (2 and 6 years). Although the lesions are almost undetectable in early stages (*upper picture*), more advanced stages (*lower picture*) are characterized the typical pattern of FOP-associated mature osteochondroma (*arrows*)

in the overlying muscles since they are not influenced by the degree or position of heterotopic ossification. In addition, such lesions tend to be bilaterally symmetrical, in

contrast to the ectopic bone formation which typically progresses through an asymmetrical pattern. On the other hand, unlike spurious (reactive) metaphyseal calcifications, true osteochondromas are orthotopic osteocartilaginous growths composed of cortical and trabecular bone with an overlying hyaline cartilage cap covered with a thin layer of fibrous tissue that is continuous with the perichondrium [35, 36]. Whereas specific imaging features of osteochondroma could be difficult to disclose in plain radiographs, by using MRI imaging we were able to demonstrate continuity between the bone marrow cavity of the lesion and the underlying parent medullary canal (Fig. 3). Even though a cartilaginous cap could not be observed (perhaps due to their small size and sharpened pattern), our observation pointed out that these lesions are true osteochondromas. The fact that in a number of our cases (Fig. 1; frame number 7) “Erlenmeyer flask” bone deformity—a lesion associated with skeletal dysplasia’s of a varied nature [34] but not documented in FOP thus far—is concomitant with such lesions, reinforces the notion that bone modeling could be involved in the pathogenesis of the osteochondromas observed in FOP disease, as well as in the formation of the heterotopic skeleton that characterizes this devastating illness [37]. It is also worth to note that in our small cohort, and under these research conditions, no patient has developed any complication associated with osteochondromas, conspicuously malignant degeneration.

The presence of osteochondromas in multiple skeletal areas is consistent with the results of a study using a knock-in mouse model for FOP disease (Acvr1R206H/+) [38]. As in patients with FOP, besides postnatal extra-skeletal bone formation, these chimeric mice develop the full spectrum of congenital malformations observed in such cases, including osteochondromas. Additionally,

the presence of widespread osteochondromas in this model might suggest that cells of the perichondrium can be highly sensitive to BMPs pathway [38]. This is in line with other data suggesting that signaling through BMPs and their receptors is a key mechanism for regulating chondrogenesis and endochondral bone formation [39–41]. For instance, it has been established that BMP signal transduction is essential for proliferation, differentiation, and maturation of the mesenchymal cells that precede the development of cartilage and bone [42]. Also, BMP signaling stimulates chondrocyte differentiation at multiple steps during embryonic cartilage development [43]. Moreover, the BMP receptor *ACVR1* has been demonstrated to be expressed primarily in resting and proliferating chondrocytes present at growth plates, highlighting the BMP system as a crucial factor for the growth of skeletal elements [44]. Interestingly, involvement of local BMP-2 signaling, via either autocrine/paracrine pathways or promoting chondrocyte apoptosis, has been related to the process of cap's growth in osteochondroma [20]. All together, these data demonstrate that overactive BMP signaling pathway affects normal skeletal development at multiple stages, playing a key role on the pathogenesis of developmental FOP-associated skeletal malformations [45]. Furthermore, the unveiling of BMPs as the key morphogens for bone modelling renders BMP signaling as a critical regulator in the pathogenesis of osteochondroma and might allow classifying FOP disease among osteochondroma-related conditions, alongside hereditary multiple exostoses [46]. Understanding the molecular and genetic basis of these abnormalities does not only offer hope for FOP patients and their families, but also contribute to unravel the underlying basis of the development of the human musculoskeletal system.

In short, our data confirm that osteochondromas—more often observed at distal femur and proximal tibia, but also present at other metaphyseal areas—represent one of the most frequent and characteristic features of FOP phenotype. When placed at distal femur, they acquire a striking morphological appearance not described to date. While further investigation is needed to elucidate the natural history and potential consequences of this lesion, evidence provided by basic research supports the notion that deregulated BMP signaling caused by FOP metamorphogene could be a link between the development of skeletal osteochondromas and the formation of heterotopic bone, in FOP patients. A better understanding of these presumptive shared molecular mechanisms may help to illuminate pathways that steer physiological bone morphogenesis.

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Conflict of interest Dr. Morales-Piga, Dr. Bachiller-Corral, Dr. González-Herranz, Dr. Medrano-SanIldelfonso, Dr. Olmedo-Garzón, and Dr. Sánchez-Duffhues declare no conflict of interests related to this work.

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