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The phenotype and genotype of fibrodysplasia ossificans progressiva in China: A report of 72 cases ☆

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ABSTRACT

Fibrodysplasia ossificans progressiva, an ultra-rare and disabling genetic disorder of skeletal malformations and progressive heterotopic ossification (HO), is the most catastrophic condition of skeletal metamorphosis in humans. We studied 72 patients with FOP in China and analyzed their phenotypes and genotypes comprising the world's largest ethnically homogeneous population of FOP patients. Ninety-nine percent of patients (71/72 cases) were of Han nationality; and 1% of patients (1/72 cases) were of Hui nationality. Based on clinical examination, 92% of patients (66/72 cases) had classic FOP; 4% of patients (3/72 cases) were FOP-plus; and 4% of patients (3/72) were FOP variants. Importantly, all individuals with FOP had mutations in the protein-coding region of activin A receptor, type I/activin-like kinase 2 (ACVR1/ALK2). Ninety-seven percent of FOP patients (70/72 cases) had the canonical c.617G>A (p.R206H) mutation, while 3% of FOP patients (2/72 cases) had variant mutations in ACVR1/ALK2. Taken together, the genotypes and phenotypes of individuals with FOP from the Han nationality in China are similar to those reported elsewhere and support the fidelity of this ultra-rare disorder in the world's most highly populated nation and across wide racial, ethnic, gender and geographic distributions.

Introduction

Fibrodysplasia ossificans progressiva (FOP; MIM #135100) is an ultra-rare disorder characterized by malformations of the great toes and progressive extra-skeletal ossifications that form a disabling second skeleton of heterotopic bone [1,2]. In FOP, heterotopic ossification (HO) is episodic and results from flare-ups that occur spontaneously or secondary to trauma; disability is cumulative [1]. Progression of FOP lesions occurs in specific anatomic patterns [3]. Due to the rarity of FOP, most patients are misdiagnosed [4]. The mean age of death is 40 years, most commonly from respiratory insufficiency due to severe restrictive disease of the chest wall [5,6]. Treatment is palliative and symptomatic. Presently, there is no effective prevention or disease-altering treatment [1]. FOP is an autosomal dominant disorder, but the etiology of most cases is a de novo mutation which is not inherited from patient's parents [7].

FOP is classified as one of three types based on clinical criteria [7]: (1) classic FOP — affected individuals have two defining clinical features, i.e. characteristic congenital malformations of the great toes and progressive heterotopic ossification in characteristic anatomic patterns. Additionally, >50% of classic FOP patients have proximal medial tibial osteochondromas, orthotopic fusions of the cervical vertebrae, short and broad femoral necks, conductive hearing impairment, and malformations of the thumbs; (2) FOP-plus — affected individuals have the classic clinical features of FOP plus one or more atypical features. (3) FOP variants — affected individuals have major variations in one or both of the classic defining features of FOP. In all types of FOP, the condition can be diagnosed clinically. Genetic studies are confirmatory [8].

FOP is caused by heterozygous activating mutations in activin A receptor, type I/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor, in every individual with FOP [7,10–13]. Approximately 97% of FOP patients worldwide have the classic FOP

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phenotype that is associated with the canonical R206H mutation in ACVR1/ALK2 [11,12]. Approximately 3% of FOP patients have variant phenotypes and genotypes. The ACVR1/ALK2 R206H mutation and all of the variants reported exhibit mild constitutive activity and enhanced ligand-dependent activity of BMP signaling in vitro [7,9–13]. A recently described knock-in mouse model of the classic FOP mutation recapitulates all of the clinical features of FOP in humans [14,15].

FOP has been reported worldwide. However, in China, the world's most populous nation, there have been only six well-documented cases of classic FOP and two FOP variants reported [16–21]. From 2005 to 2012, we prospectively recruited (through Chinese television) and evaluated 72 individuals with FOP from China, and analyzed the natural history, phenotype, genotype, and radiographic features of these individuals.

Subjects and research methods

Individual case histories were obtained from patients, parents, or siblings. There were 72 FOP patients and 98 family controls. Informed consent was obtained from all study subjects. All studies were approved by the investigational review board of Shanghai Tongji Hospital Affiliated with Tongji University. Patient numbers reflect the temporal order in which they were first seen in the clinic for this study.

Medical history, physical examination, and skeletal survey were obtained on all FOP patients at the time of their first clinic visit. Patients who had clinically apparent flare-ups of FOP in the year prior to the visit (41 patients) had ^{99m}Tc-MDP radionuclide bone scans and serum analysis for high-sensitivity C-reactive protein (hsCRP) [22].

All study subjects had ACVR1 gene analysis from a peripheral blood sample obtained after informed consent. ACVR1 gene sequencing and analysis were performed according to reported protocols [7,9].

Fisher's exact test of Chi-square tests was used to compare male and female patient distributions among various onset ages. SPSS13.0 was used for the statistical analysis.

Results

Epidemiology of FOP

Seventy-two individuals with FOP were evaluated from twenty-five provinces of China. No geographical clustering was found. Ninety-nine percent of patients (71/72 cases) were of Han nationality; and 1% of patients (1/72 cases) were of Hui nationality, generally reflecting the demography of China. Forty-nine percent of patients (35/72 cases) were male; and 51% (37/72 cases) were female. The age at the first visit was 18 ± 11 years (mean ± SD) for both males and females; the age at first flare-up was at least one year earlier and also not significantly different between males and females. There was no evidence of FOP in any of the parents or siblings of FOP patients, indicating that all cases of FOP were sporadic.

At their initial evaluation, 99% of FOP patients (71/72 cases) had malformed great toes with radiographic confirmation. All 72 patients had decreased range of motion of the neck and back and functional ankylosis of at least three sites including the neck, trunk and an upper limb. All 72 patients had skeletal surveys which showed heterotopic ossification in areas of previous flare-ups.

Patients with classic FOP

According to clinical classification schemes for FOP [7], 92% of patients in our study (66/72 cases) had classic FOP (Table 1). All 66 individuals had the canonical ACVR1/ALK2 c.617G>A (p.R206H) mutation, and had both defining clinical features, i.e. characteristic congenital malformations of the great toes (Fig. 1) and progressive heterotopic ossification. Additionally, some patients had common but variable features of FOP including proximal medial tibial osteochondromas, cervical spine malformations, and short, broad femoral necks (Fig. 2). Some common features described in classic FOP, including clinically conductive hearing impairment and malformations of the thumb [7], were rarely seen in our patients, but audiology evaluations were not performed routinely.

Patients with FOP-plus (classic FOP plus atypical clinical features)

Three patients (patients 27, 46, and 70) had FOP-plus (Table 1). All three patients had the canonical ACVR1/ALK2 c.617G>A (p.R206H) mutation. Each of the three patients had features of classic FOP plus atypical features that are summarized below:

Patient 27 was diagnosed with FOP at 12 years of age. He was also diagnosed with Marfan syndrome based on disproportionately long limbs, arachnodactyly, tall and asthenic body habitus, high-arched palate, and congenital heart disease, but had no genetic testing for Marfan syndrome.

Patient 46 injured his right shoulder while playing basketball when he was 19 years old and rapidly ankylosed his right shoulder. Several years later he developed spontaneous flare-ups and ankylosis of the

Table 1
Clinical features of classic FOP, FOP-plus, and variant FOP patients.

	Classic FOP	Atypical features of FOP-plus or FOP variant patients					
Patient code	66 cases	7	27	42	46	54	70
ACVR1 mutation							
① Codon change	R206H	R258S	R206H	R206H	R206H	G356D	R206H
② Nucleotide change	c.617G>A	c.774G>C	c.617G>A	c.617G>A	c.617G>A	c.1067G>A	c.617G>A
Gender	M & F	M	M	M	M	F	M
Age of HO onset	1 day–14 years	7 years	12 years	3 years	19 years	3.5 years	6 years
High resolution karyotype	–	Normal	–	–	–	–	–
Classic FOP features							
① Characteristic malformations of great toes	Y	N	Y	N	Y	Y	Y
② Progressive HO	Y	Y	Y	Y	Y	Y	Y
Common variable FOP features							
① Perceived conductive hearing impairment	5.6%	N	N	N	N	N	N
② Cervical spine malformations	48%	Y	Y	N	N	Y	N
③ Femoral or tibial osteochondromas	56%	Y	Y	Y	Y	N	Y
④ Short broad femoral necks	68%	N	Y	Y	Y	Y	Y
⑤ Thumb malformations	1.5%	N	N	N	N	Y	N
Atypical FOP features	N						
① Normal or minimal changes in great toes		Y	N	Y	N	N	N
② Childhood glaucoma		N	N	N	Y	N	N
③ Marfan's syndrome		N	Y	N	N	N	N
④ Cryptorchidism		N	N	N	N	N	Y

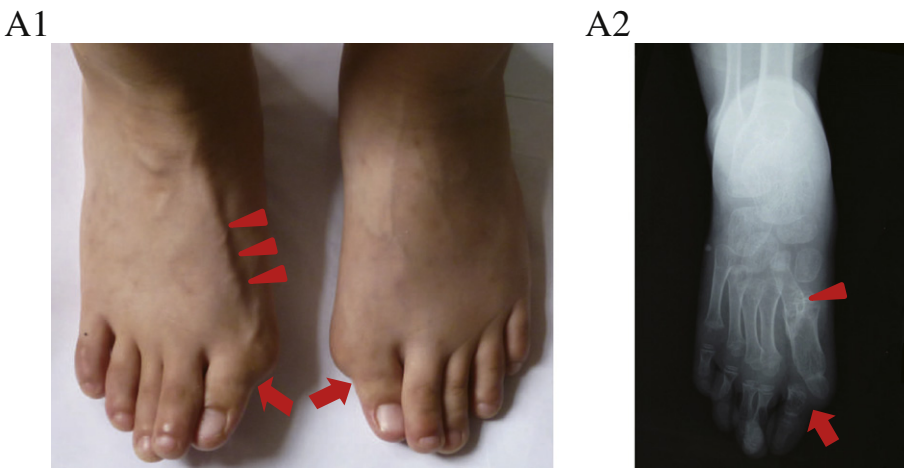

Fig. 1. Representative appearance of the feet of a patient with classic FOP [ACVR1/ALK2 (R206H)]. A photograph (A1) of the feet of a 6-year-old boy with classic FOP shows bilateral hallux valgus deformity with the lack of a toe crease at the metatarso-phalangeal joints (arrows) and incidental heterotopic ossification of a tendon in the foot (arrowheads). An anterior–posterior radiograph of the right foot (A2) shows characteristic malformation of the great toe (arrow) with incidental heterotopic bone proximally in a tendon (arrowheads).

neck and left shoulder. He also had childhood glaucoma, and was blind when he came to our clinic at 22 years of age.

Patient 70 had operative correction of cryptorchidism at six years of age. Post-operatively, he developed soft masses at the operative site as well as at the site of lumbar puncture for spinal anesthesia. Later, flare-ups and subsequent ankylosis developed in the back, neck and both shoulders.

Patients with FOP variants

Three patients were phenotypic variants of FOP (Table 1):

Patient 7, who has previously been reported by our group, had severe digital malformations and a variant mutation in ACVR1/ALK2, c.774G > C (p.R258S) [21]. Patients with this mutation were also described in other nations [23,24].

Patient 42 had normal appearing great toes and thumbs clinically and radiographically but showed characteristic patterns of postnatal heterotopic ossification. He had the canonical ACVR1/ALK2 c.617G>A (p.R206H) mutation.

Patient 54 was previously reported by our group [20], and had initially been classified as FOP-plus, but she has much more severe malformations of the toes than the classically affected patients and is more appropriately considered to be an FOP variant. At 3.5 years of age, she developed flare-ups and limited motion of her left shoulder, neck, chest, elbows and hips. She had limited motion in the interphalangeal joints of both thumbs and both index fingers. She had a variant mutation in ACVR1/ALK2 at c.1067G > A (p.G356D). This mutation has previously been reported in other FOP variant patients [7,25].

Phenotype–genotype correlation

The R206H mutation may cause all three clinical types of FOP including classic FOP, FOP-plus and FOP variants. In this large patient series, all classic FOP and FOP-plus patients and one FOP variant carried the R206H mutation. Two FOP variant cases had non-R206H mutations. This phenomenon is consistent with a previous report [7] which only detected non-R206H mutations in variant FOP patients. None of the 98 unaffected controls, including parents and siblings, had mutations in ACVR1. Penetrance of the ACVR1/ALK2 mutation was 100%.

Onset of FOP

The parents of the FOP patients could recall the onset and features of flare-ups in all cases. In this study, the onset of FOP was considered to be the time when the first spontaneous flare-up appeared or the first HO lesion emerged after trauma.

Spontaneous onset

Sixty-nine percent of patients (50/72 cases) experienced the spontaneous onset of flare-ups. Thirty-six percent of patients (18/50 cases) experienced the spontaneous onset of a flare-up prior to two years of age; 58% of patients (29/50 cases) experienced the spontaneous onset of a flare-up between two and ten years of age; and 6% of patients (3/50 cases) experienced the spontaneous onset of a flare-up after age 10. There was no significant difference between male and female patient's distributions among various onset ages (Table 2).

No patient with spontaneous onset of FOP had any premonitory signs or symptoms prior to the onset of a flare-up. The signs and symptoms accompanying the onset of a flare-up were different at different anatomic sites. If the flare-up was in the head, neck or trunk, the onset was usually acute with large painless or painful soft masses appearing within twelve hours. If the flare-up involved the extremities, patients were more likely to have had focal pain with decreased range of motion as their initial complaint, with or without the appearance of soft tissue swelling.

Fifty-two percent of patients (26/50 cases) who experienced spontaneous onset of flare-ups presented with soft tissue swellings in the occipital region. Typically, as one mass subsided, another one emerged and sequentially spread toward the back of the neck and trunk. Most masses eventually ossified, but some resolved completely. Twenty-three of the 26 patients who had spontaneous occipital masses had radiographic evidence of HO in the occipital and posterior neck regions at the first visit to our clinic, but three of the 26 patients who had reported flare-ups in the occipital region had no radiographic evidence of HO in the occipital region, although these three patients had HO at other sites where intercurrent flare-ups had occurred.

Forty percent of patients (20/50 cases) with spontaneous onset of FOP presented with soft tissue swelling or focal edema in the neck, back, trunk or shoulder, and all of the soft tissue masses become ossified. Eight percent of patients (4/50 cases) with spontaneous onset of FOP presented with HO in the hips, knees, or ankles. However, none of the four patients had any premonitory soft tissue masses or swelling. One of these four cases was a patient who is a phenotypic and genotypic variant of FOP (patient 7). The other three had classic FOP.

Trauma-induced onset

In 31% of patients (22/72 cases), the initial onset of FOP occurred following trauma. In 18 of the 22 cases, the onset occurred following blunt

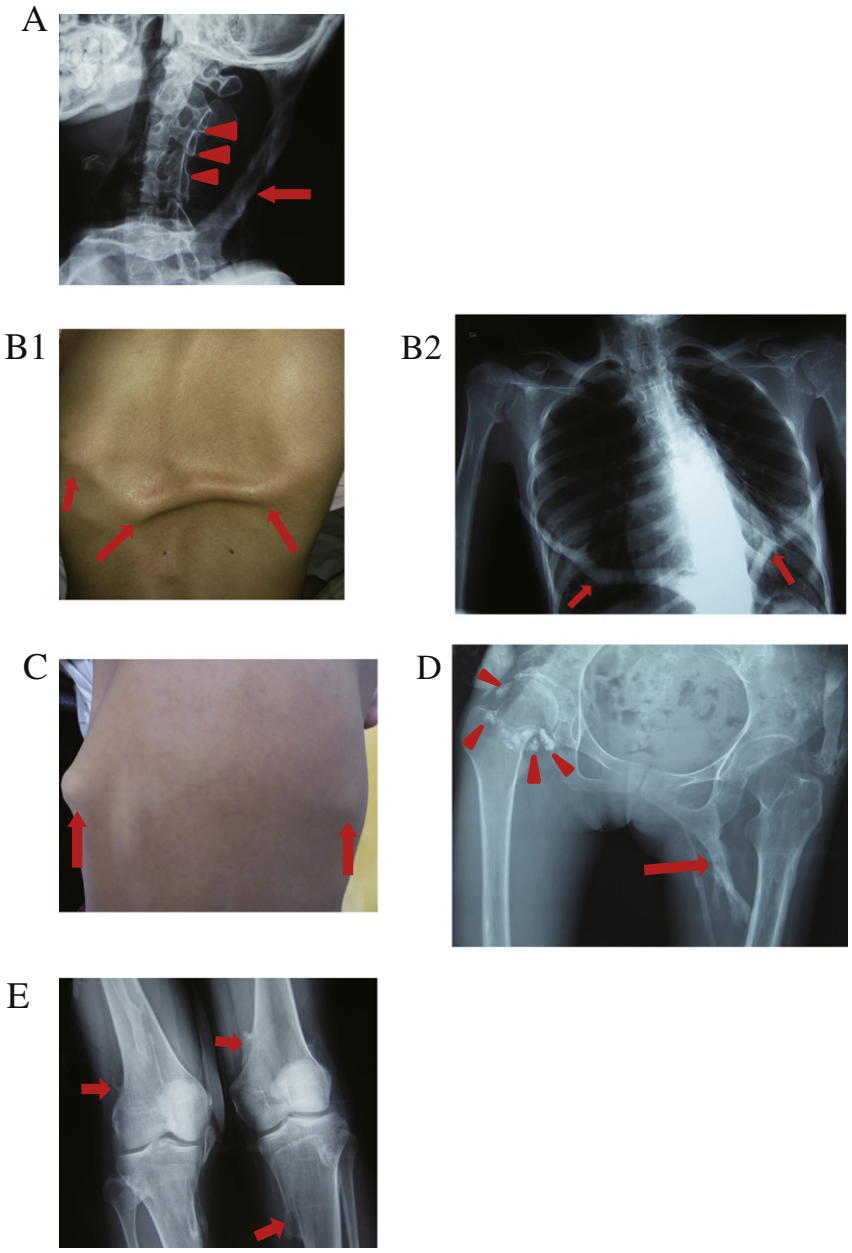

Fig. 2. Characteristic and common-variable features of classic FOP [ACVR1/ALK2 (R206H)]. (A) Lateral radiograph of the cervical spine of a 22-year-old male FOP patient shows heterotopic bone in the nuchal ligament (arrow) and posterior orthotopic fusion of the facet joints of several cervical vertebrae (arrowheads). Photograph (B1) and anterior–posterior radiograph (B2) of the chest of a 16-year-old girl with classic FOP showing subcutaneous bands of heterotopic bone (arrows) in the back. (C) Photograph of the back of a 5-year-old girl with classic FOP showing two prominent subcutaneous flare-ups (arrows). (D) Anterior–posterior radiograph of the pelvis of a 29-year-old female with classic FOP showing mature heterotopic ossification bridging the left hip (arrow) and more proximally both the left and right pelvis, as well as intra-articular synovial osteochondromatosis of right hip (arrowheads). The patient also has characteristic femoral necks that are short and broad. (E) Anterior–posterior radiographs of the knees of a 22-year-old male with classic FOP showing a large sessile osteochondroma of the left proximal medial tibia and small pedunculated osteochondroma of the right distal femur (arrows). Additionally, there are prominent areas of heterotopic bone in both knees.

trauma during routine childhood play; in 4 of the 22 cases, the onset occurred after surgical biopsy of an unsuspected FOP lesion. Most of the parents could not recall the definitive time interval between the blunt trauma and the resulting flare-up. Only in six patients was the interval clearly remembered by their parents to be one week (three cases), ten days (one case), two weeks (one case), and three weeks (one case). The trauma experienced by these 22 patients included blunt trauma to the occipital region, back of neck, shoulder or elbow, and surgical procedures for torticollis, congenital hip dysplasia, osteochondroma of the proximal medial tibia, and fracture of the femoral shaft. In all the 22 patients, spontaneous flare-up would occur subsequent to the trauma-induced onset.

Table 2
Patient distribution among various onset ages.

	<2 years	2–10 years	>10 years
Male	10	12	1
Female	8	17	2
Total	18	29	3

$p = 0.525$ between male and female patients (by Fisher's exact test).

Progression of FOP

The spatial progression of FOP lesions was similar to that previously reported [3]. There was no predictable interval between flare-ups for

those affected with spontaneous onset or for those who had spontaneous flare-ups following an initial post-traumatic flare-up.

Pathological findings

Eighty-four percent of patients (61/72 cases) were misdiagnosed or had not been given any diagnosis in local hospitals prior to their visit to our clinic or our visit to their home. Thirty-six percent of patients (26/72 cases) had undergone a diagnostic biopsy of an FOP lesion prior to the definitive diagnosis of FOP. One hundred percent of those patients (26/26) developed heterotopic ossification at the operative site as a result of the biopsy. The pathological findings were dramatically different from patient to patient and reflected both the stage of the lesion at the time of the biopsy and the ignorance of the medical team regarding the true cause of the pathology. Pathologic misdiagnoses occurred in 92% of patients (24/26 cases) and included panniculitis, eosinophilic fasciitis, fibromyoma, nodular fasciitis, benign fibroma, aggressive fibroma, rhabdomyosarcoma, chondroma, osseous fasciitis, and osteochondroma. 8% of patients (2/26 cases) were correctly diagnosed with FOP on the basis of the pathologic findings and the associated toe malformations. Unfortunately, FOP could have been diagnosed in all cases on the basis of malformed toes and soft tissue swelling and/or heterotopic ossification before an unnecessary and invasive biopsy had been performed [4]. Eighty percent of the biopsies (20/26) showed features compatible with early to mid-stage FOP lesions that included degenerated skeletal muscle with inflammatory infiltrates and early fibroproliferative tissue without any evidence of cartilage or bone [23,26,27]. Only three patients were suspected as having FOP by the pathologist on the basis of early cartilage and bone formation. Three additional biopsies showed mature heterotopic bone, but the patients were not diagnosed with FOP for unknown reasons.

Radionuclide bone scanning

Radionuclide bone scanning with ^{99m}Tc-MDP was performed to determine active or residual foci of heterotopic ossification in 41 patients who had symptoms of FOP flare-ups including focal swelling, pain and/or decreased range of motion within the year prior to their clinic visit. Radioisotope uptake indicating mature heterotopic bone was detected at remote sites of previously resolved flare-ups, as expected, in most individuals. However, if the patient was experiencing symptoms of an intercurrent flare-up of FOP at the time of the scan (focal pain, swelling) but heterotopic bone had not yet formed, no radionuclide uptake was detected. In almost all cases of suspected clinical flare-up, heterotopic bone eventually formed. In only 3 among 50 cases with spontaneous onset did the flare-up resolve spontaneously without forming clinically or radiographically evident heterotopic bone. Therefore, ^{99m}Tc-MDP bone scanning as performed in this FOP patient cohort was not a sensitive method for diagnosing early FOP flare-ups and was less accurate than clinical observation.

Laboratory evaluation

Forty-one patients who had an FOP flare-up in the year prior to their initial evaluation had measurement for serum high-sensitivity C-reactive protein (hsCRP). Only two patients among the 41 had increased levels of hsCRP which were 12.0 and 27.3 mg/L respectively (normal: <10 mg/L) [22].

Discussion

China is the world's most populous nation with more than 1.3 billion people.

Considering the extreme rarity of FOP and the predicted point prevalence of approximately 1:2,000,000, one would estimate the existence of at least 650 patients in China [2]. Until recently, only a few FOP patients from China had been reported. Here we report 72 patients with confirmed FOP in China, the largest ethnically homogeneous population of FOP patients in the world. Together with the earlier case reports of six classic FOP patients [16–21], putatively 12% (78/650) of the population of this disorder in China has been phenotypically and genotypically identified. Therefore, 88% of the expected FOP patients in China remain either undiagnosed or unknown to this medical team and are at risk of lifelong complications from misdiagnosis unless active educational programs are instituted to identify patients at risk. The early diagnosis of FOP can alert doctors and patients alike to avoid diagnostic misadventures [4,8].

Unfortunately, the misdiagnosis experience for FOP in China is similar to that reported elsewhere [4]. Twenty-six of seventy-two patients had unnecessary diagnostic biopsies of early FOP lesions, all of these at local hospitals, and were not properly or promptly diagnosed as having FOP for the same reason that FOP is misdiagnosed elsewhere. Because of the rarity of FOP, many physicians in China, as elsewhere, lack experience in diagnosing FOP and have no prior awareness of the signature presence of malformed great toes, a harbinger of soft tissue pre-osseous flare-ups. The diagnosis of FOP is a clinical one and mutational analysis remains a confirmatory study once the diagnosis is suspected [1,8]. Our data show that the frequency of FOP variant individuals from China is similar to that reported elsewhere in the world [7,9,23,24,26–31], and supports the fidelity of this rare disorder across wide racial, ethnic, gender and geographic distributions.

FOP lesions mature through an endochondral process [32,33]. Early pre-chondrogenic flare-ups of FOP are intensely inflammatory [34]. Yet, in our patient population there was no consistent marker of systemic inflammation. The serum hsCRP levels in 95% of our patients (39/41 cases) whose FOP had been active at least one year prior to their evaluation in our clinic were normal. This finding suggests that there may be either a lack of generalized inflammation in this disease or a very brief period of systemic inflammation that has remain undetected due to a paucity of studies that examine longitudinal and stage-specific biomarkers in this disease. Clearly, there is a need for such studies. Importantly, we found that radionuclide bone scan was unhelpful in following the early progression of FOP in our patients. As with previously reported studies, plain radiographs were more than sufficient in monitoring the clinical course of the disease [35,36].

Conclusion

In summary, we have reported the clinical and genetic profiles of FOP in China. The results of this study may highlight awareness of this patient population in the worldwide FOP community, aid in understanding worldwide trends in natural history and associated genotype, serve in identifying a new population for participation in future clinical trials, and bring critical awareness to the Chinese medical community so that prompt and correct clinical diagnosis might ensue and diagnostic delays might be avoided for the remaining Chinese FOP patients yet to be diagnosed.

Conflict of interests

None.

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