The developmental phenotype of the great toe in fibrodysplasia ossificans progressiva

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic disorder of ectopic bone formation in which extensive bone aberrantly forms in soft connective tissues, such as skeletal muscle, in a process known as heterotopic ossification (HO)[1]. The *ACVR1* gene mutation that causes FOP and HO also alters the normal development of the skeleton. The most frequently occurring mutation among FOP patients (~97%) is *ACVR1* c.619G>A (ACVR1-R206H). ACVR1-R206H, as well as other, rarer ACVR1 mutations found in FOP, enhance signaling from this bone morphogenetic protein (BMP) type I receptor to increase activation of the downstream BMP signaling pathway.

A diagnostic congenital skeletal malformation associated with FOP is that of the first digit of the foot, also called the great toe or hallux. Previous reports identified reduced first digit length, hallux valgus, altered first metatarsal morphology, and distal phalangeal coalition (fusion) in multiple post-axial digits (i.e. digits 2-5) in patients diagnosed with FOP; however, these studies examined only small cohorts (16 and 15 patients, respectively)[2,3]. While other collections of case reports have been examined, none have focused extensively on the forefoot malformations. To investigate the frequency and type of malformations in all the digits of the foot, we conducted a detailed analysis of radiographs from 41 FOP patients with the ACVR1-R206H mutation.

METHODS

In this retrospective analysis, we reviewed radiographic images of the forefoot in 41 individuals with classic FOP. All individuals were established patients of one of the authors (FSK). Clinical diagnoses of FOP were subsequently validated by molecular genetic analysis that confirmed the presence of the recurrent *ACVR1* c617G>A;R206H FOP mutation in all individuals. Plain anterior-posterior radiographs of the feet had been obtained on all subjects as part of routine clinical care. This study was noninterventional and all patient data were deidentified prior to analyses. The evaluation was approved by the institutional review board of The University of Pennsylvania.

Eight subjects (4M, 4F) including unaffected family members served as age-matched controls. For cases without age-matched controls, radiographs were compared against anatomical sketches[4].

RESULTS

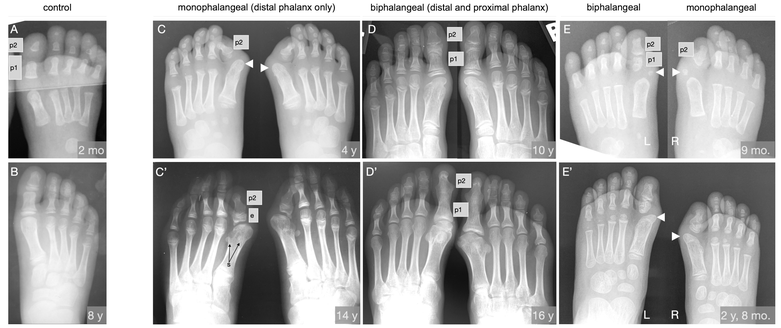
Figure 1. The FOP great toe malformation with monophalangeal or biphalangeal hallux. (A, B) Representative control radiographs from patients at 2 months and 8 years of age, respectively, with an annotated sketch in F. (C-E) Radiographs from three FOP subjects illustrate the two major presentations of this malformation: monophalangeal hallux (distal phalanx only; C, E) and biphalangeal hallux (distal and proximal phalanx; D, E), with G and H as annotated sketches, respectively.

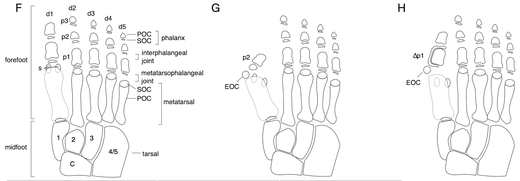
(C) Radiograph of a subject at 4 years of age shows bilateral monophalangism. Ectopic ossification centers (arrowheads; also see Figure 2) have fused to the metatarsals and there is severe lateral displacement of the phalanx, also called hallux valgus. (C') At age 14, the same subject shows large epiphyses (e) of the hallux, mildly deviated sesamoids (s), and dysmorphic distal phalanges.

(D) Radiographs of a subject at 10 years of age showing biphalangism. Hallux valgus is minor. (D') At age 16, the phalanges of the first digit have completely fused, as is the case in all subjects aged 14 or older who have both phalanges present.

(E) One examined subject uniquely presented with both a proximal and distal phalanx in the left foot and only the distal phalanx in the right foot. Note the asymmetric, amorphous shape of the proximal phalanx as contrasted with the rectangular, symmetrical morphology of the proximal phalanges in A. Both feet have an ectopic ossification center (EOC) distal and medial to the first metatarsal (arrowheads), suggesting the EOC is not a reduced proximal phalanx, but is instead a truly ectopic body. (E') The same subject two years later.

(F-H) Annotated sketches for reference. d, digit; p, phalanx, POC/SOC, primary/secondary ossification center; s, sesamoids; Δ indicates delta phalanx phenotype; C, calcaneus.



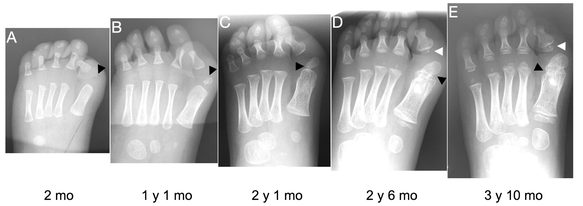


Feature	Prevalence in subjects with FOP	Prevalence in general population
Hallux valgus	93% (38/41)	7.8% <18 yo, 23% 18-65 yo[5]
Deviated hallucal sesamoids	62% (13/21)*	
Ectopic ossification centers	93% (38/41)	
Monophalangeal hallux	51% (21/41)	unique to FOP[6]
Lateral epiphyseal bracket, p1 of d1	76% (16/21)**	9 total[7-9]
Biphalangeal 5th toe	22% (9/41)	42%[6]

Table 1. Major abnormal features of the forefoot in FOP patients. Incidence of various malformations in digits of 41 analyzed subjects. Citations to studies of the general population provided as available.

*21/41 patients had fully visible hallucal sesamoids that could be reasonably assessed.
**21/41 patients had a distinct proximal phalanx of the first digit.

Figure 2. Progression of the FOP great toe malformation. Radiographs from a single FOP subject with monophalangeal hallux over time, illustrating the persistence of hallux valgus and the progression of the ectopic ossification center (EOC; black arrowhead) from birth to approximately four years of age. (A) At birth, the EOC is evident as a miniscule radio-positive region distal and medial to the head of the first metatarsal. (B-C) Over time, the EOC increases in size and proximity to the metatarsal, with little to no growth distally relative to the phalanx. (D) The secondary ossification center of the remaining hallux forms immediately proximal to it, distinct from the EOC (white arrowheads D and E). (E) Finally, bone appears to bridge the EOC and the metatarsal, fusing them together.



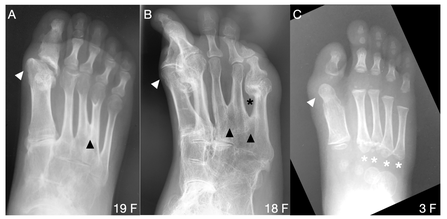
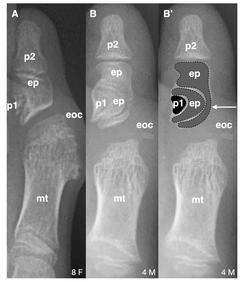


Figure 3. Uncommon forefoot phenotypes in FOP. (A,B) Radiographs from two patients reveal osseous syndactyly (black arrowheads) between metatarsals of digits 3 and 4 (A) and among digits 3, 4, and 5 (B). White arrowheads in all panels indicate the dysmorphic metatarsal heads, corresponding to the position of the ectopic ossification center noted in nearly all subjects with FOP. Asterisk in B indicates extra-articular HO bridging the metatarsophalangeal joint of digit 5. HO is evident in d2, but the extent of it is difficult to ascertain. (C) One of two patients presenting with proximal metatarsal growth plates in digits 2-5 (white asterisks). Age and sex of each subject are indicated in each panel, bottom right.

Feature	d1	d2	d3	d4	d5
absent phalanx	51.2%	0.0%	0.0%	0.0%	22.0%
absent/delayed phalanx SOC(s)	9.8%	19.5%	26.8%	29.3%	43.9%
distal inter-phalangeal fusion	12.2%	2.4%	9.8%	14.6%	24.4%
malformed metatarsal	100%	4.9%	4.9%	4.9%	4.9%

Table 2. Frequency of anomalous radiographic features of the forefoot of individuals with FOP. Incidence of specific skeletal features in radiographs of the forefoot of FOP subjects, based on comparisons to expected features (see Fig 1F). All percentages were calculated based on the 41 subjects examined. A digit was scored as having distal interphalangeal fusion if the morphology of the medial phalanx was both clearly present and continuous with the distal phalanx. All subjects had a malformed first metatarsal with a dysmorphic head and/or broad diaphysis. Two subjects accounted for all other metatarsal malformations (see Fig. 3).

Figure 4. Longitudinal epiphyseal bracket in subjects with FOP. (A) Radiograph showing longitudinal epiphyseal bracket (LEPB; ep) of the proximal phalanx (p) of the great toe in a subject with FOP. An apparent ectopic ossification center (eoc) distal to the metatarsal (mt) head is also noted. (B) Radiograph showing compound LEPB of the proximal phalanx, with outlines for clarity in B'. Dotted lines denote distinct osseous bodies occurring in concentric hemi-circles, with presumed labels of individual ossification centers. Age and sex of each subject are indicated in each panel, bottom right.



CONCLUSIONS

- The great toe phenotype of FOP is unique and highly penetrant but has two distinct presentations.
- The digital malformation phenotype indicates altered proximal-distal patterning during early embryogenesis.
- Endochondral ossification during skeletal growth appears dysregulated, consistent with the phenotype of extra-skeletal endochondral bone formation in FOP.
- Altered morphologies, particularly at sites of joint formation, suggest that joint formation during embryonic development the processes of joint development may be impaired.

FUTURE DIRECTIONS

A genetic knock-in mouse model of FOP presents with skeletal features of FOP, including severely dysmorphic of joints in the limb, particularly the first digit of the hindlimb. Studies are underway to confirm the molecular and cellular mechanisms and thus elucidate the underpinnings of this unique developmental phenotype.

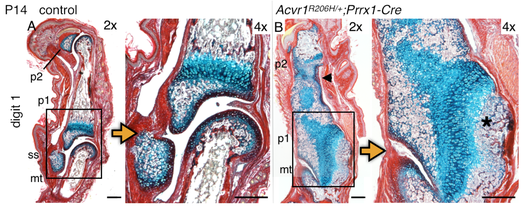


Figure 5. A mouse model of FOP recapitulates the first digit phenotype of FOP. Sagittal sections of P14 control (A) and knock-in (B) mouse digit one stained for cartilage (blue) and collagens (red). Orange arrows highlight a complete cleavage furrow in control animals contrasted with an incomplete furrow in the mutant that leads to a fused and malformed first digit. Asterisk in B indicates the severely altered growth plate polarity and dysregulated chondrogenesis. Scale bars, 100 μm.

REFERENCES

1. Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006;38(5):525-527. doi:10.1038/ng1783
2. Harrison RJ, Pitcher JD, Mizel MS, Temple HT, Scully SP. The radiographic morphology of foot deformities in patients with fibrodysplasia ossificans progressiva. Foot Ankle Int. 2005;26(11):937-941. doi:10.1177/107110070502601107
3. Schroeder HW, Zasloff M. The hand and foot malformations in fibrodysplasia ossificans progressiva. Johns Hopkins Med J. 1980;147(2):73-78.
4. Sarrafian SK. Sarrafian's Anatomy of the Foot and Ankle : Descriptive, Topographic, Functional. 3rd ed. LWW; 2011.
5. Nix S, Smith M, Vicenzino B. Prevalence of hallux valgus in the general population: a systematic review and meta-analysis. J Foot Ankle Res. 2010;3:21. doi:10.1186/1757-1146-3-21
6. Le Minor J-M, Mousson J-F, de Mathelin P, Bierry G. Non-metric variation of the middle phalanges of the human toes (II-V): long/short types and their evolutionary significance. J Anat. 2016;228(6):965-974. doi:10.1111/joa.12462
7. Neil MJ, Conacher C. Bilateral delta phalanx of the proximal phalanges of the great toes. A report on an affected family. J Bone Joint Surg Br. 1984;66(1):77-80.
8. Low K, Smith J, Lee S, Newbury-Ecob R. A mother and daughter with a novel phenotype of hand and foot abnormalities and severe pectus excavatum. Am J Med Genet A. 2013;161A(8):2056-2059. doi:10.1002/ajmg.a.36016
9. Verma V, Batra A, Singla R, Gogna P, Magu N, Gupta R. Longitudinal Bracketed Epiphysis of Proximal Phalanx of the Great Toe With Congenital Hallux Varus Managed Simultaneously With Monorail External Fixator: A Case Report. Foot Ankle Spec. 2014;7(1):68-70. doi:10.1177/1938640013502724

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