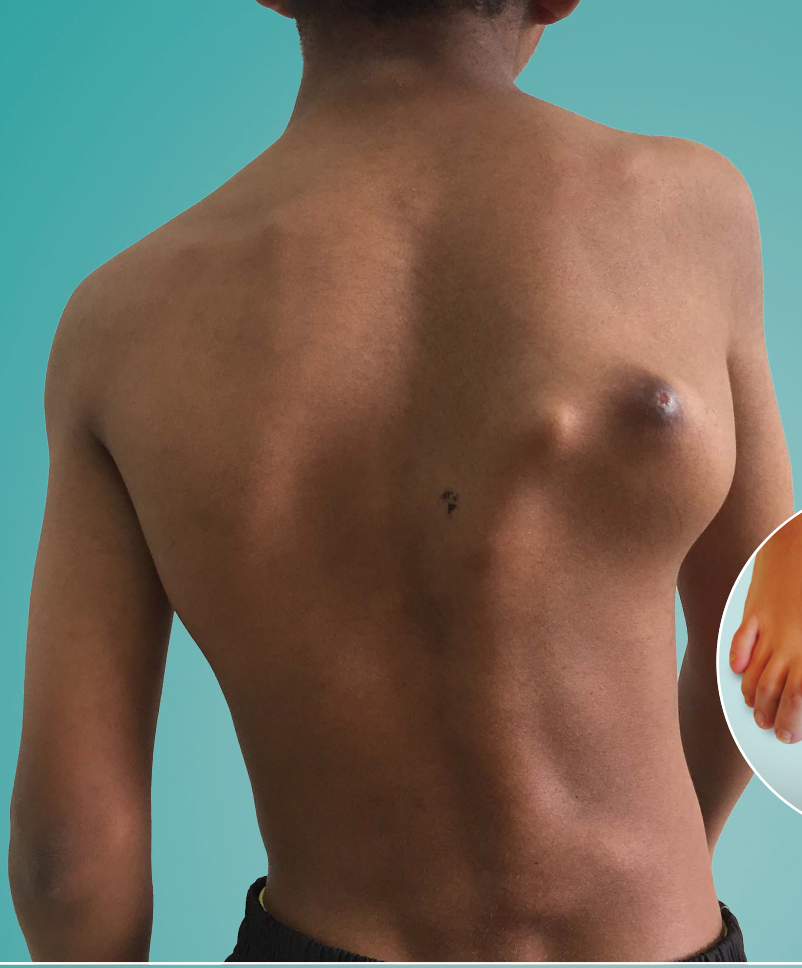
FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

If you see lumps or locked joints like these



10-year-old male patient with FOP.

Adapted from Pachajoa H, Botero AF. *BMJ Case Rep*. 2015;2015:bcr2015209804.

Adapted from Pignolo RJ et al. *Orphanet J Rare Dis*. 2011;6:80.

Go feet first

FOP is a progressive disorder that leads to a loss of mobility.[1,2] If you see bilateral great toe malformations and soft tissue swellings, lumps, or heterotopic ossification (HO), think FOP.

18-year-old male patient with FOP.

Adapted from Sharma B et al. *Neurol India*. 2018;66(2):531-534.

36-year-old female patient with FOP.

Adapted from Rogoveanu O et al. *J Med Life*. 2013;6(4):454-458.

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Learn more at **FocusOnFOP.com**

Understand FOP: When soft tissue turns to bone[1,2]

Fibrodysplasia ossificans progressiva (FOP) is characterized by flare-ups that often lead to progressive heterotopic ossification (HO), the abnormal and irreversible formation of bone in muscles, tendons, and ligaments

Skeleton of Harry Eastlack, a patient with FOP, showing heterotopic bone formation; displayed at the Mütter Museum at The College of Physicians of Philadelphia.

Image used with permission from The College of Physicians of Philadelphia. Photo credit Evi Numen.

- **ULTRA-RARE, GENETIC DISORDER:** FOP has an estimated prevalence of 1.36 people per million[3]*
    - FOP has no racial, ethnic, gender, or geographic predisposition[1]
- **RESULTS IN IRREVERSIBLE LOSS OF MOBILITY:** As heterotopic bone accumulates, range of motion is progressively lost, leading to loss of mobility[2]
- **AN EARLY DIAGNOSIS IS CRITICAL:** Identify as soon as possible to avoid invasive measures that might cause injury and trigger irreversible HO[4]
- **DISEASE MANAGEMENT:** Current FOP care is focused on symptom management and prevention of HO through avoiding interventions that could lead to a flare-up[4,5]

ICD-10 Code for FOP:

M61.1 Myositis ossificans progressiva

All claim forms should include an accurate and appropriately documented diagnosis code. Physicians should select the code that most closely and appropriately represents the diagnosis of the patient.

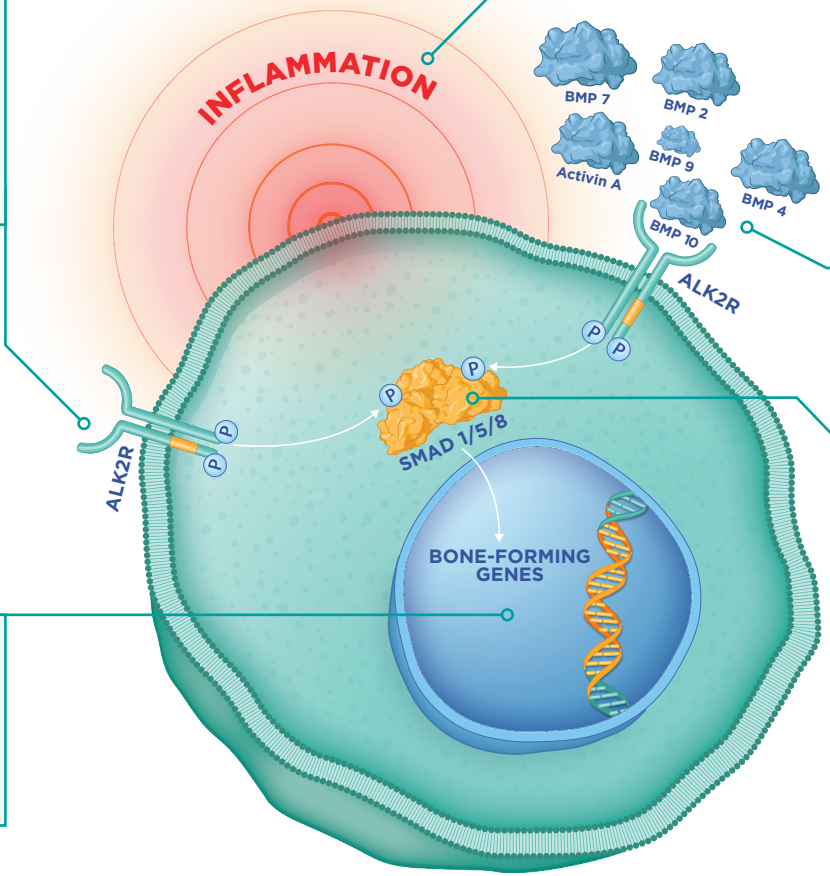
*From an estimate of FOP prevalence in France, based on a record linkage of 2 national databases.[3]

Mechanism of HO in FOP

HO is the formation of extraskeletal bone in muscle and soft connective tissues. In FOP, HO is a complex process that occurs due to inflammation combined with abnormal activation of the bone morphogenetic protein (BMP) signaling pathway[6,7]

1

The genetic cause of FOP is a gain-of-function point mutation in the *ALK2/ACVR1* gene, which encodes the ALK2 receptor, a protein in the BMP signaling pathway.[6]



2

Inflammation triggers activation of ALK2 on the surface of stem cells, which leads to enhanced signaling in FOP.[7]

3

While the mutated receptor is constitutively active,* BMP signaling is increased through the binding of at least 6 ligands.[8,9]

*When the receptor is turned onto an active signaling state in the absence of a ligand.

4

Transcription factors Smads 1/5/8 are activated through phosphorylation.[9]

5

Activation of Smads 1/5/8 results in expression of genes that promote differentiation of stem cells to bone.[9]

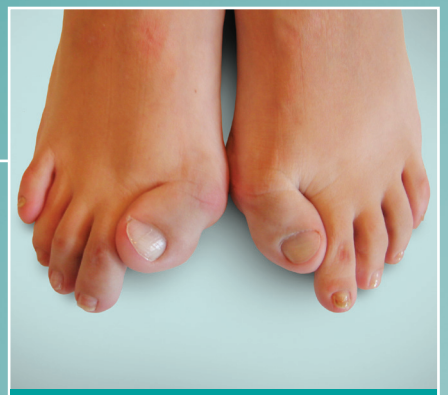
Characteristic clinical signs define FOP

Suspect FOP if a patient has a bilateral great toe malformation and a presence or history of soft tissue swellings[3]

MALFORMED GREAT TOES[4]

Symmetrical, malformed great toes, which are shortened and bent inward, are present from birth and remain throughout life

This congenital great toe malformation is present in almost all patients with FOP, and can vary from a fibular deviation to their complete absence; sometimes, this malformation is misdiagnosed as bunions[4,10]



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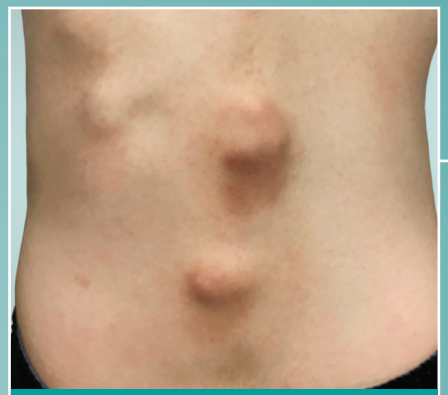


Adapted from Kitoh H. *Biomedicines*. 2020;8(9):325.

SWELLINGS ON THE NECK, UPPER BACK, OR HEAD[3,11,12]

Soft tissue swellings (during flare-ups) are commonly mistaken for tumors and often precede HO. They may involve hallmarks of inflammation, including pain, redness, and warmth to the touch

THINK FOP

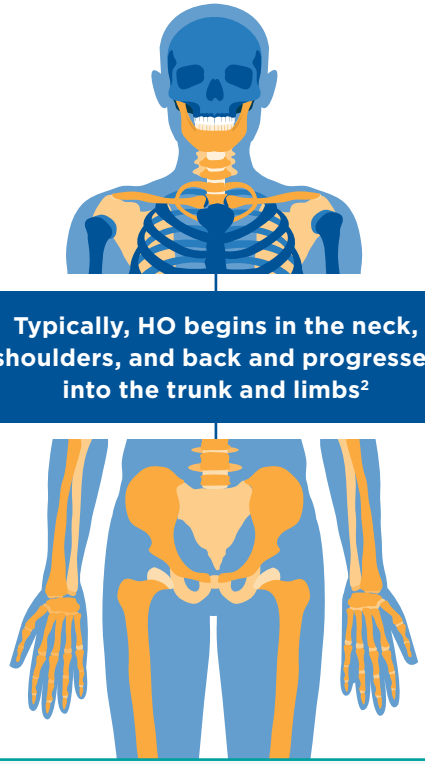
SUSPECT FOP? AN ACCURATE DIAGNOSIS MAY HELP PREVENT HARM.[4,5]

Genetic testing for mutations in *ACVR1* can confirm a clinical diagnosis.

HO in FOP is episodic, but disability is cumulative and irreversible[2,5]

Patients with FOP experience sporadic and unpredictable episodes of soft tissue swelling, pain, reduced movement, stiffness, and fever, referred to as "flare-ups"[3,11,12]

The replacement of muscles and connective tissues with heterotopic bone often results in irreversible immobility[2]



Typically, HO begins in the neck, shoulders, and back and progresses into the trunk and limbs[2]

By the second decade of life, ankylosed joints often cause patients to lose mobility[3]

Most patients with FOP are confined to a wheelchair by the third decade of life and require caregiver assistance to perform daily living activities[3]

By the fourth decade of life, many patients are at risk of early death due to thoracic insufficiency syndrome or thrombosis[3]

Patients with FOP reach a median age of 40 to 50 years; death is often due to cardiorespiratory failure (as a result of thoracic insufficiency syndrome, which is usually caused by progressive restrictive chest-wall HO) or thrombosis[2,3,13]

YOU CAN HELP PREVENT FURTHER DISABILITY

Early awareness and intervention for FOP can help prevent injury that leads to irreversible HO formation.[4,5]

Be aware of FOP.
Help prevent harmful injury and interventions.

Current FOP care is focused on symptom management, which can help patients avoid injury and iatrogenic harm[4,5]

A questionnaire of International Fibrodysplasia Ossificans Progressiva Association (IFOPA) members was completed by 138 individuals with FOP from 5 continents:

FOP IS FREQUENTLY MISDIAGNOSED[4]

87% of patients were initially **misdiagnosed**

Misdiagnoses often include: cancer, aggressive juvenile fibromatosis, ankylosing spondylitis, and bunions

Patients typically receive a diagnosis of FOP **4.1 years (± 7.9 years)** after symptom onset, and after consultation with **6 different physicians (range: 1-51)**

A MISSED DIAGNOSIS MAY LEAD TO HARM[4]

67% of patients reported **unnecessary and potentially harmful** diagnostic procedures

68% of patients reported receiving **inappropriate therapies** (including surgical removal of abnormal mass, multiple surgical procedures, chemotherapy, physiotherapy, and radiotherapy)

49% of patients had **permanent loss of mobility** resulting from **invasive medical interventions** that caused posttraumatic ossification

IF FOP IS SUSPECTED, CAREFULLY CONSIDER DEFERRING ALL ELECTIVE PROCEDURES UNTIL A DEFINITIVE DIAGNOSIS IS MADE, INCLUDING[5]:

Biopsies

Surgeries

Intramuscular injections

All medical procedures should be determined on an individual basis by considering the risk and benefit to the patient in consultation with their HCP.

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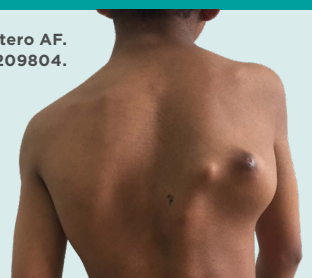

OBSERVE TUMOR-LIKE SWELLINGS? ADD FOP TO YOUR DIFFERENTIAL DIAGNOSIS.

Genetic testing can confirm your suspicion.

According to The International Clinical Council on FOP (ICC), a multidisciplinary team is essential for managing FOP

Selected recommendations from the 2019 ICC Treatment Guidelines

Avoid mandibular blocks, overstretching of the jaw, and muscle fatigue[5]

Encourage activities for respiratory health, such as singing and water exercises[5]

Refer to an audiologist for screening, since hearing impairment is common[5,13]

Connect patients with mental health resources to help with emotional support; family therapy may also be helpful[5,13]

"Each patient should have a primary physician who is willing to consult with an FOP expert and help coordinate a local care team."[5]

-The ICC

The ICC is an independent group of 21 internationally recognized physicians who are clinical experts in FOP from 14 nations. As part of their mission, they publish treatment guidelines for managing FOP.[14]

Support is available for your patients

- Patients and families should consider connecting with IFOPA for support, community, and resources at IFOPA.org[5]
- The ICC Guidelines include emergency medical and dental contact information[15]

Understanding and awareness of FOP are essential for appropriate management[4]

Fibrodysplasia ossificans progressiva (FOP) is a progressive, disabling, ultra-rare genetic disorder of cumulative heterotopic ossification (HO)[1,2]

You can help prevent injury, iatrogenic harm, and irreversible HO in patients with FOP[4,5]

Genetic testing for mutations in *ACVR1* can confirm a clinical diagnosis.

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For more information, go to FocusOnFOP.com

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References: 1. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am*. 2010;92(3):686-691. **2.** Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. *Pediatr Endocrinol Rev*. 2013;10 Suppl 2(0 2):437-448. **3.** Baujat G, Choquet R, Bouée S, et al. Prevalence of fibrodysplasia ossificans progressiva (FOP) in France: an estimate based on a record linkage of two national databases. *Orphanet J Rare Dis*. 2017;12(1):123. **4.** Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. *Pediatrics*. 2005;116(5):e654-e661. **5.** Kaplan FS, Al Mukaddam M, Baujat G, et al. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. The International Clinical Council on FOP (ICC) & Consultants. Published March 2019. Updated June 2019. **6.** Shore EM. Fibrodysplasia ossificans progressiva: a human genetic disorder of extraskeletal bone formation, or—how does one tissue become another? *Wiley Interdiscip Rev Dev Biol*. 2012;1(1):153-165. **7.** Kaplan FS, Lounev VY, Wang H, Pignolo RJ, Shore EM. Fibrodysplasia ossificans progressiva: a blueprint for metamorphosis. *Ann N Y Acad Sci*. 2011;1237:5-10. **8.** Katagiri T, Tsukamoto S, Nakachi Y, Kuratani M. Discovery of heterotopic bone-inducing activity in hard tissues and the TGF-β superfamily. *Int J Mol Sci*. 2018;19(11):3586. **9.** Culbert AL, Chakkalakal SA, Theosmy EG, Brennan TA, Kaplan FS, Shore EM. Alk2 regulates early chondrogenic fate in fibrodysplasia ossificans progressiva heterotopic endochondral ossification. *Stem Cells*. 2014;32(5):1289-1300. **10.** Hüning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. *Mol Syndromol*. 2014;5(5):201-211. **11.** Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): a comprehensive global assessment. *J Bone Miner Res*. 2016;31(3):650-656. **12.** Piram M, Le Merrer M, Bughin V, De Prost Y, Fraitag S, Bodemer C. Scalp nodules as a presenting sign of fibrodysplasia ossificans progressiva: a register-based study. *J Am Acad Dermatol*. 2011;64(1):97-101. **13.** Di Rocco M, Baujat G, Bertamino M, et al. International physician survey on management of FOP: a modified Delphi study. *Orphanet J Rare Dis*. 2017;12(1):110. **14.** International Clinical Council on Fibrodysplasia Ossificans Progressiva. International Clinical Council (ICC) on Fibrodysplasia Ossificans Progressiva (FOP). Revised July 17, 2020. Accessed October 20, 2020. www.iccfop.org. **15.** For Medical Professionals. International Fibrodysplasia Ossificans Progressiva Association (IFOPA). Accessed October 20, 2020. www.ifopa.org/for_medical_professionals.

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