Frequently Asked Questions in Fibrodysplasia Ossificans Progressiva (FOP)

FOP BACKGROUND

1. WHAT IS FOP?

FOP is an ultra-rare genetic disease characterized by congenital skeletal malformations and progressive, irreversible formation of extraskeletal bone in muscles and soft tissues, known as heterotopic ossification.[1,2] Recurrent episodes of HO start in childhood and restrict movement over time, leading to disability and decreased life expectancy.[1]

2. HOW COMMON IS FOP?

The rarity and heterogeneity of FOP make prevalence hard to measure,[1] and estimates vary widely throughout the world.[3] In 2021, the US prevalence was estimated at 0.88 per million; however, the authors believe this could be an underestimation due to potentially undiagnosed patients and those who were not connected with the database used.[1]

A study in France estimated the prevalence at 1.36 per million, which is likely to be more accurate due to the robust methodology of the study and specific characteristics of the French healthcare system.[4]

3. WHAT CAUSES FOP?

All cases of FOP are caused by spontaneous missense mutations in the *ALK2/(ACVR1)* gene, which encodes a receptor in the BMP signaling pathway.[5,6] In the absence of mutations, BMPs bind to the *ALK2/ACVR1* receptor, inducing heterodimerization with the type 2 receptor and phosphorylation of Smad 1/5/8, resulting in downstream activation of genes involved in the differentiation and activation of chondrocyte and osteoblast-like cells.[7–9] This is regulated by the inhibitory factor FKBP12, which binds to the BMP type 1 receptor and stabilizes the inactive form.[10] In the presence of mutated *ALK2/ACVR1, FKBP12* binding is reduced, leading to activation of BMP signaling in a BMP-independent manner.[10,11] This mutant receptor also enhances BMP signaling in response to BMP.[11] Almost all patients (approximately 97%) carry the same specific *ALK2/ACVR1* gene mutation (c.617G>A; p.R206H) in the glycine and serine activation domain of the gene.[5,6] Other mutations in the *ALK2/ACVR1* gene have been identified in approximately 3% of patients with FOP;[6] these rare mutations can occur in the glycine and serine domain or the serine/threonine kinase domain.[11] Few examples of inheritance are known; when observed, genetic transmission occurs in an autosomal dominant manner.[12]

4. ARE CERTAIN PEOPLE AT A HIGHER RISK OF HAVING FOP?

No ethnic, racial, sex, or geographic predisposition to FOP has been described. There are a small number of inherited FOP cases that show germline transmission is possible; however, the majority of cases are caused by sporadic, non-inherited mutations.[13]

5. WHAT ARE THE CHARACTERISTIC FEATURES OF FOP?

There are two phenotypes of FOP:

- **Classic FOP**, affecting 97% of patients with FOP worldwide,[6] is associated with the R206H *ALK2/ACVR1* gene mutation and is characterized by malformations of the great toes present at birth and occurrence of HO in specific anatomic patterns[5]
- **Atypical FOP**, which has a non-classic disease course with additional features or major variations in the classic defining features of FOP,[11] affects 3% of the population with FOP[6]

Other clinical features observed in patients with FOP include proximal medial tibial osteochondromas, cervical spine malformations, short, broad femoral necks, hearing impairment, and shortened thumbs.[11] A registry-based study of 43 patients with characteristic skeletal malformations involving the great toes found that scalp nodules were present in 40% of individuals and usually represented the first manifestation of FOP.[14]

6. HOW DOES FOP PROGRESS?

Episodes of HO usually start in childhood and recur throughout the patient's life.[15] While FOP progresses most notably around flare-ups, approximately ~50% of patients report HO formation in the absence of discrete flare-ups.[16] Typically, HO begins in the dorsal, proximal, axial and cranial regions of the body (neck, shoulders, back) and progresses into ventral, caudal and distal regions (trunk and limbs).[13,15,17] HO develops into ribbons, sheets, and plates of extra bone throughout the body and across joints, progressively restricting movement.[18,19] Once ossification occurs, it is permanent.[15] Consequently, disability in FOP is cumulative and most patients become immobilized and confined to a wheelchair by their third decade of life.[19]

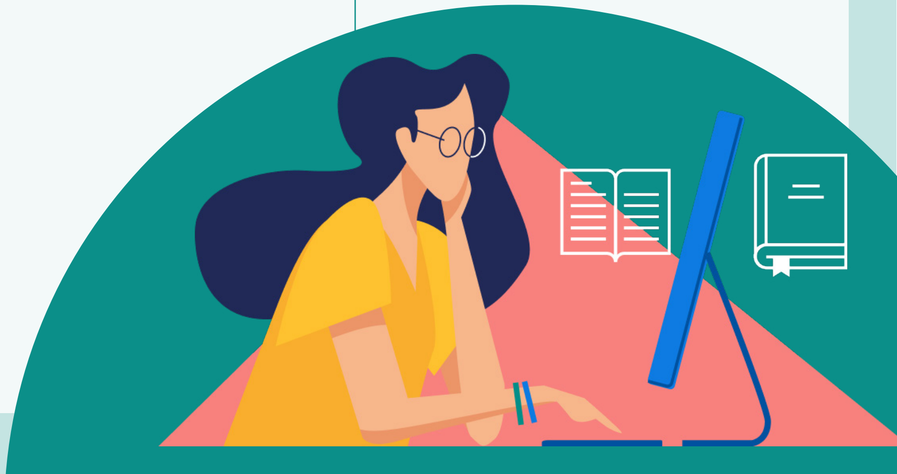
7. WHAT ARE FLARE-UPS?

Patients with FOP experience sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness, and warmth, referred to as 'flare-ups'.[19]

Although there is variability in the rate of FOP disease progression, flare-ups occur more frequently in the upper limbs before 8 years of age and more frequently in the lower limbs thereafter.[15,19] Flare-ups may appear spontaneously or after muscle fatigue, minor trauma, intra-muscular injections or influenza-like viral illnesses, and develop rapidly during the course of several hours.[17,19,20]

8. WILL FOP AFFECT THE LIFE EXPECTANCY OF MY PATIENT?

Patients with FOP reach a median age of 56 years; death is often due to cardiorespiratory failure (as a result of respiratory insufficiency that is usually caused by progressive restrictive chest wall HO) or thrombosis.[21] Other life-limiting complications include severe weight loss due to jaw ankylosis[15] and falls.[21]



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DIAGNOSIS

1. HOW IS FOP DIAGNOSED?

The clinical diagnosis of FOP should be based on the presence of:[19]

- Skeletal malformations, including bilateral malformation of the great toes
- Soft tissue swelling
- Abnormal bone growth and progressive HO

Clinical suspicion of FOP should be confirmed by genetic analysis (presence of an *ALK2/ACVR1* gene mutation) for a definitive diagnosis. If FOP is suspected, surgeries, biopsies and immunizations, which can cause further harm in patients with FOP, should all be deferred until the diagnosis is confirmed or excluded.[19]

2. WHY IS EARLY DIAGNOSIS OF FOP IMPORTANT?

A review of experimental models of FOP suggested that a timely disease diagnosis could extend patient longevity, by prompting the appropriate prevention of flare-ups, and avoidance of surgical procedures and iatrogenic injuries that accelerate HO.[22] However, according to recent IFOPA registry data, patients typically receive a diagnosis on average 1.5 years after symptom onset, following consultation with an average of 3.3 different healthcare professionals.[23] While the diagnostic delay appears to have shortened in recent years,[23] increased education among physicians is needed to aid early diagnosis and avoid unnecessary treatment that may exacerbate disease progression.[24]

3. CAN FOP BE DIAGNOSED BEFORE THE ONSET OF HO?

Bilateral skeletal malformations of the great toes are present at birth in almost all patients with classical FOP,[19,25] and episodic flare-ups (soft tissue swellings) may precede the appearance of HO in some patients.[19] Awareness of these early signs can trigger genetic testing to provide a diagnosis of FOP before HO development begins.[19]

4. HOW COMMON IS MISDIAGNOSIS IN FOP AND WHAT ARE THE COMMON DIFFERENTIAL DIAGNOSES?

The ultra-rare nature of FOP means patients are commonly misdiagnosed. Over 50% of patients in the FOP Registry (N=415) noted receiving a misdiagnosis, the most common of which were cancer (29%), juvenile fibromatosis (13%), myositis ossificans (10%), Klippel-Fiel syndrome (4%), hallux valgus (3%) and osteochondromas (3%).[23]

MANAGEMENT

1. WHAT IS MY ROLE AS A PRIMARY CARE PHYSICIAN (PCP)?

As a PCP, you play an important role in your patient's multidisciplinary care team, ensuring they receive appropriate care. This will involve consulting with an FOP expert and helping to co-ordinate a local care team. You can also help support your patient and their caregivers by providing them with the information they need, informing them about organizations such as the International Clinical Council on FOP (ICC), and connecting them with patient organizations and support groups.[19]

2. IF I SUSPECT A PATIENT HAS FOP, WHO CAN I REFER TO?

To find your nearest regional care center, visit the 'Connect with a local center' page where you can find contact details of FOP regional care centers and physicians who are familiar with FOP management.

3. WHAT SPECIALTIES NEED TO BE INVOLVED IN THE CARE OF MY PATIENT WITH FOP?

Patients with FOP and their caregivers require specialist, multidisciplinary care, as FOP does not fall solely under one medical specialty.[19] Some specialties may be needed on a regular basis, forming the 'core care network', while others may only be needed in specific cases. It is the goal of the ICC to create a network of regional FOP centers of care, where each center provides medical, surgical and dental expertise, anesthesia, and physical and occupational therapy for patients with FOP, all in one physical location.[26] For more information on the types of specialists involved with the care of patients with FOP, see our 'Multidisciplinary network' page.

4. HOW CAN I HELP FACILITATE MULTIDISCIPLINARY CARE OF MY PATIENT?

It is recommended that all patients have a PCP who is willing to consult with a FOP expert where necessary and help to co-ordinate a local care team.[26] Details about the patient's case and any other pertinent FOP information should be made readily available to the PCP and other local physicians involved in their care.[27] An emergency medical form can be provided to the patient to help with continuity of care; the form provides critical care and personalized medical information to assist any healthcare professional in providing the best care possible for that patient. A customizable form developed by the IFOPA and the ICC is available at https://www.ifopa.org/personalized_medical_form.[28]

5. WHAT ARE THE GOALS FOR FOP MANAGEMENT?

Current management is focused on early diagnosis of FOP, avoidance of injury or iatrogenic harm, amelioration of symptoms associated with flare-ups and HO, and optimization of residual mobility.[19]

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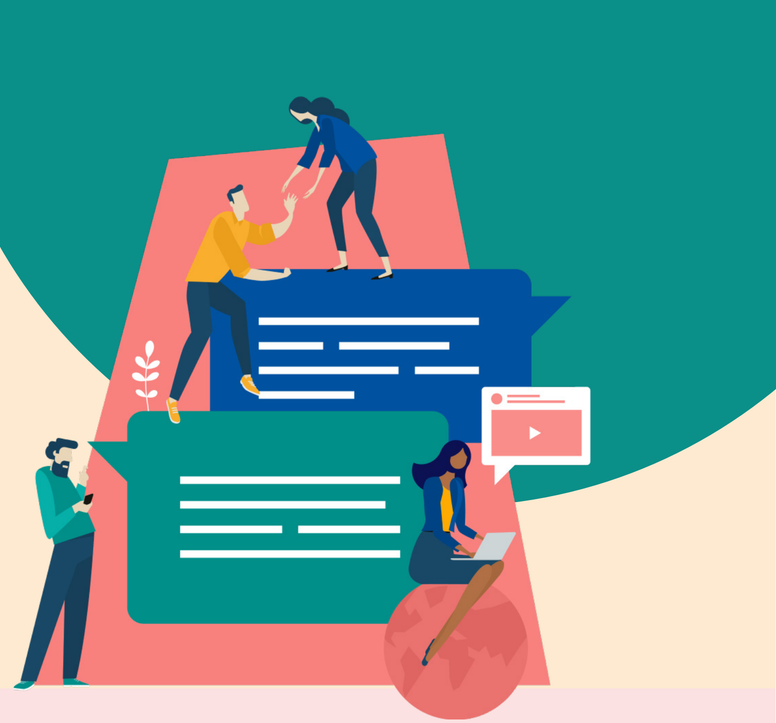
6. HOW CAN I HELP MY PATIENT PREVENT FLARE-UPS?

Patients should be educated on the known causes of flare-ups (e.g., blunt muscle trauma, muscle fatigue, muscular stretching and intramuscular injections), so that they can practice avoidance. For instance, activities that pose a high risk of injury, such as contact sports, should be advised against. An individualized lifestyle plan can be developed, that helps to enforce precautions while also considering a patient's preferences, age, limitations and cultural norms.[27]
If blunt muscle trauma occurs, therapeutic interventions can be considered, while steroid prophylaxis is recommended prior to unavoidable dental or surgical procedures. Subcutaneous immunizations are preferred over intramuscular; where intramuscular is the only option, the benefits and risks should be discussed with the patient. All immunizations should be avoided during a flare-up.[27]

7. CAN I HELP IMPROVE MY PATIENT'S QUALITY OF LIFE?

In an analysis of patient questionnaires filled out by members of the FOP Registry, it was found that increased pain severity was associated with decreased emotional health, physical health and overall quality of life, suggesting that pain management could help improve quality of life for some patients. However, 36–48% also reported emotional problems during times of little or mild pain.[28]

Patients' functional limitations can also affect their quality of life; the ICC guidelines suggest recreational therapy and creative art therapies can help in making meaningful use of leisure time and ameliorating disability, while psychologists, social workers and other mental health counsellors may help patients adjust to the limitations and inconveniences imposed by their illness. Occupational therapy consultations may be useful to determine household adaptations and assistive devices that may benefit the patient and help them lead a productive and fulfilling life.[19] If clinical evaluation suggests the patient is depressed, psychological support should be sought.[19]



ADDITIONAL SUPPORT

1. WHERE IS MY NEAREST FOP EXPERT?

To find your nearest regional care center, visit the 'Connect with a local center' page where you can find contact details of FOP regional care centers and physicians who are familiar with FOP management.

2. IS THERE A FOP REGISTRY PATIENTS CAN JOIN?

The FOP Registry is a global database open to all individuals with FOP. It helps the entire FOP community by facilitating potential participation in clinical trials or other research and serving as a repository for natural history data, providing information on the functional, emotional and physiological impact over time. It may also help advance the understanding of treatment outcomes. Patients can join the registry at https://fopregistry.org.[29]

3. WHERE CAN MY PATIENT HEAR FROM/CONNECT WITH OTHER PATIENTS WITH FOP?

The IFOPA is a non-profit organization that provides education and support programs to the FOP community and organize FOP family gatherings and other social events. Further information, as well as patient stories, contact details for patients, and links to patient and family blogs can all be found on their website at https://www.ifopa.org/patients_families.[30]

4. WHERE CAN I FIND GUIDELINES ON FOP MANAGEMENT?

The ICC has developed in-depth guidance that provides a background to FOP and considerations for treatment.[19] The latest version can be found at https://www.iccfop.org/guidelines/.[31]

ACVR1, activin A receptor, type I; ALK2, activin receptor-like kinase 2; BMP, bone morphogenetic protein; FKBP12, FK506-binding protein 12; HO, heterotopic ossification; ICC, International Clinical Council on FOP; IFOPA, International Fibrodysplasia Ossificans Progressiva Association; PCP, primary care physician

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