Characteristics and Burden of FOP

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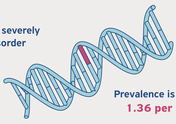
WHAT IS FIBRODYSPLASIA OSSIFICANS PROGRESSIVA?

Fibrodysplasia ossificans progressiva (FOP) is a genetic disorder characterized by progressive, cumulative, and irreversible heterotopic ossification (HO) in soft and connective tissues, which restricts movement and leads to severe disability and a shortened life expectancy[1,2]

FOP is an ultra-rare, severely disabling genetic disorder



Prevalence is estimated to be up to 1.36 per million individuals[3]

Classic FOP
97% of cases
characterized by malformations of the great toes present at birth and occurrence of HO in specific anatomic patterns

Atypical FOP
3% of cases
have a non-classic disease course and additional or missing typical features

FOP FEATURES[5]

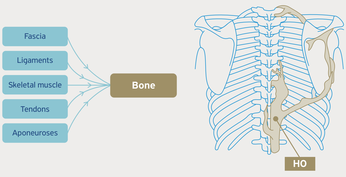
- **Bilateral malformation of the great toes**
- **Shin bone osteochondromas**
- **Spine malformations**
- **Short, broad femoral necks**
- **Hearing impairment**
- **Shortened thumbs**

ADDITIONAL ATYPICAL FEATURES[5]

- Severe variable reduction of the digits
- Cataracts, retinal detachment, childhood glaucoma
- Cerebellar abnormalities, mild cognitive impairment, seizures
- Absence of finger or toe nails
- Sparse hair

HETEROTOPIC OSSIFICATION

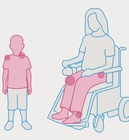
Heterotopic ossification (HO) transforms soft and connective tissues into ribbons, sheets, and plates of extra bone throughout the body[1]



FLARE-UPS

HO is often preceded by sporadic and unpredictable episodes of soft-tissue swelling, pain, reduced movement, stiffness, and warmth, referred to as "flare-ups"[6]

Flare-ups are more frequent in the **upper limbs before 8 years of age**[6]



Flare-ups are more frequent in the **lower limbs after 8 years of age**[6]

Flare-ups affecting the hips are among the most disabling and painful, and can take longer to resolve than other flare-ups[6]

QUALITY OF LIFE

FOP is a severely disabling disease associated with decreased quality of life (QoL). Pain severity is significantly negatively correlated with:[7]

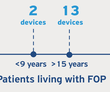
45–74% of patients reporting "moderate to severe" pain (≥4; 0 to 10 pain scale) reported anxiety, depression or irritability[7]

36–48% of patients reported emotional problems during "no pain" to "mild pain" states[7]

DISEASE PROGRESSION

Disability in FOP is cumulative and patients living with FOP require lifelong assistance in performing activities of daily living[2,8]

International Fibrodysplasia Ossificans Progressiva Association (IFOPA) registry data showed an increase in the median number of assistive devices with age:[8]



Most patients become immobilized and confined to a wheelchair by their third decade of life[2]

Patients living with FOP reach a median age of 56 years; death is often due to cardiorespiratory failure as a result of respiratory insufficiency or thrombosis[9]

Patients living with FOP

Life expectancy at birth in the European Union[11]

Life expectancy at birth in the United States[10]

General population

DIAGNOSIS AND MISDIAGNOSIS

Misdiagnosis and delayed diagnosis can contribute to the accumulation of disability in patients living with FOP[1,2]

1.5 years
is the mean time for patients to receive a diagnosis after symptom onset…[13]

…after consultation with a mean of **3.3 HCPs**[13]

Diagnosis takes longer in patients who have atypical FOP compared with classic FOP[13]

Atypical FOP
Mean age at diagnosis: **18.6 years**

Classic FOP
Mean age at diagnosis: **7.0 years**

FOP is **misdiagnosed** in **slightly over half** of individuals (**52.5%**)[13]

A 2001–2002 survey of IFOPA members found that, as a result of FOP misdiagnosis:[12]

68%
received inappropriate therapies

67%
of respondents underwent unnecessary biopsies

49%
reported permanent loss of mobility resulting from invasive medical interventions that caused post-traumatic ossification

TREATMENT

There are currently no effective treatments to prevent HO in FOP; therapeutic approaches are limited to symptom management and flare-up prevention[1,4]

Consequently, there is a critical unmet need for disease-modifying therapies for patients living with FOP

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Mechanism of Disease in FOP

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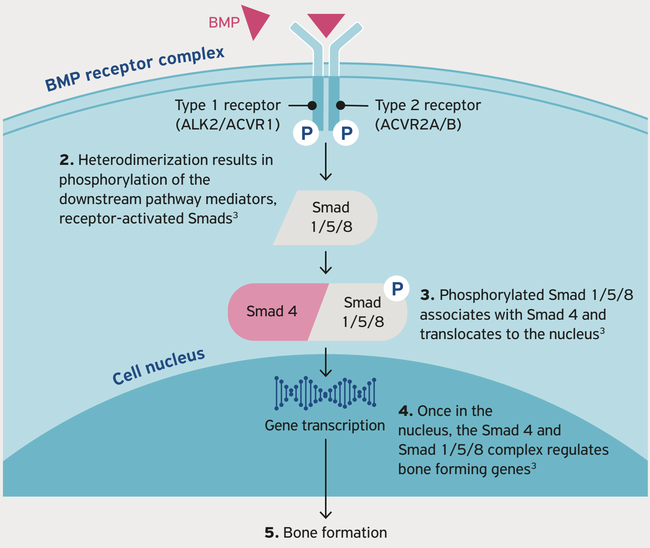
CELL SIGNALING IN NORMAL BONE FORMATION

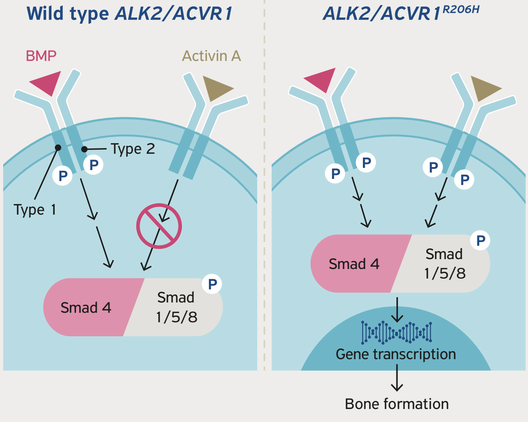
Bone morphogenetic proteins (BMPs) are a group of signaling molecules with a role in bone and cartilage formation. BMPs signal through cell surface receptor complexes that consist of two distinct transmembrane serine/threonine kinase receptors, Type 1 and Type 2[1]

1. In the absence of mutations, BMPs bind to the Activin Receptor-Like Kinase 2 (ALK-2)/Activin A Receptor Type 1 (ACVR1) receptor, which induces heterodimerization with the Type 2 receptor[2]



CELL SIGNALING IN FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

Almost all patients with fibrodysplasia ossificans progressiva (FOP) carry the same gain-of-function *ALK2/ACVR1* gene mutation, R206H[4]



Signaling molecules of the transforming growth factor (TGF)-β superfamily, including BMPs and Activin A, bind to the ALK2/ACVR1 receptor[5]

Activin A regulates processes such as myogenesis, skeletogenesis, and muscle and bone metabolism and repair[6–9]

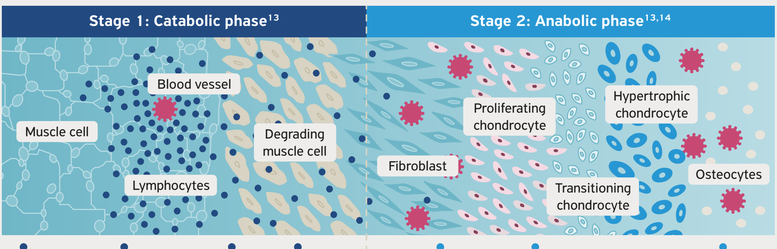
In FOP:

The R206H mutation alters ALK2/ACVR1 response to Activin A[10]

Activin A binding in FOP leads to phosphorylation of Smad, causing new bone formation[10]

DISEASE PATHOGENESIS

Soft and connective tissues are replaced by ribbons, sheets, and plates of heterotopic bone through a process of endochondral ossification that leads to an accumulation of bone and progressive restriction of movement[11,12]



Normal skeletal muscle

Stage 1A

Early FOP lesions contain intense mononuclear and perivascular infiltrates

Stage 1B

Intramuscular invasion

Stage 1C

Migration of mononuclear inflammatory cells into affected muscle precedes widespread death of skeletal muscle

Stage 2A

Fibroproliferation and angiogenesis: Histologically indistinguishable from aggressive juvenile fibromatosis,[15] but replete with BMP2/4 expression in lesional cells

Stage 2B

Chondrogenesis: Fibroproliferative tissue undergoes metamorphosis to bone through heterotopic endochondral ossification

Stage 2C

Osteogenesis: The resultant new ossicle of heterotopic bone is histologically normal and contains marrow elements

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