

# Fibrodysplasia Ossificans Progressiva (Stone Man Disease)

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## I. Introduction

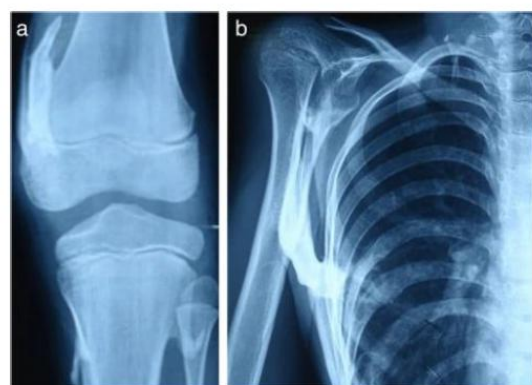
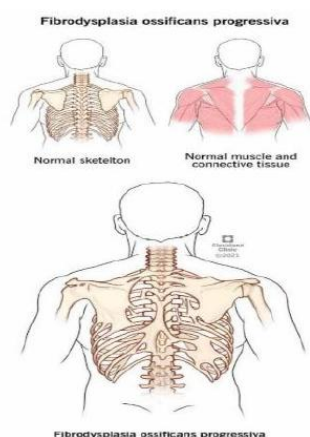
Fibrodysplasia Ossificans Progressiva (FOP), also colloquially termed “Stone Man Disease,” is one of the rarest and most disabling genetic conditions known to medicine. Characterized by progressive heterotopic ossification (HO), this disorder causes soft connective tissues, such as muscles, tendons, and ligaments, to transform into bone outside the normal skeletal framework. The prevalence is approximately 1 in 1.5 to 2 million individuals worldwide, with no ethnic, racial, or geographic predilection. First described in the 17th century and later defined in greater detail by Drs. Victor McKusick and Frederick Kaplan, FOP is a devastating and life-altering condition with no definitive cure to date.

## II. Explanation in Detail

FOP is caused by mutations in the **ACVRI** gene (Activin A receptor type I), which encodes a bone morphogenetic protein (BMP) type I receptor. This receptor is part of the **TGF- $\beta$  (Transforming Growth Factor Beta)** signaling pathway, which plays a critical role in skeletal development. The mutation leads to inappropriate activation of the BMP pathway, even in the absence of ligands, triggering osteogenesis in non-skeletal tissues.

Patients with FOP typically appear normal at birth, except for characteristic malformations of the great toes. However, within the first decade of life, they begin to experience episodes of painful soft tissue swellings known as "flare-ups," which often occur spontaneously or after trauma, such as injections or muscle injuries. These flare-ups resolve with the formation of heterotopic bone, progressively restricting movement and leading to cumulative disability.

The disease follows a characteristic anatomical pattern, beginning in the neck and shoulders and advancing to the trunk and limbs. Over time, this process can lead to complete ankylosis of nearly all joints, rendering the individual immobilized.





### III. Symptoms

Key clinical features of FOP include:

- **Congenital toe malformations:** Typically, hallux valgus or monophalangism of the great toes.
- **Painful flare-ups:** Episodic swelling in soft tissues, often mistaken for tumors or infections.
- **Progressive ossification:** Formation of bone in muscles, tendons, and ligaments.
- **Restricted movement:** Loss of joint mobility over time due to ankylosis.
- **Respiratory issues:** Ossification of intercostal muscles and diaphragm reduces pulmonary function.
- **Hearing loss:** Due to ossification of the middle ear ossicles in some cases.

It is critical to note that cognitive functions remain unaffected.

### IV. Causes

The root cause of FOP is a **mutation in the ACVR1 gene**, specifically the recurrent **c.617G>A (R206H)** missense mutation found in almost all classical cases of FOP. This gain-of-function mutation leads to ligand-independent activation of the BMP signaling pathway, resulting in ectopic bone formation. FOP is inherited in an **autosomal dominant** manner; however, most cases are **sporadic**, resulting from **de novo mutations**. There is no known environmental factor that directly causes the disease, though trauma can precipitate flare-ups in genetically susceptible individuals.

### V. Diagnosis

**Diagnosis of FOP** is primarily clinical but should be confirmed via genetic testing. Key diagnostic criteria include:

- Congenital malformation of the great toes.
- **Progressive heterotopic ossification**, particularly after minor trauma or spontaneously.
- **Radiographic evidence** of heterotopic bone formation.
- **Genetic confirmation** of the ACVR1 R206H mutation using molecular testing.

Misdiagnosis is common, especially early in life, with many patients initially thought to have soft tissue tumors, muscular dystrophies, or juvenile fibromatosis. Biopsies are strongly discouraged due to the risk of exacerbating ossification.

### VI. Treatment

There is **no known cure** for FOP as of 2025. Management is primarily supportive and aimed at reducing flare-ups and preserving function.

**Management strategies include:**

- **Avoidance of trauma:** Intramuscular injections, surgical procedures, and dental work should be minimized or done under expert guidance.

- Pharmacologic interventions: **Corticosteroids** (e.g., prednisone): Short courses may help during early flare-ups.
- **NSAIDs and COX-2 inhibitors**: For pain and inflammation.
- **Bisphosphonates**: Have been explored, though with limited efficacy.
- Experimental therapies: **Palovarotene** (a RAR $\gamma$  agonist): Currently under clinical trials and shows promise in reducing HO.
- **Monoclonal antibodies targeting ACVR1** or BMP ligands.
- **Gene therapy and CRISPR-based interventions** are being studied but remain experimental.
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Physical therapy is controversial—while beneficial for maintaining joint function in some conditions, it can provoke flare-ups in FOP. Surgical removal of heterotopic bone is contraindicated, as it often triggers more aggressive ossification.

## VII. Summary

Fibrodysplasia Ossificans Progressiva is a rare, profoundly disabling genetic disorder resulting from mutations in the ACVR1 gene. Characterized by progressive heterotopic ossification, FOP leads to cumulative loss of mobility and severe physical impairment. Despite the absence of a cure, early diagnosis and careful management of flare-ups can mitigate complications. Ongoing clinical trials and research into molecular targets offer hope for future therapeutic breakthroughs.

## VIII. Case Study

### Case Study: Mohammed Almir

Mohammed Almir, a kid from the Kalyan- Maharashtra- India, is one of the individual livings with FOP. He is currently 8 years old and at the age of 3, FOP was diagnosed for him. Initially he found difficulty in walking and slight puffiness in chest portion and on back as he fell down in school during playing. Currently he is unaware about the disease.

Almir's case exemplifies the need for early, accurate diagnosis and the dangers of invasive interventions. He also personifies the strength and adaptability of individuals with chronic and disabling conditions.

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