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**REVIEW ARTICLE**

# Fibrodysplasia Ossificans Progressiva *an* ACVR1 *Gene Mutation*

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**ABSTRACT**

It is a rarest and most severe genetic disabling disease which may effect on the muscles and leads to irreversible muscle to bone termination, which may cause a worse body shape of human body. This disorder was affects 1 out of 2000000 people, around 3500 people are affected till now throughout the world. In that 850 cases are disposed. It's an impulsive and post traumatic flare-up shown by intense connective tissue edema with perivascular lymphocytic penetration into skeletal muscle. Angiogenic fibopriline ferative lesions. Surgery makes the condition worse Formation of FOP bones is only occurs before the age of 10. Bone surgery and opiods are the common treatments.

**Keywords:** Fibrodysplasiaossificans progressiva, connective tissue, flare-ups, ACVR1 gene

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**CONTENTS**



## 1. Introduction

It is a rarest and most severe genetic disabling disease which may effect on the muscles and leads to irreversible muscle to bone termination, which may cause a worse body shape of human body. [1] This situation was characterized by the frequent episodes of soft tissue painfulness and swelling and the formation of sub cutis and muscle tissue tumours development FOP – Fibrodysplasiaossificans progressiva means process of formation of bone within the muscle at the site of the injured place making abnormal and significant growth of fibrous tissue. [2]

**Fibro dysplasia** = Fibrous + dysplasia = Abnormal and significant growth of Fibrous tissue

**Ossificans** = Formation of bone within the muscle at the site of the injured place

**Progressive** = Process

**Etiology**

When compare with black race FOP mainly occure in whites due theire gene defects and immunity problems. [3]

This disorder was affects 1 out of 2000000 people, around 3500 people are affected till now throughout the world. In that 850 cases are disposed. Gender and ethnicities are victims for this FOP. FOP typically starts in early embryonic stage with utero engrossment and skeleton distortion at the time of natal. [4]

## 2. Discovery of FOP

In the era (17 century) of Jan 1, 1601 to Dec 31, 1700 of Gregorian calendar was a major significant days which raised the effect of FOP. The FOP was identified by French physician in England from a male patient on 1692 in England. [5]

**Discovery of FOP Gene**

Mysterious. It is a hereditaryautosomal overriding disorder with complete dissemination but variable gene perspicuity. Findings suggest that FOP maps to band 4q27- 31, a region that contains at least 1 gene involved in the BMP (Bone morphogenetic protein) gesticulating alleyway [6, 7 and 8].

- BMPs are memberships of the transforming growth factor beta family, used in the enhancement of bone and other tissues. The condition is multifocal, starting to develop usually after traumatisation.
- A recurrent mutation in the BMP type-I receptor ACVR1causes hereditaryand sporadic FOP. In one study, it was mapped to 2q23¬24 by linkage scrutiny.
- In order to identify the chromosomal locus for the FOP gene, a conservative genome-wide linkage investigation was accompanied using a subset of five families with the most severe and unmistakable features of FOP.
- This approach acknowledged linkage of FOP to 2q23–24. The gene indoctrinationactivin receptor IA (ACVR1) [also known as activin-like kinase 2 (ALK2)], a BMP type I receptor, was recognized in the linkage interval.
- DNA sequencing of the ACVR1 gene determined that the same heterozygous mis-sense metamorphosis in the glycine–serine (GS) activation domain (c.617G>A; R206H) occurs in all typically affected individuals inspected.The detection of the FOP gene was the culmination of a colossal 15-year search.
- The FOP gene in the 17q21- 22 region had been observed with several trans figurations describedin the NOG gene (located in 17q22) in 4 FOP patients, including the G91C mutation, which was transmitted dominantly in a Spanish fop family.
- This alteration is a guanine to adenine change at nucleotide 283 (283G>A) of the NOG gene and was transmitted by the affected mother to her 2 affected children.
- Impulsive and post traumatic flare-ups shown by intense connective tissue edema with perivascular lymphocytic penetration into skeletal muscle. Angiogenic fibopriline ferativelesions.
- That feasts along the muscles planes and evolves through endo-condral ossification to form mature lamellar bone. Leads to immobilisation of joints making programme unbearable, later death due starvation (aknylosis of jaw) from preventive disease of chest wall. May be mediated by mast cells. [9]

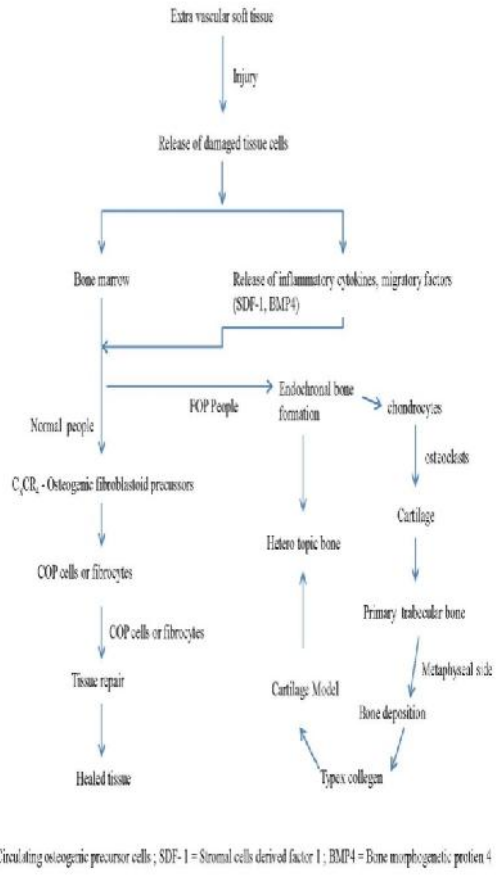


**Figure 1:** Process of Ossification

**Figure 2**

## 3. Clinical Features and Diagnosis of FOP

- Characteristic malformations of the great toe
- Flare- ups occur spontaneously or following bodily trauma such as:
- Child hood immunizations, falls while playing, and viral illnesses.

- Precocious soft tissue swelling, Pain or less movement in the shoulders, arms, chest areas and finally on the feet. Cervical vertebrae, Heterotopic ossification, the bone extend from lance to the pelvix.
- Surgery makes the condition worse Formation of FOP bones is only occurs before the age of 10. [10]

**Diagnosis**

Routine biochemical assessments of bone mineral metabolism are usually normal, although serum alkaline phosphatase activity may be elevated, especially during disease flare-ups.Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of fibroproliferative lesions. Nephrolithiasis is more common in olderpatients with FOP, and may be due to increased immobilization and dehydration in the setting of generalized increased bone remodelling and mineral turnover [11].

- Biochemical analysis of alkaline phosphate
- Bone-specific alkaline phosphatise
- Osteoma cutis and
- X- ray & CT Scan
- Misdiagnosed in a majority of cases as: cancer, aggressive juvenile fibro mitosis and fibrous dysplasia

**Awareness of Fop**

The mutant ACVR1 gene that causes muscles, joints, tendons, and connective tissue to turn to bone was discovered 10 years ago on April 23rd. In the rare disease community, this is a huge deal. Knowing the gene for a rare disease is over half the battle. Since that time, strides have been made at finding a treatment. [12]


**Figure 3**

## 4. Management of FOP

This very brief guide will summarize the current symptomatic management of FOP.

**Activities:** Evade soft tissue injuries, contact sports, overstretching of soft tissues and muscle fatigue. Evade biopsies, surgical removal of heterotopic bone and all non-emergent surgical procedures.

**Anesthesia:** A general anesthesia is necessary, to perform awake intubation by nasotrachealfibre-optic technique

Falls: Protected upper limbs may accentuate head trauma from falls. Epidural haematomas are common (surgical emergency). Use protective headgear in children who have upper limb involvement

**Flare-up (back/chest):** Use non-steroidal anti-inflammatory medications with gastrointestinal precautions. Use analgesics and/or muscle relaxants, as desirable.

**Flare-up (limbs/throat):** Prednisone – 2 mg/kg PO once daily for 4 days; begin within first 24 h of flare-up. Keep medication on-hand for emergencies. Use analgesias and/or muscle relaxants, as needed, with gastrointestinal precautions.

**Flare-ups (protection):**

Most flare-ups result from over-use and soft tissue injuries. Prednisone 2 mg/kg PO once daily for 3 days to prevent flare-up after severe soft tissue injury. Do not use after minor bumps or bruises

**Hearing:** Conductive hearing damage is common. Perform periodic audiology assessments. Hearing aids may improve conductive hearing loss

**Immunizations:**

Evade all intramuscular immunizations. Subcutaneous immunizations are acceptable when FOP is quiescent. Evade any immunizations during flare-ups

**Influenza:**

Administer influenza vaccines subcutaneously, but never during flare-ups. Evade live attenuated flu vaccine; it may cause flu-like symptoms and exacerbate FOP. Household contacts of FOP patients should be immunized annually.

**IVs:** Superficial IV access and venipuncture is satisfactory. Traumatic IVs and arterial punctures may cause HO.

**Limb swelling:**

Lymphedema and transient neuropathy may occur with flare-ups of limbs. Elevate legs while sleeping and recumbent. Use support stockings. Take one baby aspirin daily with food. Rule-out deep vein phlebitis with Doppler ultrasound.

**Occupational therapy:** Perform periodic occupational therapy evaluations as activities of daily living change

**Physiotherapy:** Evade passive range of motion. Warm water hydrotherapy may be helpful

**Pulmonary function:**

Perform baseline pulmonary function tests and echocardiogram. Repeat periodically. Supplemental oxygen should not be used in an unmonitored setting

**School:** Use school aides to protect and assist children. Request medical letter and preschool evaluation.

**Surgery:** Evade surgery, except in emergencies

**Teeth:** Evade mandibular blocks, overstretching of the jaw and muscle fatigue.

**Present Scenario**

- The discovery of the FOP gene reveals a highly conserved target in the transforming growth factorbeta/bone morphogenetic protein signaling pathway and compels therapeutic approaches for the development of small- molecule signal transduction inhibitors for activinkinase- 2
- Effective therapies for fibrodysplasia ossificans progressiva may be based on blocking activin kinase¬2 or blocking of active in receptor IA/activin–like kinase 2 signalling.
- FOP is actually in clinical trials with Clementia pharmaceuticals as we speak and many other things are on the horizon. [15]

## 5. Prevention

**General:** There is currently no known method of prevention for fibro dysplasiaossificansprogressiva (FOP). Most cases occur randomly and are not passed down among families. Below are some ways to help prevent flare-ups and reduce the risk of FOP complications.

**Evade unnecessary intramuscular injections:**

Injections into the muscle are considered dangerous for FOP patients because they may trigger a flare-up and bone formation at the injection site. Immunizations and local anesthetics are two types of shots that are given intramuscularly. Once a person is diagnosed with FOP, intramuscular injections should be Evadeed. Most children have already received the standard childhood immunizations before they are diagnosed with FOP. Injections that are given underneath the skin are generally considered safe for people with FOP.

**Good oral hygiene:** If extra bone develops in the jaw joints, a person may have difficulty speaking or eating. Therefore, preventative care of the jaw and mouth is especially important. If individuals practice good hygiene, they are less likely to need dental procedures, which can trigger flare-ups of FOP.

Minimize the risk of traumatic injuries, Diagnose the pregnant women whether there is any FOP background in family, Observe the children under 10 years of age.

**Living FOP People**

The living statue who refuses to give up is Ashley, 31, on living with rare condition that slowly turns her muscles to bone and has already robbed her of one arm. She'ssuers from Fibrodysplasia Ossifficans Progressiva. Just 800 people worldwide have the illness which turns muscle to bone She has already lost an arm and the movement in one leg to the condition. [17]

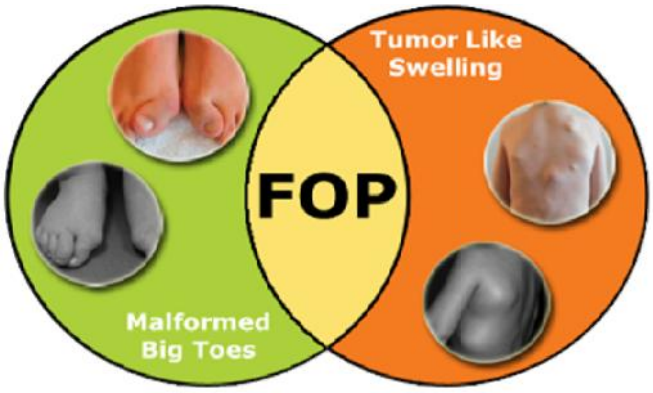


**Figure 4**

## 6. Conclusion

In conclusion, FOP is an extremely rare case. By far, this is the first case of FOP found and reported in Indonesia. It is difficult to diagnose and manage FOP, therefore delayed or misdiagnosis and also inappropriate management is common.

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