Review Article

# Stone Man Syndrome: A Rare and Debilitating Genetic Disorder with a Misguided Immune Response

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## Abstract

Stone Man Syndrome, also known as Fibrodysplasia Ossificans Progressiva(FOP), is a rare genetic disorder characterized by progressive bone formation and connective tissue ossification. The condition affects approximately 1 in 2 million people worldwide and typically becomes apparent during early childhood. Individuals with Stone Man Syndrome experience the formation of extra bone in their muscles, tendons, and ligaments, which eventually leads to joint immobility and skeletal abnormalities. The condition progresses gradually and often leads to the fusion of the spinal column and rib cage, resulting in respiratory problems and limited mobility. FOP is caused by a mutation in the ACVR1 gene, which encodes a protein involved in bone formation and repair. The mutation leads to the activation of a specific signalling pathway, causing the body to produce excess bone tissue in response to injury or trauma. Currently, there is no cure for Stone Man Syndrome, and treatment options are limited. Physicians can only manage the symptoms of the condition and help patients maintain mobility through physical therapy, pain management, and surgery. However, surgery can be risky due to the risk of triggering new bone formation. The diagnosis of Stone Man Syndrome is typically based on clinical evaluation and genetic testing. Early diagnosis is critical to developing effective treatment plans and providing support for patients and their families. In conclusion, Stone Man Syndrome is a rare genetic disorder characterized by the progressive formation of extra bone tissue, leading to joint immobility and skeletal abnormalities. Although there is currently no cure for the condition, early diagnosis and management of symptoms can improve patients' quality of life.

**Keywords:** Progressive osseous heteroplasia , Osteosarcoma, lymphedema, Soft tissue sarcoma, Desmoid tumors, Aggressive fibromatosis, Heterotopic ossification

## Introduction

FOP also known as Stoneman Syndrome, is an extremely rare genetic disorder that causes the formation of bone outside the skeletal system, particularly in muscles, tendons, and ligaments. This extra-skeletal bone formation leads to a limited range of motion and can severely impact an individual's quality of life. Typically, this disorder becomes apparent in early childhood, starting in the neck and shoulders and gradually progressing down the body and into the limbs. Individuals with FOP may also exhibit malformed toes, along with skeletal abnormalities and growths, making it a distinct disorder from other muscle and skeleton-related diseases. The extra bone growth can lead to the loss of mobility as the joints become affected, and can also cause difficulty in speaking and eating due to limited mouth opening. Breathing difficulties can also occur due to bone growth around the rib cage, which restricts lung expansion. Trauma to the muscles, such as falls or medical procedures, can trigger inflammation and rapid ossification, as can viral illnesses like influenza. Malnutrition

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may occur due to eating problems caused by FOP, leading to further complications. It's important to note that these characteristics remain relevant and up-to-date.[1,2]

## Methodology

This comprehensive review provides insightful information on Stone Man Syndrome including updated details on possible treatments in all areas. The information was collected through a computerized search from various research articles and reputable websites especially research-based search engines like Google Scholar, EMBASE, Research Gate, PubMed etc.

## Background

Stone Man syndrome condition is characterized by the gradual replacement of soft tissues such as mu0scles, tendons, and ligaments with bone, which restricts movement and can lead to severe disability. The research article on Stone Man syndrome aims to provide a comprehensive review of the current knowledge about the disorder, including its clinical features, genetics, and pathophysiology. The article will also explore the diagnostic criteria and treatment options available for patients with FOP. The study will draw on a wide range of sources, including published literature, medical databases, and case reports, to provide a comprehensive overview of the current state of research on FOP. The article will be of interest to clinicians, researchers, and patients and families affected by the disorder. The ultimate goal of this research article is to contribute to a greater understanding of Stone Man syndrome and to improve the diagnosis and treatment of this debilitating condition.

## Epidemiology

FOP is an incredibly rare disease, with only around 800 cases confirmed worldwide as of 2017. This rarity means that FOP is considered one of the most uncommon diseases known to man. Despite its low prevalence, FOP affects people of all ethnicities and has an estimated incidence of 0.5 cases per million individuals. It's important to note that these statistics remain current and relevant to this day.[3]

## Etymology

The term "Stone Man Syndrome" is a colloquial name for the medical condition known as **Fibrodysplasia Ossificans Progressiva (FOP)**. The name Stone Man Syndrome is derived from the appearance of patients with the condition, who gradually develop a hardened, stone-like appearance due to the formation of extra bone tissue. The formal medical name for the condition, Fibrodysplasia Ossificans Progressiva, is derived from its key features. "Fibro" refers to fibrous tissue, "dysplasia" refers to abnormal development, "ossificans" refers to the formation of bone tissue, and "progressiva" refers to the progressive nature of the disorder. The term "Fibrodysplasia Ossificans Progressiva" was first used in medical literature in the early 20th century to describe a patient with the condition. The colloquial term "Stone Man Syndrome" emerged later as a way to describe the condition to the general public, and it has since been used in media and popular culture. Overall, the etymology of Stone Man Syndrome and Fibrodysplasia Ossificans Progressiva reflects the medical features of the disorder and the physical appearance of affected individuals.[4]

## History

The first recorded medical reports of individuals affected by FOP can be traced back to Dr. Guy Patin in 1692. Initially referred to as myositis ossificans progressiva, the disease was believed to be caused by muscular inflammation (myositis) that resulted in bone formation. However, in 1970, Victor A. McKusick renamed the disease after discovering that soft tissues such as ligaments were also affected by the condition.

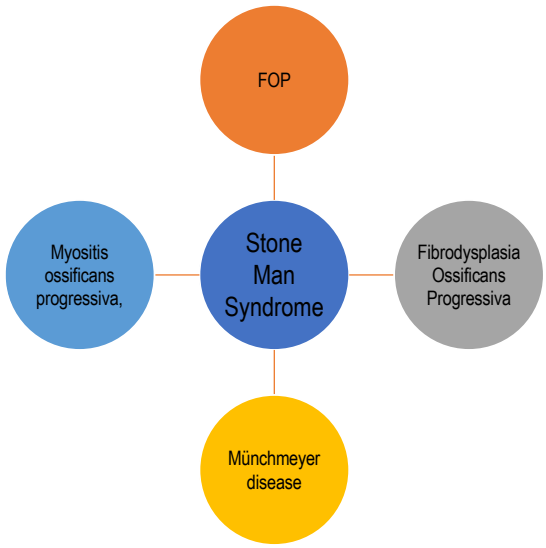
One of the most well-known cases of FOP is that of Harry Eastlack (1933-1973), whose symptoms began at the age of ten. By the time of his death from pneumonia in November 1973, just six days shy of his 40th birthday,

Eastlack's entire body had ossified, leaving him only able to move his lips. Throughout his life, he never had the opportunity to meet another person with FOP. However, Eastlack generously donated his body to science, and his skeleton now resides at the Mütter Museum in Philadelphia, where it serves as a vital resource for the study of FOP. Carol Orzel (April 20, 1959 - February 2018), another individual with FOP, also donated her body to the museum, and her skeleton was put on display next to Eastlack's in February 2019.[5,6]

## Definition

FOP is an uncommon and progressive disorder that affects connective tissue, and it is caused by a genetic mutation in the body. The ACVR1/ALK2 gene is where the mutation is known to occur, although much about the condition's pathophysiology remains unclear. FOP affects approximately one in two million people and is defined by the development of bone outside of the skeleton in response to soft tissue damage. This can happen as a result of a variety of factors, including viral infections, intra-muscular injections, falls, muscular stretching, and fatigue.[7]

## Other Names




## CAUSES

FOP is caused by a mutation in the **ACVR1 gene**, which provides instructions for making type 1 receptors that respond to a protein called BMP, found in cartilage and muscles.

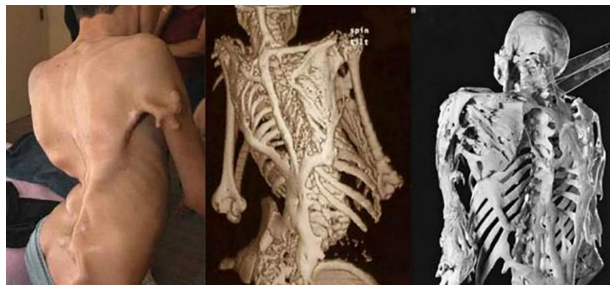
BMP controls the growth and development of muscles and bones. In individuals with FOP, the ACVR1 mutation results in the receptor being always turned on, like a light switch that cannot be switched off. FOP is inherited in an autosomal dominant pattern, which means only one parent needs to pass on the altered gene to their child for the child to inherit the condition. There is a 50% chance of a child inheriting the condition if one parent has the FOP gene. Most cases of FOP are caused by a new mutation in the ACVR1 gene (de novo), and the gene is not necessarily present in the family history. These mutations occur randomly.

## CLINICAL FEATURES

Due to the rarity of FOP, it can sometimes be mistaken for other, less severe muscular disorders. However, the distinct symptoms of FOP make it relatively easy to diagnose. If an individual or their blood relatives have this genetic disorder, there is a high likelihood that it will be passed down to their offspring. Signs of FOP can be observed in the toes and thumbs of Newburn babies, who may have malformed big toes and thumbs. As children with FOP grow, they may exhibit other symptoms of the condition, such as:

- Restricted movements of the joints, particularly neck and shoulders at the primary stages.
- Deformed spine.
- Frequent inequity while moving shadowed by low-grade fever, inflammation, and joint pain.
- Surface reflection of nonstandard bone growth all over the body (except the diaphragm, tongue, cardiac muscle, extraocular muscles and smooth muscle).
- Difficulty in breathing, eating, and speaking.
- Hearing impairment.
- Visible swelling in the affected area.

These symptoms will get more spartan as the child raises, as the tissues not only ossify in the upper region of the body, but also makes their way downhill to the trunk, back, hips, and limbs till a person completely gets powerless.



## DIFFERENTIAL DIAGNOSIS & PITFALLS

The list of potential diagnoses includes progressive osseous heteroplasia, osteosarcoma, lymphedema, soft tissue sarcoma, desmoid tumors (also known as aggressive fibromatosis), aggressive juvenile fibromatosis, and non-hereditary (acquired) heterotopic ossification.[8]

## TREATMENT

There is currently no known cure for genetic disorders such as fibrodysplasia ossificans progressiva. Surgical removal of the affected bone may actually lead to the growth of new, more painful heterotopic bone. To address this, medical professionals have developed several medications that can slow down the growth and intensity of ossification:

- In the early stages of FOP, a high dosage of corticosteroids such as Prednisone can be used to reduce pain and swelling flare-ups. It is important to administer this medication within 24 hours of the first flare-up. NSAIDs are typically recommended to be given between flare-ups, rather than during an active flare-up.

- Muscle relaxants.
- Mast cell inhibitors.
- Aminobisphosphonates.
- Assistive devices such as struts or special shoes to help with walking.
- Occupational therapy.

During the course of treatment for fibrodysplasia ossificans progressiva, it is important to monitor for anything that may increase ossification and physical discomfort. Procedures and medical diagnoses involving bone, such as biopsies, intramuscular injections, and jaw stretching during dental procedures, should be avoided to prevent damage to the skeletal system and the potential for a flare-up of ossification in the affected area. It is also important to avoid injury, as blunt trauma can cause a flare-up in the heterotopic bone. Physical activities that pose a risk of falls or other injuries should be restricted. FOP can be particularly dangerous for pregnant women, and it is advised to avoid childbirth if she has this genetic disorder for two main reasons. **Firstly**, her faulty genetics can be passed down to her offspring, making their survival difficult for the rest of their lives. **Secondly**, the growing foetus in the mother's womb can increase the risk of flare-ups, which can be life-threatening for **both mother and baby.**[12]

## COMPLICATIONS

In addition to causing pain, inflammation, and swelling, the extra bone growth associated with FOP can eventually expand to affect other areas of the body. This can include the chest, leading to compression of vital organs such as the lungs, heart, and oesophagus. This can result in difficulty speaking, eating, or walking in the later stages of the disease, and in severe cases, can cause respiratory infections and heart failure. Heterotopic bone growth can also cause curvature of the spine, either from side to side or top to bottom, making it difficult for individuals to walk and perform daily activities.

## PROGNOSIS

Individuals with FOP often experience changeable episodes of soft tissue pain, swelling, abridged movement, and stiffness, recognized as 'flare ups'. Although these flare-ups can be relieved without any specific course of treatment, it is important to manage them to reduce discomfort and slow down the formation of heterotopic ossification. Flare-ups can be identified by symptoms such as sudden pain, redness, bumpy or lumpy swelling, stiffness, and warmth in the affected area. They can be activated by daily tedious incidents and activities such as bodily injury or exhaustion, muscular stretching, medical procedures like intramuscular injections, dental procedures, or biopsy, or viral or bacterial infections. To manage flare-ups and their discomfort, it is important to avoid trigger points and follow medical prescriptions given by the doctor. Keeping track of the episodes and daily routine can help provide a better understanding of the severity of the illness. It is also important to share the concerns and track records with the doctors to receive the best-recommended treatment.[9]

## REPORTED CASES

**Case No. 1:** A 10-year-old female patient presented with congenital deformities of bilateral great toes and multiple focal, rubbery to hard, tender soft tissue swellings over the body, which had been progressively increasing. The patient had also been experiencing progressive bilateral hearing loss for four years. Some of the swellings had been hastened by numerous diagnostic measures like biopsies or by negligeable trauma. The patient had movement restriction at multiple joints, with associated skeletal deformities. There was no significant prenatal, perinatal or postnatal history, nor was there any other contributory family history. Physical examination supported the patient's complaints and demonstrated hallux valgus and dorso-lumbar scoliosis. The patient's biochemical indices were within normal limits, except for anaemia.[10]

**Case No. 2:** An 8-year-old male child was presented with complaints of multiple hard non-tender swellings over the neck, chest, and abdomen with restricted movements in the neck and back for the past 2 years and deformity of the great toe on both sides since birth. The patient had no history of pain or previous trauma, and there was no family history of similar complaints. Physical inspection presented multiple non-tender hard swellings in the neck, chest, and abdominal wall with bilateral hallux valgus deformity. The patient was indorsed radiographic evaluation.[11]

**Case No. 3:** A male child, weighing 30 kg and aged 11 years, was suspected to have cysticercosis due to multiple hard swellings on the nape of neck, paraspinal region, arms, thighs, and legs. Despite previous treatment with antitubercular drugs and albendazole, the patient had no remission. An excision biopsy of the back swellings was planned under general anesthesia. Pre-operative assessment revealed restricted neck movement, a Mallampati class III airway, and a mouth opening of 2.5 cm. All routine investigations were found to be normal, and the patient was induced with sevoflurane and propofol. During laryngoscopy with Truview PCD™ video laryngoscope (TVL), the Cormack and Lehane (CL) grade was III but improved to 2b with external laryngeal manipulation. The patient was intubated using a size 6.0 flexometallic endotracheal tube. During surgery, bony tissue was encountered in the nodules, and the surgeon became suspicious of FOP. The surgery was abandoned, and subsequent histopathology and skeletal survey confirmed the diagnosis of FOP. The patient was extubated after reversal of neuromuscular blockade and discharged 2 days later with post-operative pain management.[13]

## Conclusion

The research article on Stone Man Syndrome explores the clinical manifestations, pathophysiology, and management of the rare genetic disorder known as FOP. FOP is characterized by the formation of heterotopic ossification, which leads to progressive loss of mobility and eventual disability. The article highlights the importance of early diagnosis and management of FOP to prevent the progression of the disease. Diagnostic criteria, including genetic testing and clinical assessments, are outlined to aid in the diagnosis of FOP. Current treatment options, such as glucocorticoids and bisphosphonates, are discussed, along with emerging therapies, such as anti-Activin A monoclonal antibodies. Overall, the article emphasizes the need for increased awareness and understanding of FOP among healthcare providers and the public to improve the quality of life for individuals living with this debilitating condition.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| FOP | - | Fibrodysplasia Ossificans Progressiva |
| BMP | - | Bone Morphogenetic Protein |
| NSAIDs | - | Nonsteroidal anti-inflammatory drugs |
| ACVR1 | - | Activin A Receptor Type 1 |
| ALR | - | Alanine Racemase |

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**CONFLICT OF INTEREST**

Have no conflict of interest relevant to this article

**ETHICAL CLEARANCE**

Not required.

## References

1. Kamal G, Gupta A, Batla S, Gupta N. Anaesthetic management of a child with stone man syndrome: Look before you leap! Indian J Anaesth [Internet]. 2017 Mar 1 [cited 2023 May 4];61(3):266.
2. Fiori JL, Billings PC, Serrano De La Peña L, Kaplan FS, Shore EM. Dysregulation of the BMP-p38 MAPK signaling pathway in cells from patients with

fibrodysplasia ossificans progressiva (FOP). Journal of Bone and Mineral Research. 2006 Jun;21(6):902–9.

3. Martelli, Anderson; Santos, Arnaldo Rodrigues (3 July 2014). "Cellular and morphological aspects of fibrodysplasia ossificans progressiva: Lessons of formation, repair, and bone bioengineering". Organogenesis. 10 (3): 303–311. doi:10.4161/org.29206. PMC 4750545. PMID 25482313.
4. Piotto L, Taranath A. Fibrodysplasia ossificans progressiva: Diagnosis with ultrasound. Australas J Ultrasound Med. 2021 Aug 1;24(3):173–7.
5. McCullough, Marie (28 February 2019). "New Mutter Museum exhibit grants final wish for woman who turned to bone". The Philadelphia Inquirer. Retrieved 28 February 2019.
6. "Mütter Museum Reveals New Exhibit: Philadelphia Woman's Skeleton with Rare Bone Disease". Mütter Museum. 5 March 2019. Archived from the original on 28 August 2021. Retrieved 7 March 2020.
7. Orphanet: Stone man syndrome [Internet]. [cited 2023 May 10]. Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php
8. Fibrodysplasia Ossificans Progressiva: Causes, Symptoms, Treatment, Outlook [Internet]. [cited2023 May 10]. Available from: https://my.clevelandclinic.org/health/diseases/24476-fibrodysplasia-ossificans-progressiva
9. American Academy of Orthopaedic Surgeons (May 2006). "Fibrodysplasia Ossificans Progressiva (FOP)". orthoinfo.aaos.org. Archived from the original on 21 June 2012. Retrieved 7 October 2011.
10. Verma AK, Aga P, Singh SK, Singh R. Rare disease: The stone man disease: fibrodysplasia ossificans progressiva: imaging revisited. BMJ Case Rep [Internet]. 2012 [cited 2023 May 10];2012.
11. Dhivakar M, Prakash A, Garg A, Agarwal A, Dhivakar M, Prakash A, et al. Fibrodysplasia Ossificans Progressiva (Stoneman Syndrome) – A Rare Skeletal Dysplasia. Indian Journal of Musculoskeletal Radiology [Internet]. 2020 Jun 29 [cited 2023 May 10];2(1):69–72.
12. Stone Man Syndrome | Pivotal Motion Physiotherapy [Internet]. [cited 2023 May 4]. Available from: https://pivotalmotion.physio/stone-man-syndrome-fibrodysplasia-ossificans-progressiva/
13. "The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations" (PDF). International Fibrodysplasia Ossificans Progressiva Association. January 2020.