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A succinct review on fibrodysplasia ossificans progressiva - rare disease/orphan disease

Abstract

Rare (orphan) diseases are life threatening or chronically debilitating conditions that affect a small proportion of the population. Despite their individual rarity, over 7000 such disorders collectively affect hundreds of millions worldwide. Most are genetic, severe and associated with delayed diagnosis and limited therapeutic options. Small patient populations and reduced commercial incentives often hinder drug development, creating substantial unmet medical needs. Addressing rare diseases is therefore both a public health priority and a scientific opportunity as studying them frequently uncovers fundamental biological pathways relevant to more common conditions.

Fibrodysplasia ossificans progressiva (FOP) exemplifies these challenges. The present write up focuses on FOP, which is a progressive genetic disorder caused by mutations in the ACVR1 gene leading to heterotopic ossification in which soft tissues progressively transform into bone. This disabling process results in cumulative immobility and severe complications. At present, the treatment is mostly supportive, with lack of definitive cure. The urgent need for effective therapies underscores the importance of advancing targeted molecular strategies and innovative translational research to develop disease modifying interventions for FOP.

Keywords: Rare/orphan disease, FOP, genetic disorder, ossification, ACVR1 gene

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Introduction

A medical condition that affects a small percentage of population is called "Rare Disease" (RD). According to United States health standards a condition that affects fewer than 1 in 2000 people and fewer than 200,000 globally is considered a rare disease.[1] The term "Orphan disease" is also synonymously used due to the disease rarity resulting in little or no funding for the research and the drugs that are used to target these conditions are termed "Orphan drugs". There exist approximately 6000 distinct rare diseases, out of which 80 percent are of genetical origin.[2] The most prevalent rare diseases include, Fibrodysplasia ossificans progressiva (FOP)- also called stone man syndrome, Hutchinson-Gilford progeria syndrome, Methamoglobinemia, Urbach-Wiethe Disease, Darier's Disease, Creutzfeldt-Jakob disease, Felty's syndrome, Field's syndrome, RPI deficiency, Parry-Romberg syndrome.[3,4] Most of these rare diseases originate in early childhood. There is a great need to focus on the most prevalent of these rare diseases and government should provide funding for research targeting rare diseases. The prevalence of rare diseases differs across different geographical areas depicted in the following Figure 1.[5]

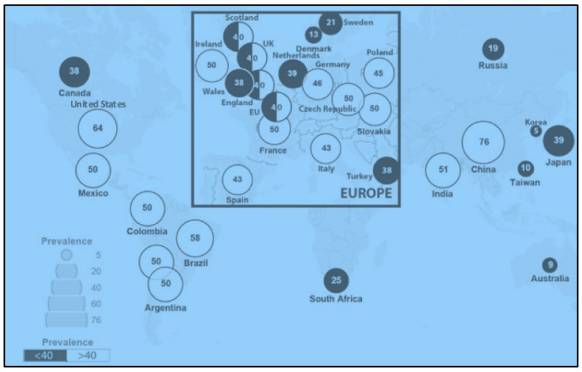

Figure 1 RD prevalence per 100,000 across jurisdictions.[5]

Fibrodysplasia ossificans progressiva (FOP)

Background

This rare disease is a connective tissue disease, where the connective tissues such as muscles, tendons, ligaments tend to ossify and result in the formation of bone. This newly formed bone fuses with the existing skeletal structure leading to mobility issues.[6] Due this reason this condition is also known as Stone man disease. The history of this rare condition dates to 1692. According to the statistics by 2017, about 800 cases of FOP have been reported and confirmed world widely. The world prevalence of FOP is approximately 1 in 2 million people making this disease the rarest among the rare diseases.[7]

The clinical presentation of FOP consists of heterotopic ossification- bone growth in areas of human body where normally bone is not present. The skeletal muscles and soft connective tissues gradually change into bones. The progressive symptoms of FOP include malfunction of major toes, chronic inflammatory swellings in various parts of the body, stiffness in joints, mild cognitive impairment, sparse scalp hair, severe growth retardation, mobility issues, difficulty in speaking and eating.[8,9] The onset of FOP in genetically predisposed individuals typically begins between the ages of 5-10.

Types of FOP

Classic FOP: A rare genetic disorder, usually caused by activating mutations in the ACVR1/ALK2 gene. Classic FOP presents in childhood with progressive heterotopic ossification that fuses muscles, tendons, and ligaments to the skeleton, leading to severe joint immobilization. Atypical forms are milder, with later onset and slower progression.

Progressive myositis ossificans (PMO): Also known as fibrodysplasia ossificans congenita, this condition involves progressive replacement of muscle and connective tissue with bone. It shares features with FOP but may differ in onset and progression, and episodes can be triggered by trauma or inflammation.

Progressive osseous heteroplasia (POH): A rare disorder characterized by abnormal bone formation in skin and soft tissues, often beginning in childhood. Unlike FOP, ossification is more diffuse and less associated with joint fusion, resulting in a distinct clinical presentation.

Occurrence of the condition

It is a rare disease that occurs via genetical inheritance, the transmission being autosomal dominant can be inherited via both parents. Being an autosomal dominant disorder, a child of an affected heterozygous parent and unaffected parent has a 50% probability of disease inheritance, and two affected individuals can produce an offspring who is unaffected. An offspring of two unaffected individuals could be affected due to mutation. The homozygous dominant form is more severe compared to heterozygous form.[10] FOP condition results due to a mutation in the gene ACVR1.[11] This ACVR1 gene encodes activin receptor type-1 and bone morphogenetic protein type-1. To determine the chromosomal location of the FOP gene, a genome -wide linkage analysis was performed in five families exhibiting the most definitive clinical features of FOP. The analysis mapped the disorder to the chromosome 2q23-24 region, which encodes the bone morphogenetic protein.[12] The mutation of ACVR1 gene causes a codon substitution at position 206, from arginine to histidine leading to missense mutation, destabilization of glycine-serine activation domain and abnormal activation of ACVR1, which in turn triggers the transformation of soft connective tissues and muscles into secondary skeletal structures.[13,14]

Individuals with FOP develop progressive restriction of movement as muscles and connective tissues gradually ossify. Symptoms typically begin in childhood in the neck and shoulders and extend downward over time. Trauma- such as surgery, falls, or viral illnesses -can trigger painful inflammatory flare-ups that accelerate new bone formation. Progressive ossification may impair jaw mobility, leading to difficulties with eating and speech, and involvement of the rib cage can restrict lung expansion, resulting in respiratory complications. The leading cause of mortality in patients with Fibrodysplasia ossificans progressiva is cardiorespiratory failure secondary to thoracic insufficiency syndrome.[15]

Diagnosis

Fibrodysplasia ossificans progressiva (FOP) is diagnosed by clinical features, imaging, and confirmation with ACVR1 gene testing. Key signs include congenital great toe malformations and recurrent painful soft-tissue swellings. Imaging shows characteristic extraosseous bone formation bridging joints; MRI and ultrasound detect early inflammatory lesions before ossification, and PET can identify metabolically active sites.[16,17]

Early radiologic recognition is essential to avoid biopsies or injections, as minor trauma can worsen disease progression. FOP is often misdiagnosed as cancer or infection, making clinician awareness critical.[18]

Definitive genetic testing is available for FOP and can confirm the diagnosis before the onset of heterotopic ossification. Early clinical suspicion- based on congenital malformation of the great toes and episodic soft tissue swelling- enables prompt genetic evaluation confirmation. Recognizing these early signs is critical to avoid unnecessary diagnostic procedures and harmful interventions, and to implement strict precautions to prevent trauma and iatrogenic injury.

Treatment

Currently, there is no cure for FOP, which is very unfortunate leaving the patients with palliative treatments such as medications to reduce inflammation. This reduces the flare ups that cause muscle damage. Symptomatic management of the condition includes treatment strategies such as pain management with high doses of corticosteroids, physical therapy assisting in maintaining mobility and function, preventing injuries as they flare up bone growth.[19] Prednisone is the widely for hospitalized patients, which is considered class 1 medication for acute flare-ups involving major joints. COX-2 inhibitors and NSAIDs are considered class 2 medications, used for symptomatic management of flare-ups and chronic arthropathy when corticosteroids are not indicated. Class 3 drugs include the new investigational drugs such as selective ACVR1/ALK2 signal transduction inhibitors.

A breakthrough in FOP treatment is Sohonos (palovarotene), the first FDA-approved therapy.[20,21] This selective RARγ agonist reduces new heterotopic ossification in eligible patients (males >10 years, females >8 years). However, long-term use is associated with retinoid-related adverse effects, including premature physeal closure in skeletally immature patients, decreased vertebral bone density, and increased fracture risk.

Future modalities

There has been a great amount of research done on targeted therapies for treatment of FOP. However, the studies are still in the preclinical stages. Developing new therapies for FOP is challenging due to its rarity and heterogeneity, incomplete understanding of its pathophysiology, limited availability of suitable animal models, and safety concerns, including the risk of triggering flare-ups.[22] The following Table 1 provides summary of investigational therapies for FOP.[23]

Table 1 Summary of some promising investigational studies[23]

Authors	Year	Study design	Intervention	Results
Zasloff et al.[11]	1998	Clinical trial	Isotretinoin	Decreased incidence of HO, but no prevention of flare-ups.
Chakkalakal et al.	2016	Preclinical study	Palovarotene	Palovarotene is efficacious for FOP in mice.
Pignolo et al.[12]	2023	Clinical trial	Palovarotene	Reduced new Heterotopic ossification volume and flare-ups per participant month of exposure
Williams et al.	2012	Preclinical study	saracatinib	Good candidate for preventing heterotopic ossification
Di Rocco et al.	2023	Phase II clinical trial	Garetosmab	Significantly reduced new Heterotopic ossification lesions in period 2 despite all patients experiencing treatment-emergent adverse events.

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Studies have been directed towards gene editing, for fixing the mutation in the ACVR1 gene.[24–26] Researchers aim to inhibit heterotopic ossification and promote healthy tissue regeneration by delivering mesenchymal stem cells (MSCs) to sites of abnormal bone formation.[27,28] Another potential approach is to utilize nanoparticle delivery that can transport the medication selectively to the affected area.[29–31] Several other strategies aiming at the BMP 1 and bone formation cycle targets are being studied for targeted therapy development. Currently 6 clinical trials are in process for the treatment of FOP.

Conclusion

Investigation of novel therapeutic targets in FOP may open new avenue in transforming disease management by slowing progression, enhancing symptom control, enabling targeted and personalized therapies, minimizing adverse effects, and expanding insight into bone biology—offering renewed hope for individuals affected by this debilitating condition.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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