

Case Report

Genotype-phenotype correlations in a case of fibrodysplasia ossificans progressiva: a case report

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is an ultrarare autosomal dominant genetic disorder. Most of the musculoskeletal characteristics of FOP are related to dysregulated chondrogenesis. Activating mutations of activin receptor A type I (*ACVRI*), a bone morphogenetic protein (BMP) type I receptor, are responsible for the skeletal and nonskeletal features. Characteristic features include congenital bilateral hallux valgus malformation and early-onset heterotopic ossification occurring spontaneously or, more frequently, precipitated by trauma. As disease progresses, thoracic insufficiency syndrome appears, with respiratory distress, pneumonia and right-sided heart failure. Diagnosis is confirmed by the identification of a heterozygous pathogenic variant in the *ACVRI/ALK2* gene. Avoiding unnecessary surgical procedures, prescribing prophylactic corticosteroids, preventing falls represent essential interventions for care management.

Key words: Heterotopic ossification, Hallux valgus malformations, Thoracic insufficiency syndrome

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant genetic disease affecting soft connective tissues. FOP is characterized by changes in muscles, tendons, and ligaments, converting them into bone through an endochondral ossification process.¹ Bone formation is a local inflammatory response, which subsequently triggers local chondrogenesis and osteogenesis. There is also a level of base line chronic heterotopic ossification (HO) present in FOP patients.

CASE REPORT

A 5 yr old girl child presented with multiple hard subcutaneous nodules 1-2 cm in diameter, in elbows, arms, knees, thighs, back, anterior chest wall. These nodules developed after intramuscular injections, vaccinations, trauma, even spontaneously (Figure 1). The

mother had felt small nodules in the posterior skull of the child, in infancy, which subsequently disappeared. At 4.5 yrs of age, the left knee joint was swollen, painful, with restricted movement. Within 2 months, she developed a firm to hard mass in the left buttock, following an intramuscular analgesic injection, and severely restricted movement and pain in the left hip joint. She was unable to sit, she could either stand, leaning on the right side or lie supine. O/E she had short broad great toes, scoliosis, severely restricted neck movement, and deformity in the thoracic cage, with a hard bony mass extending from left armpit to lowest rib. The protruding masses were bony hard, immobile, and painful. There was no difficulty in respiration, or chewing; jaw movement was normal. Intelligence, hearing and speech were all normal, with developmental milestones achieved age appropriately. X Ray -spine – scoliosis involving T4 – T7 vertebrae, X ray hand and foot – normal metatarso and metacarpo phalangeal joints.

Table 1: Whole exome sequencing report of proband.

Gene	Variant	Location	Zygosity	Disease	Inheritance	Variant classification
ACVR1	c.617G>A	Exon6	Heterozygous	Fibrodysplasia ossificans progressive	Autosomal dominant	Pathogenic

**Figure 1 (a and b): Heterotopic ossifications.**

The provisional diagnosis was fibrodysplasia ossificans progressive. Confirmed by Exome sequencing (Table 1).

DISCUSSION

Fibrodysplasia ossificans progressiva (FOP) is a rare, autosomal dominant genetic disorder, with a prevalence of 1 in 1.3 million-2 million.² FOP is characterized by congenital bilateral hallux valgus malformations and early-onset heterotopic ossification (bone formation outside the skeleton), either spontaneous or precipitated by trauma including intramuscular vaccinations.³ Hallux valgus malformations may be detected in prenatal scans.⁴ The first metatarsal is short, hallux valgus is malformed with/without a single dysplastic phalanx. Soft-tissue swellings (flare-ups) are painful, recurrent and may precede heterotopic ossification. Heterotopic ossification can occur anywhere, but typically appear close to the axial skeleton in the early stages, before progressing to the appendicular skeleton. Movement restriction occurs if ossification hinders joint mobility.

Heterotopic ossification occurring in the throat, thoracic or submandibular region, may cause respiratory distress. In addition, costovertebral involvement, ossification of intercostal and paravertebral muscles, and progressive kyphoscoliosis may cause thoracic insufficiency syndrome, and death. Pneumonia, hypoxemia, hypercarbia, pulmonary hypertension, and right-sided heart failure complicate thoracic insufficiency syndrome. Dysphagia and dysarthria can occur with ossification affecting the jaw, head, and neck. Conductive hearing loss (present in 50% of individuals) may slowly progress,

caused by middle ear ossification. There is a threefold increased risk of renal stones, and fracture risk.

Pathophysiology

FOP is caused by a heterozygous, usually de novo, R206H gain-of-function mutation in the ACVR1 gene. This mutation changes the BMP type I receptor to a mildly active form in the basal state, with hyperactive sensitivity to BMP signaling, and the ALK2 receptor becomes aberrantly responsive to Activin A, which induces phosphorylation of SMAD 1/5/8, leading to bone formation in abnormal locations.⁵

The proinflammatory cytokine response of TNF α , IL-1 β , and IL-6 is elevated and prolonged in mast cells of patients with R206H mutation in the ACVR1 gene.⁶ Trauma, even mild, is an important trigger for heterotopic ossification.

Genotype-phenotype correlations

The c.617G>A (p.R206H) pathogenic variant is associated with the 95% cases of classic FOP phenotype.⁷ Currently, at least 13 other mutations have been found in the glycine-serine rich or kinase domain of ALK2 that cause atypical phenotype of FOP (Figure 2).

Treatment of manifestations

Intramuscular injections, arterial punctures, biopsy of lesions are to be avoided to prevent soft-tissue & muscle injury, since all can precipitate heterotopic ossification. Prompt treatment by oral analgesics, ice application and

corticosteroids are necessary. Adequate dental care is important; plenty of fluid intake to be ensured, to prevent renal stones. In case of hearing disability, hearing aides may be needed. Fractures in individuals with FOP usually heal with minimal heterotopic bone formation. Open reduction and internal fixation can trigger rapidly developing heterotopic ossification and is best avoided.

Therapies under investigation

Several drugs are currently being investigated in clinical trials. These include blocking antibodies that stop Activin

A from triggering the mutant ALK2 receptor (REGN2477), ALK2 kinase inhibitors (AZD0530; IPN60130), mTOR inhibitors (rapamycin) which modulate the inflammatory response to tissue injury and aim to affect the early hypoxic stages involved in chondrogenesis; and retinoic acid receptor gamma agonists, which block the chondrogenic signaling required for endochondral bone formation (palovarotene)⁸. All of these drugs have been shown to be effective in FOP mouse models.

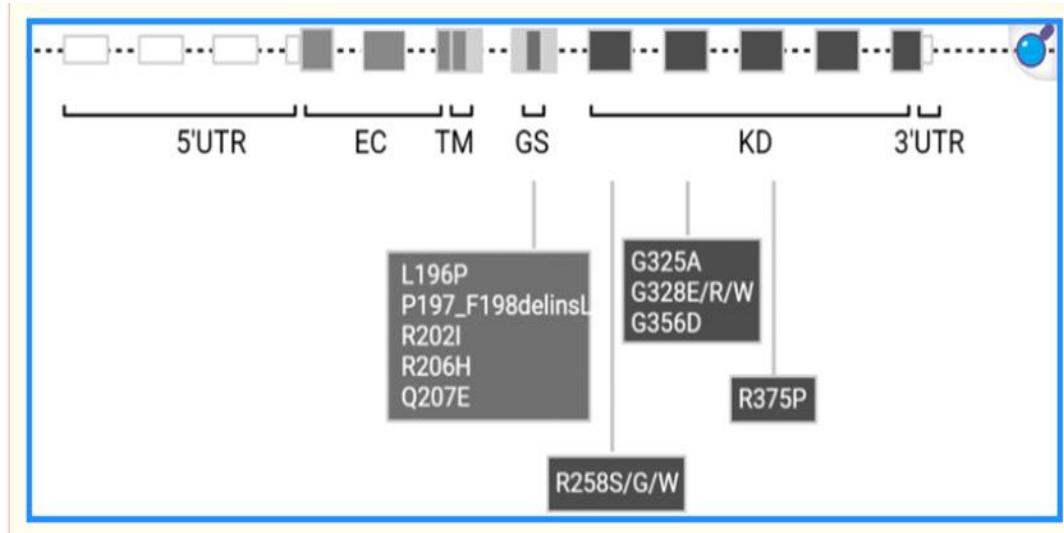


Figure 2: Overview of FOP mutations in the exons of the different domains of the ACVR1 EC-extracellular; GS-glycine-serine rich; KD-kinase domain.

Table 2: Targeted therapy.

Treatment class	Mechanism of action	Specific drug	Dosage
Retinoid	Retinoic acid receptor (RAR) gamma agonist that reduces BMP signaling	Palovarotene	5 mg orally 1x/day Adjust dose as needed for younger persons & flare-ups.

Table 3: Gene therapy options in Fibrodysplasia ossificans progressiva for in vivo treatment.

	Approach	Target	Effect
Gene replacement	Expression of wild-type ALK2	mRNA	Normal ALK2 competes against mutant ALK2 receptor
Gene silencing	Mutant ALK2-specific RNAi	mRNA	Suppression of mutant ALK2 receptor expression
Gene replacement and silencing	Combination of the two above	mRNA	Combined effect of the two above
Gene editing	CRISPR/CAS-mediated correction of ALK2 mutation	DNA	Only normal ALK2 receptor is produced

Targeted therapy

Palovarotene (Sohonos®) has been approved by the US FDA for treatment of FOP in adults and children (females age ≥ 8 years and males age ≥ 10 years) (Table 2).

Retinoic acid receptor (RAR) gamma agonists potently downregulate the bone morphogenic protein (BMP) signaling pathway and activate the retinoid signaling pathway, inhibiting chondrogenesis and heterotopic ossification.

Gene therapy

For FOP, gene therapy strategies are gene replacement, gene silencing, combination of gene replacement and silencing, and gene editing (Table 3). Gene replacement - introduction of healthy proteins which will compete against abnormal proteins produced by mutations such as the classic ALK2 mutation in FOP. Gene silencing can suppress the expression of abnormal proteins (produced by mutation of the ALK2 receptor).⁹ A combination of gene replacement and silencing removes abnormal proteins and expresses healthy proteins simultaneously. Finally, gene editing aims to correct DNA mutations in the genome by using the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system.¹⁰

Genetic counseling

Fibrodysplasia ossificans progressiva (FOP) is inherited in an autosomal dominant manner, with ~100% penetrance. Most FOP individuals have a de novo ACVR1 pathogenic variant. Rarely, FOP is inherited from an affected parent. Physical examination of parents of a proband with the ACVR1 c.617G>A (p.Arg206His) pathogenic variant should be done, if asymptomatic, FOP in the parents can be excluded; confirmatory genetic testing of the parents is not required.

The risk to the sibs of the proband depends on the genetic status of the proband's parents: If a parent of the proband is affected and/or has the pathogenic variant, the risk to the sibs is 50%. With unaffected parents, risk to the sibs of a proband is low.

Offspring of a proband- Each child of an individual with FOP has a 50% chance of inheriting the ACVR1 pathogenic variant. Prenatal testing for the known variant in ACVR1 gene should be done by sanger sequencing of amniotic fluid.

Pregnancy in women with FOP is uncommon, since reproductive potential is limited. FOP has life-threatening risks to mother and fetus because heterotopic ossification affecting the pelvis and surrounding regions complicate antenatal and intranatal periods. Breathing difficulties in later pregnancy can impose risks secondary to restrictive chest wall disease. Immobility increases risk of thromboembolism.

CONCLUSION

FOP is a complex disease, whose efficient treatment will involve combined gene and pharmacological therapy. Underlying risk factors and the natural course of the disease needs to be ascertained, and various new drugs and gene therapy are under early trials. Clinical studies are needed to advance FOP treatment and should be prioritized in the next decade.

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