

# My phenotype speaks: please do not harm me with biopsy needle

Saini I, Bagri N<sup>1</sup>, Gupta N<sup>1</sup>

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## INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a disabling genetic disorder of connective tissue characterized by congenital malformation of the great toes and progressive heterotopic ossification of muscle and connective tissue<sup>1</sup>. It is extremely rare and has a prevalence of one in two million people<sup>1</sup>. Children are normal at birth except for a malformation of the great toes<sup>2</sup>. The progressive heterotopic ossification usually begins in the first decade of life, and occurs in a specific anatomic pattern<sup>3</sup>. FOP has a relapsing and remitting nature and is often precipitated by trauma, intramuscular injections, muscle fatigue, viral infections, or diagnostic biopsies and invasive surgical procedures, and results in debilitating pain and permanent disability<sup>1,4</sup>.

## CASE

A 4-year-old boy presented with multiple hard lumps over his neck and back, and which had gradually developed and progressively worsened over the past 2 years. There was no family history of similar illness and there was no significant history of trauma. Physical examination revealed multiple, non-tender, mobile bony hard subcutaneous swellings in the neck, and back (Figure 1A). He also had significant neck stiffness, and the great toes were short with valgus deformity (Figure 2). Radiographs revealed ossification of the ligamentum nuchae and heterotopic ossification (HO) over the neck anteriorly in midline, left lower hemithorax, abdomen and thoracic and lumbar spine, consistent with the site of the lesions on neck and back (Figures 1B,3,4,). Biochemical evaluations of bone mineral metabolism were normal. These characteristic lesions suggested the diagnosis of fibrodysplasia ossificans pro-

gressiva (FOP). Bidirectional sanger sequencing showed presence of the common heterozygous activating mutation (c.617G>A; R206H) in the ACVR1, a bone morphogenetic protein (BMP) type I receptor. The



**FIGURE 1.** A) Bony hard masses over back; B) Chest and abdominal radiograph showing heterotopic ossification over left lower hemithorax and abdomen



**FIGURE 2.** Feet showing hallux valgus deformities

1. Pediatrics, All India Institute of Medical Sciences, New Delhi, India



**FIGURE 3.** Neck radiograph showing the ossification of ligamentum nuchae and heterotopic ossification anteriorly

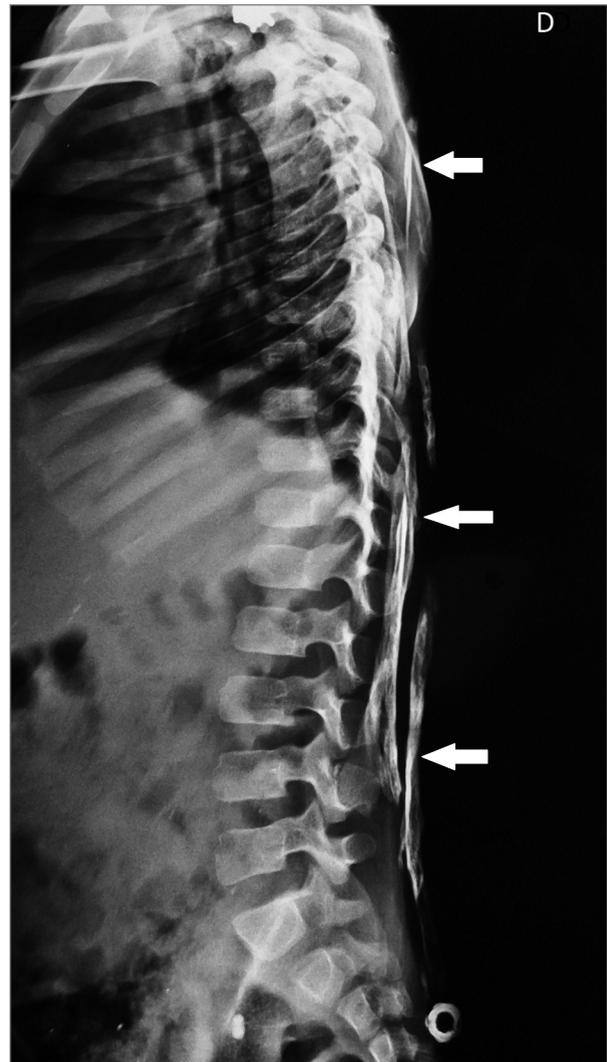
child had undergone non yielding biopsies from multiple sites before the final diagnosis was made.

## DISCUSSION

Despite the distinct constellation of defining clinical features, FOP is often misdiagnosed and 67% undergo unnecessary harmful diagnostic procedures like biopsies as in our case which leads to posttraumatic ossification and permanent loss of mobility in more than 50%<sup>4</sup>.

The mutation causing the disease is highly specific and localized to the activin receptor A type I/activin-like kinase 2 (ACVR1/ALK2) gene, which encodes a bone morphogenic protein (BMP)<sup>2</sup>. Nearly all cases arise by spontaneous mutations, but autosomal dominant inheritance has been observed<sup>2</sup>. There is no definite and effective treatment for FOP<sup>5</sup>.

The best treatment is still prevention of trauma, with possible role of glucocorticoids in the acute flare-ups. The most effective way to prevent the acute flare-ups is by early diagnosis of the condition and by subsequent avoidance of trauma and iatrogenic harm<sup>1</sup>. Mal-



**FIGURE 4.** Radiograph showing heterotopic ossification over abdomen and thoracic and lumbar spine

formations of the great toes are universal and present in all affected individuals<sup>1</sup>. Although all children with malformed great toes will not have FOP, it must be part of the differential diagnosis. Once the soft tissue swellings appear, the clinical diagnosis is certain<sup>1</sup>. Hence, clinicians need to be vigilant in any child presenting with soft tissue swellings and having malformed great toes, so that the early diagnosis may be made and iatrogenic harm avoided.

## CORRESPONDENCE TO

Narendra Bagri  
Department of Pediatrics, All India Institute of Medical Sciences,  
New Delhi, 110049  
E-mail: drnarendrabagri@yahoo.co.in

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