

# Ankylosis of the Major Joints and Jaw in Patients with Fibrodysplasia Ossificans Progressiva: A Report of Two Cases

Tetsuko Okuno<sup>1\*</sup>, Hitoshi Suzuki<sup>2</sup>, Akio Inoue<sup>3</sup> and Jingo Kusakawa<sup>4</sup>

<sup>1</sup>Department of Orthopedic Surgery, Yanagawa Rehabilitation Hospital, Japan

<sup>2</sup>Department of Orthopedic Surgery and Sports Medicine Wakamatsu Hospital, University of Occupational and Environmental Health, Japan

<sup>3</sup>Department of Orthopedic Surgery, Yanagawa Rehabilitation Hospital, Japan

<sup>4</sup>Dental and Oral Medical Center, Kurume University School of Medicine, Japan

## ARTICLE INFO

### Article history:

Received: 13 May 2017

Accepted: 12 June 2017

Published: 15 June 2017

### Keywords:

Fibrodysplasia;  
Ossificans;  
Progressive;  
Ankylosis;  
Restricted;  
Respiratory;  
Disorder;  
Restricted mouth opening;  
CT images

**Copyright:** © 2017 Okuno T et al,  
Ann Orthop Trauma Rehabil

This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Citation this article:** Okuno T, Suzuki H, Inoue A, Kusakawa J. Ankylosis of the Major Joints and Jaw in Patients with Fibrodysplasia Ossificans Progressiva: A Report of Two Cases. Ann Orthop Trauma Rehabil. 2017; 1(1):112.

### Correspondence:

**Tetsuko Okuno,**  
Special Advisor, Department of  
Orthopedic Surgery,  
Yanagawa Rehabilitation  
Hospital, 113-2 Kami-  
miyanaga, Yanagawa 832-  
0058, Japan,  
Tel: +81-944-72-0001;  
Fax: +81-944-72-1127;  
Email: okuno@kouhoukai.org

## ABSTRACT

Fibrodysplasia Ossificans Progressiva (FOP) is an extremely rare genetic condition characterized by congenital malformation and progressive heterotopic ossification (HO) caused by a recurrent single-nucleotide substitution at position 617 in the ACVR1 gene. As the condition progresses, HO leads to joint ankylosis, breathing difficulties, and mouth opening restriction. Here, we describe 2 cases of FOP confirmed by genetic testing in patients with ankylosis with malposition, rigid thorax, and restricted mouth opening. We examined the ossification sites in the body, thorax, and jaw in each case using computed tomography (CT) and 3-dimensional CT (3D-CT). In the first case, a 29-year-old woman showed marked scoliosis, multiple HO of the joints, and jaw ankylosis due to the ossification of mandibular depressors. In the second case, a 39-year-old man presented with jaw ankylosis due to the ossification of mandibular depressors. These ossification findings in the body and jaw ankylosis were only revealed by 3D-CT.

## Introduction

Fibrodysplasia Ossificans Progressiva (FOP) is a severely disabling genetic disorder of the connective tissue characterized by congenital skeletal malformations including bilateral hallux valgus and progressive heterotopic ossification (HO) [1-3]. Malformations of the cervical spine are often noted, including cervical vertebrae with small bodies and large posterior elements [3,5]. The worldwide prevalence is estimated to be about 1 in 2 million individuals [6]. FOP is caused by a recurrent activating mutation (617G>A; R206) in the ACVR1/ALK2 gene [7,8]. HO usually begins in the first decade of life and progresses throughout life [1,3,9].

HO usually occurs spontaneously or can be precipitated by a number of factors such as trauma, biopsy of nodules, excision of heterotopic bone, intramuscular injection, and dental therapy [1,3,9,10]. As the disease progresses, heterotopic bone leads to joint ankylosis [11,12-16]. The most common sites of early ossification are the neck, spine, and shoulder girdles.

The risk of jaw involvement may be trouble-free for young children, but the risk of ossification increases with age [9]. Limitation in mouth opening and loss of masticatory function may lead to malnutrition in patients with FOP [14-16]. In the present report, we used computed tomography (CT) images to describe the HO sites in the major extremities and the jaw and determine the masticatory muscles involved in order to clarify the cause of restricted mouth opening in patients with FOP. The diagnosis of FOP in two individuals was confirmed by genetic testing. The patients and their families were informed that data concerning their cases would be submitted for publication and they provided consent.

### Case presentation

#### 1. Patient 1

Patient 1 was a 29-year-old woman who was referred to our department for diagnosis because of episodes of swelling and almost non-painful small subcutaneous nodules on the occipital region, posterior portion of the neck, scapula, and lumbar regions that repeatedly appeared and disappeared. The first manifestation was a subcutaneous nodule on her back at 2 weeks after birth, which subsided spontaneously after a week. She was diagnosed as having bilateral hallux valgus, stiffness of the neck, HO in the posterior region of the neck, and malformation of the cervical spine, based on radiographic findings at the age of 2 years 6 months. (Figure 1).



**Figure 1:** Patient 1 Lateral radiograph of the cervical spine showing including the cervical vertebrae with small bodies and large posterior elements and heterotopic ossification (HO) in the posterior neck.

Family history was negative for FOP and other malformations. HO gradually progressed from the proximal joints and the axial regions of the body. She started to complain of restricted mouth opening at the age of 13 years. She had been forced to remain in standing position since she was 18 years old due to hip ankylosis. She had been treated with prednisolone when pain was unbearable due to new lesions, and a nonsteroidal anti-inflammatory drug (NSAID) Loxoprofen sodium hydrate, one tablet were administered after every meal to manage continuous chronic pain. At the age of 28 years, 3-dimensional (3D) reconstructed CT images showed that the spinal column ankylosed, with marked unbalanced C-shaped thoracolumbar scoliosis and pelvic obliquity (Figure 2). CT images of the thorax revealed that the thoracic cage was asymmetric and rigid, with almost no respiratory expansion of the thorax (Figure 3). At that time, her vital capacity percentage (%FV) was 48.1% and percentage of forced expiratory volume for 1 second (FEV1%) was 99%. The interincisal distance of mouth opening was only 5mm after shaving the central incisors. 3D-CT images of the temporal area and the face showed ossified bridging between the mentum of the mandible and the hyoid bone, formed in the region of the geniohyoid, mylohyoid, and the anterior belly of the digastric muscles, which act as mandibular depressors that open the mouth (Figure 4). There was no HO in the masticatory muscles (CT number approximately in the range of 36 to 62 Hounsfield units [: HU] with 3-mm slice thickness).

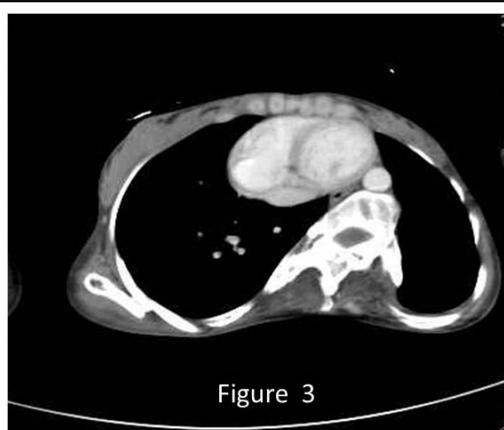
#### 2. Patient 2

Patient 2 was a 39-year-old man who was noted to have torticollis at the age of 3 months. At the age of 3 years, he felt a limitation in mouth opening after he had accidentally bumped his mouth against the corner of a table and lost two central incisors. He was diagnosed with FOP at the age of 5 years. Family history was negative for FOP and other malformations. At that time, the distance between the upper gingiva and the lower incisors was 13 mm. Ossification gradually progressed, the spinal column ankylosed, the mobility of both shoulders became more limited at the age of 17 years. His jaw movement gradually became restricted, with the

interincisal distance being reduced about 2mm. Then the incisors and canine teeth decayed, and they were extracted by himself at the age of 20 years.



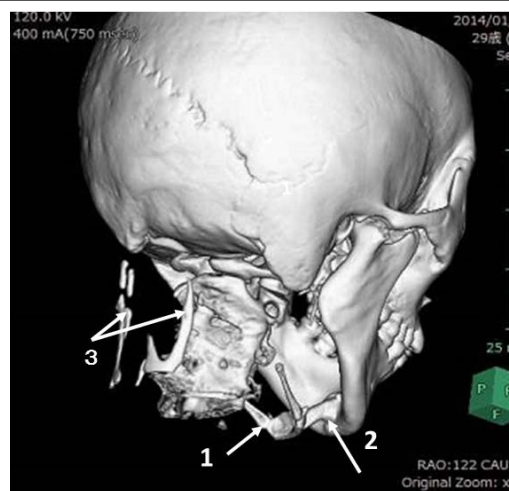
**Figure 2:** Patient 1 Three-Dimensional computed tomography (3D-CT) images of the body showing ankylosis of the major joints, with malpositioning, marked scoliosis, and extensive heterotopic ossification (arrows).



**Figure 3:** Patient 1 Computed Tomography (CT) images of the thorax revealing asymmetric deformity and rigidity of the thoracic cage. There was almost no respiratory expansion of the thorax.

He got a job in a personal computer office at the age of 20 and he could not sit in a chair and had to remain in standing position due to hip ankylosis at the age of 25 year. He was forced to retire from the company cause by the head injury as the result of the fall at the age of 36. At the age of 38 years, he had marked forward flexed spinal column, with marked respiratory deficit (%VC, 50. 3%; FEV1%, 82%). He could walk with a quadcane in the house (Figure 5A). His left shoulder and elbow movements were intact, and he could use his left hand to take soft food through the small inter gingival space (3 mm). Etodolac (NSAID) 100mg, 4 tablets in two

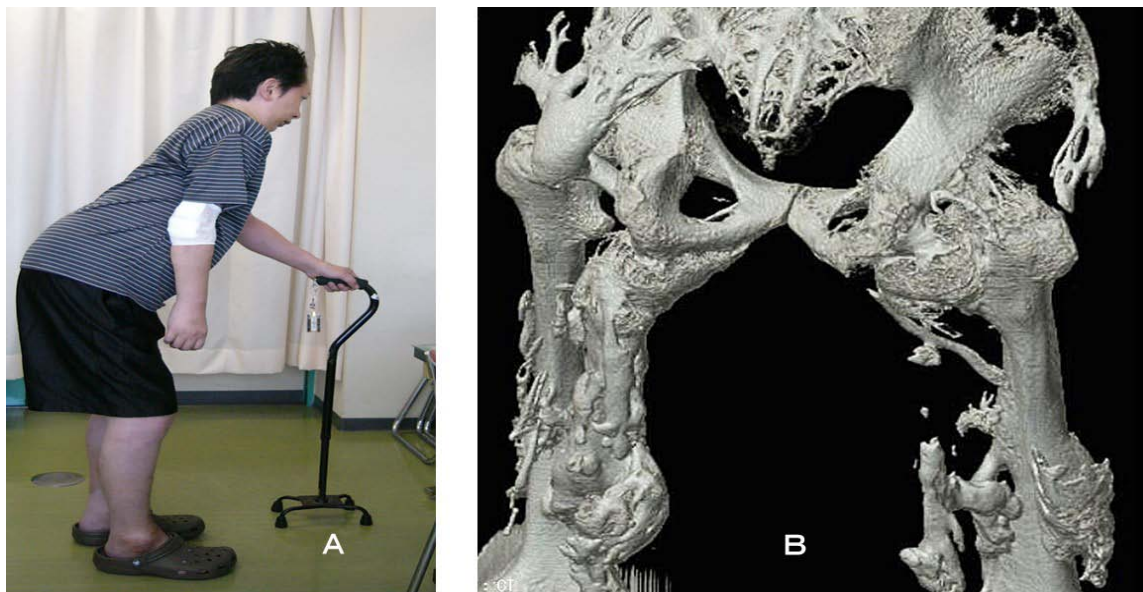
divided doses taken in the morning and evening for continuous pain. The 3D-CT images of the hips showed at the age of 38, remarkable ossification of the abductor muscles, hamstrings, quadriceps and ligaments around the pelvis to hip and knee on the right side, and ossification of the articular capsules, ligaments and muscles on the left side (Figure 5B). The 3D-CT images of the jaw revealed an almost ankylosed jaw bridged from the mentum of the mandible to the hyoid bone, which was more remarkable than that of Patient 1, on the region of the geniohyoid, mylohyoid, and anterior belly of the digastric muscles, which act as mandibular depressors (Figure 6). There were no findings of HO in the masticatory muscles (CT number, average 39 to 72 HU, with 3-mm slice thickness).



**Figure 4:** Patient 1 Three-Dimensional Computed Tomography (3D-CT) images of the jaw at 28 the age of years showing Heterotopic Ossification (HO) of the bridge from the mentum to the hyoid bone (arrow 1) in the region of mandibular depressors (arrow 2) and initialstage of HO in the posterior neck (arrow 3).

## Discussion

FOP is a severely disabling heritable disorder of connective tissue characterized by congenital malformation of the great toes, including hallux valgus and cervical spine, and progressive heterotopic ossification (HO) that forms qualitative normal bone in characteristic extra skeletal site (Figure 2). The diaphragm, tongue, extra-ocular muscle, cardiac muscle, smooth muscle and the skin are spared from HO in FOP [3,15]. HO proceed in a direction that is axial to

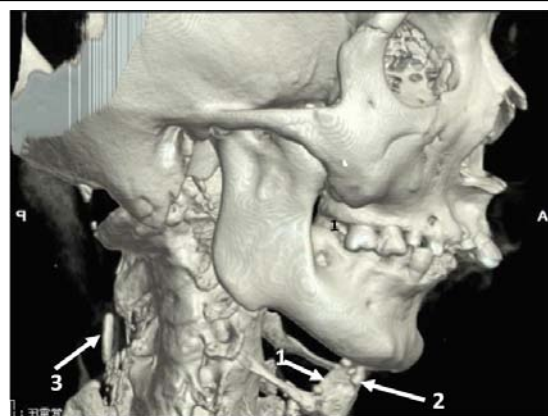


**Figure 5:** Patient 2 The photograph showing marked forward flexed spinal column with rigid thorax and walking with a quad cane in the house at the age of 38 years (A). Three-Dimensional Computed Tomography (3D-CT) images of the hips at age 38 years showing HO of the abductor muscles, hamstrings, quadriceps, and ligaments on the right hip and HO of the capsules, muscles, ligaments on the left hip (B).

appendicular, cranial to caudal, and proximal to distal; this pattern appear typical for FOP [3,9]. HO in reported cases was most marked before puberty, but new lumps were still occurring in the sixth and seventh decades of life [3]. In the study of Cohen et al [9], the average age of onset of HO was 5 years and affected the neck, spine, and shoulder. The hips and elbows became involved at the age of 13 years (mean). Most patients with FOP will have restriction in mouth opening by the age of 18 years [9]. Jaw changes progress to ankylosis through extra-articular ossification. In Patient 2, the patient had early onset of restricted mouth opening at the age of 3 years old, which was thought to be triggered by the trauma to his mouth. In Patient 1, her restricted mouth opening started at the age of 13 years, and almost major joint, the hips and jaw ankylosed by the age of 18 years. In Patient 2, the hips had ankylosed at the age of 25 years. The patients of the jaw in Patient 1 and 2, became ankylosed due to the conspicuous ossification of the mandibular depressors, as can be seen only in the 3D-CT images. To our knowledge, such ankylosis of the jaw as a result of FOP was perhaps the first described by us.

In Roberts et al [16]. Report on dental manifestation of FOP in 5 patients, a woman showed chin-on-chest deformity [4] and jaw ankylosis and died at the age of

52 years, during which her joints were immobile, except the fingertips, and during her terminal stages, her 2 incisors were removed to facilitate nutrition through a straw. The other patient, a 44-year-old bedridden woman, showed severely restricted mouth opening and had multiple carious teeth; her upper and lower teeth were removed to prevent sepsis. In a case reported by Herford and Boyne [17], a 24-year-old man, confined to a wheelchair, with temporomandibular (TMJ) ankylosis underwent coronoid gap arthroplasty because of rampant tooth decay and abscess; his intraoperative maximal incisal opening was 40 mm, but it decreased to 15 mm a year postoperatively.



**Figure 6:** Patient 2 Three-Dimensional Computed Tomography (3D-CT) images of the lateral aspect of the head and face at the age of 38 years showing ankylosis of the jaw ossified bridge between the mentum and hyoid bone (arrow 1) in the region of the mandibular depressors (arrow 2), and initial stage of ossification of the posterior neck (arrow 3).



Progressive spinal deformity is common in patients who have FOP; 26 (65%) of 40 of patients with FOP had scoliosis, and of these, 88% were unbalanced C-shaped curves. Severe scoliosis can lead to severe pelvic obliquity, impair trunk balance. And these ossification was thought to be the primary cause of restrictive disease in the chest wall regardless of whether or not the patient had scoliosis [14]. Most patients are confined to a chair or to a bed because of joint restriction by the age of 30 years [1-3]. There are no definitive medical treatments to halt the progression of bone formation [3,15]. Surgery is always contraindicated because it triggers further ossification [1,18]. However, recently, surgical excision of heterotopic bone with single-fraction irradiation and indometacin has been described by Benetos et al [5]. Currently, preventative management is based on prophylactic measures against falls, risk of injury, respiratory diseases, especially pneumonia, viral infections, and malnutrition and oral hygiene due to limitation of mouth opening [13,15,18,19]. Mobility restriction from joint ankylosis severely impairs balancing mechanisms, causing instability, resulting in the subsequent fall [19]. Symptomatic treatment is given for flare-ups, which mean acute inflammatory symptoms with severe pain and precede HO, and oral steroids, NSAIDs and COX-2 inhibitors are usually administered [15,18]. In the optimal rehabilitation plan in patients with FOP often involves medical doctors, occupational and physical therapists, dentists, wheelchair vendors, and psychologists can help in giving the patients and their families comfort and practical advice [20].

### Conclusions and Comments

As the disease progresses, HO leads to ankylosis of the major joints, with the decreased expansion of the chest wall, spinal deformity, and limitation of mouth opening. Preventative management is based on prophylactic measures against falls, risk of injury, respiratory diseases, especially pneumonia, viral infections, and malnutrition and oral hygiene due to limitation in mouth opening. CT or 3D-CT images are very helpful to examine detail HO of the muscles and ligaments cause of ankylosis of the major joints and jaw in patients with

FOP. HO by the mandibular depressors in the jaw as a result of FOP was only revealed by 3D-CT and perhaps the first cases described by us.

### Acknowledgment

We thank Professor Takenobu Katagiri, Division of Pathophysiology, Research Center for Genomic Medicine, Saitama Medical University, for performing the genetic testing. This paper was supported in part by a Grant-in-Aid for Young Scientists (B), No. 26860164, to (H.S) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

### References

1. Rogers JG, Geho WB. (1979). Fibrodysplasia ossificans progressiva. A survey of forty-two cases. *J Bone Joint Surg Am.* 61: 909-14.
2. Smith R, Russell RG, Woods CG. (1976). Myositis ossificans progressiva. Clinical features of eight patients and their response to treatment. *J Bone Joint Surg Br.* 58: 48-57.
3. Connor JM, Evans DA. (1982). Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients. *J Bone Joint Surg Br.* 64: 76-83.
4. Moore RE, Domans JP, Drummond DS. (2009). Chin-on-chest deformity in patients with fibrodysplasia ossificans progressiva. A case series. *J Bone Joint Surg Am.* 91: 1497-502.
5. Benetos IS, Mavrogenis AF, Themistocleous GS. (2006). Optimal treatment of fibrodysplasia ossificans progressiva with surgical excision of heterotopic bone, indomethacin, and irradiation. *J Surg Orthop Adv.* 15: 99-104.
6. Shore EM, Feldman GJ, Xu M, Frederick S, Kaplan. (2005). The genetics of fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab.* 3: 201-4.
7. Fukuda T, Kohda M, Kanomata K, Nojima J, Nakamura A, et al. (2009). Constitutively activated ALK2 and increased SMAD1/5 cooperatively induce bone morphogenetic protein signaling in fibrodysplasia ossificans progressiva. *J Biol Chem.* 284: 7149-56.
8. Van Dinther M, Visser N, de Gorter DJ, Doorn J, Goumans MJ, et al. (2010). ALK2 R206 H mutation

linked to fibrodysplasia ossificans progressiva confers constitutive activity to the BMP type 1 receptor and sensitizes mesenchymal cells to BMP-induced osteoblast differentiation and bone formation. *J Bone Miner Res.* 25: 1208-15.

9. Cohen RB, Hahn GV, Tabas JA, Peeper J, Levitz CL, et al. (1993). The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. A study of forty-four patients. *J Bone Joint Surg Am.* 75: 215-219.

10. Luchetti W, Cohen RB, Hahn GV, Rocke DM, Helpin M, et al. (1996). Severe restriction in jaw movement after routine injection of local anesthetic in patients who have fibrodysplasia ossificans progressiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 81: 21-25.

11. Kaplan FS, Glaser DL. (2005). Thoracic insufficiency syndrome in patients with fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab.* 3: 213-216.

12. Connor JM, Evans CC, Evans DA. (1981). Cardiopulmonary function in fibrodysplasia ossificans progressiva. *Thorax.* 36: 419-423.

13. Orhan K, Uyanik LO, Erkmen E, Kilinc Y. (2012). Unusually severe limitation of the jaw attributable to fibrodysplasia ossificans progressiva: a case report with cone-beam computed tomography findings. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 113: 404-409.

14. Shah PB, Zasloff MA, Drummond D, Kaplan FS. (1994). Spinal deformity in patients who have fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am.* 76: 1442-1450.

15. Pignolo RJ, Shore EM, Kaplan FS. (2011). Fibrodysplasia ossificans progressiva: clinical and genetic aspects. *Orphanet J Rare Dis.* 6: 80.

16. Roberts T, Stephen L, Scott C, Urban M, Sudi S, et al. (2011). Fibrodysplasia Ossificans Progressiva (FOP) in South Africa: dental implications in 5 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 112: 11-8.

17. Herford AS, Boyne PJ. (2003). Ankylosis of the jaw in a patient with fibrodysplasia ossificans progressiva. *Oral Surg Oral Med Oral Pathol Oral Radio endod.* 96: 680-4.

18. Glaser DL, Kaplan FS. (2005). Treatment considerations for the management of fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab.* 3: 243-50.

19. Glaser DL, Rocke DM, Kaplan FS. (1998). Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. *Clin Orthop.* 346: 110-6.

20. Levy CE, Bermer TF, Bendixen R. (2005). Rehabilitation for individuals with fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab.* 3: 251-6.