CASE REPORT

Clinical and molecular characterisation of two siblings with fibrodysplasia ossificans progressiva, from the Colombian Pacific coast (South America)

Harry Pachajoa, Andres Felipe Ramirez Botero

Universidad Icesi, Cali, Valle del Cauca, Colombia

Correspondence to
Dr Harry Pachajoa,
hmpachajoa@icesi.edu.co

Accepted 1 May 2015

SUMMARY

Fibrodysplasia ossificans progressiva (FOP, MIM 135 100) is an uncommon genetic disease with a dominant autosomal germline transmission pattern; however, most cases are products of spontaneous individual mutations. It is a disabling condition that affects connective tissue, and it is distinguished by progressive heterotopic ossifications and congenital malformations of the great toes. The case of 2 brothers with progressive osseous deformation, along with ankylosis of the jaw, scoliosis and mental retardation, is presented. Blood samples were taken from each patient identifying in both of them a heterozygote mutation in exon 6 of the gene *ACVR1* (c.617G>A p.Arg206His), which diagnoses the 'classic' form of FOP. The current medical treatment of this disease is early detection to avoid trauma and aggravating factors, prophylactic measures against infections and respiratory decline, symptomatic relief and physical therapy. There is currently no cure for the disease.

BACKGROUND

Fibrodysplasia ossificans progressiva (FOP, MIM 135 100) is an unusual genetic disease with a dominant autosomal germline transmission pattern. It is characterised by progressive heterotopic ossifications and congenital malformations of the great toes.¹ Its worldwide prevalence is about 1/2 000 000 people; furthermore, there are no geographic, ethnic, gender or racial traits associated with the disease, as most cases are believed to be products of spontaneous individual mutations.² Classic FOP is caused by a mutation in gene *ACVR1* (Activin A receptor type I), which codifies the homonymous protein. There are approximately 800 reported cases of FOP globally, and there is no effective cure for it.^{2 3} The case of two siblings with FOP, from the Colombian Pacific coast, is described below.

CASE PRESENTATION

This is a case of two African-American half-siblings, from the mother's side, aged 17 (patient #1) and 11 (patient #2) (figure 1), from the Colombian Pacific coast, who sought medical advice for progressive osseous deformation, associated with temporomandibular ankylosis, scoliosis and mental retardation. A substitute mother had been taking care of the siblings for the past 2 years; there was no information regarding growth and development, nor previous medical history; their biological

Figure 1 Frontal view of patients #2 and #1, left and right, respectively.

mother was mentally retarded without heterotopic ossifications, and their maternal uncle had osseous deformation and mental retardation, according to the information revealed by the substitute mother. However, these relatives were not accessible to obtain blood samples from them for gene analysis. Information regarding the biological fathers was not available.

Patient #1 had a vertebral column nuclear magnetic resonance scan that depicted thoracolumbar scoliosis of left convexity with vertex at T11-T12 and a second curvature with right convexity with vertex at L5, with no intrathecal abnormalities or evidence of tethered spinal cord (figure 2); additionally, a pelvic CT showed right pelvic tilt, dysplastic changes with verticalisation of acetabulae, lateralisation of the right femoral head secondary to subluxation, and no apparent fractures (figure 3). The patient underwent a head CT scan with three-dimensional (3D) reconstruction, presenting jaw ankylosis, alteration of the mandibular condyles and arthrosis. Additionally, the spirometry showed a severe restrictive defect: forced vital capacity (FVC) 44%, forced expiratory volume in 1 s (FEV₁) 51% and FVC/FEV₁ 86%; the neuropsychological test revealed moderate mental retardation, and normal

CrossMark

To cite: Pachajoa H, Ramirez Botero AF. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-209804

Figure 2 Patient #1: vertebral column nuclear MR that depicts thoracolumbar scoliosis of left convexity with vertex at T11-T12 and a second curvature with right convexity with vertex at L5.

renal, abdominal and cardiac echographies. The patient was evaluated by a maxillofacial surgery specialist who considered dentofacial anomaly II, coronoid hyperplasia, ankylosis of the jaw and dental malocclusion.

On physical examination, patient #1 was 17 years old, mobilised with difficulty, weighed 34.3 kg (<-3 SD), measured 1.41 m (<-3 SD) in height, and presented facial asymmetry with micrognathia, sparse eyebrows and mouth opening of 3 mm (figure 4). An oral inspection revealed dental hyperpigmentation and spaced inferior teeth; moreover, the patient had retrognathism, dysphonia and limitation in cervical movements. The patient exhibited severe kyphoscoliosis with a left

Figure 4 Patient #1 presents facial asymmetry with micrognathia, scarce eyebrows, mouth opening of 3 mm and broad superior central incisive teeth.

thoracolumbar hump (figures 5 and 6), bilateral thumb hypoplasia and generalised atrophy of the muscles of the hands, and a certain degree of arachnodactyly was observed (figure 7); additionally, he had an upward tilt of the right hemipelvis, fixed 30° flexion of the right hip, and bilateral hypoplasia of the first metatarsal bones and bilateral ulnar deviation of the halluces (figure 8).

Patient #2 had a bilateral shoulder CT scan revealing multiple heterotopic osseous formations in the muscular planes and soft tissues of the scapular region, which contained the humeral

Figure 3 Patient #1: pelvic CT scan with three-dimensional reconstruction evidencing heterotopic ossifications.

Figure 5 Patient #1 exhibits severe kyphoscoliosis with a left thoracolumbar hump.

Figure 6 Lateral view of patient #1 revealing severe scoliosis.

diaphysis on the right side. He also had a head CT scan with a 3D reconstruction showing abnormal bone growth in the left mandibular bone and prominent calcification in the muscular plane of the left posterolateral nuchal region; in addition, he underwent an orbit CT scan without irregularities, an echocardiogram diagnostic of tricuspid insufficiency, and a carpogram revealing a chronological age of 10 years and a bone age of 8 years. He was also evaluated by a maxillofacial surgery specialist who considered dentofacial anomaly II, ankylosis of the jaw and dental malocclusion.

Patient #2 was 11 years old, he mobilised with difficulty, weighed 24.8 kg (−3 to −2 SD), measured 1.28 m (−3 to −2 SD) in height, exhibited facial asymmetry with micrognathia, scarce eyebrows and jaw ankylosis with mouth opening of 4 mm (figure 9). Inspection showed a left thoracic hump with an active ulcer on the back (figure 10); hands that exhibited hypoplasia of the first metatarsal bones and short phalanges (figure 11); muscular atrophy with hypertonicity of the muscles of the right

Figure 7 View of the hands of patient #1 with bilateral thumb hypoplasia, generalised atrophy of the muscles of the hands, and a certain degree of arachnodactyly.

Figure 8 Feet of patient #1 demonstrate bilateral hypoplasia of the first metatarsal bones and bilateral ulnar deviation of the halluces.

hemibody; ankylosis of the right gleno-humeral joint and bilateral hypoplasia of the first metatarsal bones (figure 12).

A blood sample was taken from each patient for gene analysis and the familial heterozygous mutation in exon 6 of the gene *ACVR1* (c.617G>A p.Arg206His) was identified in both cases, making a diagnosis of classic FOP. The gene was analysed by PCR and sequence of both DNA strands of the entire coding region and the highly conserved exon–intron splice junctions.

It is important to emphasise that although the patients exhibited a ‘classical’ phenotype and genotype for FOP, mental retardation was an atypical FOP clinical feature.

DISCUSSION

FOP is a rare genetic disease that has not yet been linked to gender, or to geographic, ethnic or racial characteristics. It is believed that most cases are secondary to individual spontaneous mutations⁴ and there is currently no cure for it.^{2,3}

Figure 9 Patient #2 exhibits facial asymmetry with micrognathia, sparse eyebrows and jaw ankylosis, with mouth opening of 4 mm.

Figure 10 Posterior inspection of patient #2 showing a left thoracic hump with an ulcer, in the back.

All the patients with clinical FOP who have been examined by DNA sequence exhibit mutations in the *ACVR1* gene; nonetheless, approximately 90% of the patients have the 'classic' mutation R206H gene *ACVR1*,³ as in the patients discussed in the present article. Activin A receptor type I is a mediator of the bone morphogenic protein and its mutation leads to the formation of bone where there is normally soft tissue; this process is called heterotopic ossification. Chakkalal and his laboratory team built a knock-in mouse for the mutation *Acvr1*^{R206H/+}, which enables the understanding of the genetics behind heterotopic ossifications, and serves as the first in vivo model

Figure 11 Hands of patient #2 showing hypoplasia of the first metatarsal bones and short phalanges.

Figure 12 Feet of patient #2 illustrate bilateral hypoplasia of the first metatarsal bones.

demonstrating that this mutation is responsible for FOP.⁵ Furthermore, in 2006, Shore and collaborators,⁶ by DNA sequence analysis of the gene *ACVR1*, demonstrated the presence of an identical heterozygous single-nucleotide change at cDNA position 617 (617G>A) in all members affected with FOP of seven families, which is an example of documented cases of familial FOP.

Heterotopic ossification follows a specific anatomic pattern: it begins in dorsal, proximal, axial and cranial regions and later compromises ventral, caudal and distal zones; it has been reported that the following sites remain free from heterotopic ossification: smooth muscle, cardiac muscle, diaphragm, tongue and extraocular muscles.³ In the neonate period, the most common—and sometimes the only—FOP signs are malformations of the great toes; however, during childhood, the first 'flare-ups' take place in soft tissues such as muscles, tendons, ligaments and fasciae, and may progress to heterotopic bone.⁶ This leads to the ankylosis of multiple articulations, reducing the ability of patients to walk or open their mouths³; scoliosis can be so drastic in some patients that it leads to thoracic insufficiency syndrome.² Patient #1 already presents dyspnoea at rest.

Although heterotopic ossifications are episodic, the loss of function because of them is greater at every episode, similarly to the medical consequences.⁷ Some patients need personal assistance for life and are usually bound to a wheelchair by their mid-twenties. The most common complications of FOP include severe malnutrition secondary to limited mouth opening, and pneumonia and right heart failure, both consequences of a rigid thoracic box. The life expectancy is roughly 40 years; most patients die from complications of the thoracic insufficiency syndrome.^{1,4}

Both patients in this report have the c.617G>A mutation in gene *ACVR1*, and exhibit a phenotype compatible with available descriptions of 'classic' FOP. Both have axial heterotopic ossifications, bilateral hypoplasia of the first metatarsal bones and short phalanges, ankylosis of the jaw and delay in postnatal development.² Patient #1 has limited cervical movements due to ankylosis of the neck, thumb hypoplasia, generalised atrophy of the muscles of the hand, restrictive respiratory pattern and moderate mental retardation. Patient #2 does not have a formal diagnosis of mental retardation, but after being observed during the medical interview, it is very likely he does. Patient #1 has a more advanced disease than patient #2, possibly due to the fact that he is older. After comparing the characteristics of the two patients with those described by Kaplan *et al*,⁷ Zhang *et al*,⁸ Stefanova *et al*,⁹ Carvalho *et al*,¹⁰ Nakajima *et al*¹¹ and Al-Haggar *et al*,¹² many similarities were found, as seen in table 1,³ nevertheless,

Table 1 Phenotypical comparison between the patients of the present report and other patients with the c.617G>A (p.R206H) in gene *ACVR1*

Mutation in gene <i>ACVR1</i>	c.617G>A (p.R206H)	c.617.G>A (p.R206H)
Number of patients	106	2
References	Zhang <i>et al</i> . ⁸ Stefanova <i>et al</i> . ⁹ Carvalho <i>et al</i> . ¹⁰ Kaplan <i>et al</i> . ⁷ Nakajima <i>et al</i> . ¹¹ Al-Haggar <i>et al</i> . ¹²	Present report
Gender	Male, female	Male
First ossifications	2–4 years (variation 1–5 years)	No data
Ossification follows specific anatomic pattern	Yes	Yes
Ossification after trauma or surgery	>50%	No data
Course of disease in terms of immobilisation	Severe	Severe
Thoracic insufficiency and scoliosis	Early, 3–4 decade	Early; no thoracic insufficiency syndrome yet
Great toe malformations	Fibular deviation close to 100%	Yes
Finger malformations	Thumb hypoplasia more than 50%	Patient #1
Alopecia	Some patients	Not present
Facial features	Thin skin, lack of eyebrows, small mandible	Characteristic facial features, sparse eyebrows, small mandible with micrognathia
Teeth abnormalities	25–30%	Dentofacial anomaly II
Deafness	25–30%	No
Primary amenorrhoea	No data	Does not apply
Cognitive compromise	No	Moderate mental retardation

Original taken from Hüning and Gillessen-Kaesbach.³

although the two patients discussed present a ‘classical’ FOP phenotype and genotype, they present mental retardation, which is an atypical FOP clinical feature.

FOP has many differential diagnostics, such as juvenile fibromatosis, neurofibromatosis, lymphoedema, soft tissue sarcoma, lipoblastomatosis, unknown malignity, parotitis and nodular or proliferative fascitis;^{3–4} as a consequence, there is misdiagnosis in roughly 90% of the cases.⁴ This is also attributed to the deficient information regarding FOP in medical texts and the lack of clinical association from physicians between patients with soft tissue ‘flare-ups’, symmetric great toe malformations and FOP.³ It is important to emphasise that osseous biopsies are not useful in FOP, since its diagnosis is clinical and molecular.^{3–13}

Mishima and collaborators led a study¹³ in Japan with 18 patients (nine men and nine women), with an average age of 13.9 years; in this study, X-rays of the hand and the cervical column were retrospectively analysed. The findings allowed them to describe, in patients with FOP, characteristics of the hand and the cervical column that were present since early years: a high ratio of the second metacarpal bone to the distal phalange of the thumb (>+1 SD), a high proportion of the second metacarpal bone to the first metacarpal bone (>+3 SD) and a prominent C5 spinous process compared to the depth of its body (>+2 SD). These outcomes were present even in the absence of great toe malformations; hence, these could be useful tools for the early diagnose of FOP and the consequent prophylaxis, to prevent the waning of the affected individuals.¹³

In conclusion, an early diagnosis is vital in order to avoid factors related to a more severe course of the disease, such as trauma secondary to injury of soft tissues or falls, excessive muscular stretching, fatigue, intramuscular vaccines, mandibular blocks for dental works, viral infections, such as influenza, and surgeries to remove heterotopic bone.¹⁴ These surgeries are particularly dangerous on the neck, back and mandible, because they elicit more heterotopic ossification, which worsens the progressive back deformity and the ankylosis of the different impaired joints.^{3–13} On the other hand, there are certain preventive measures, such as restriction of physical activity, occupational therapy in order to learn proper ways to execute everyday chores, respiratory therapy to conserve lung function,

subcutaneous injections to prevent infections such as influenza or pneumonia, and yearly otological evaluations, since many patients suffer from conductive deafness.² Although heterotopic ossification in patients with FOP is induced by the triggering factors mentioned earlier, episodes of bone formation can occur spontaneously as well, as observed in the mouse model with the ‘knock-in’ *ACVR1* R206H mutation.⁵

Owing to the fact that FOP is an autosomal dominant disease, there is a 50% probability that a descendant will inherit this condition; hence, couples with one or more affected relatives should receive genetic counselling.² Moreover, women with FOP face a high-risk pregnancy and labour; thus, they require strict follow-up from a multidisciplinary health team during this period.² It should be emphasised that there is no routine prenatal detection test for FOP.²

A limitation of this investigation is that the two presented patients were originally from a very disadvantaged rural area of Colombia and 18 h away by bus from the nearest genetic reference centre. Furthermore, they were put up for adoption by their biological mother and had no present biological family ties, and their biological fathers were not reachable, which made it impossible to perform genetic testing on them. Additionally, the substitute mother lacked detailed information regarding the biological parents of the patients, as is stated in the ‘Case report’ section. Hence, it is not possible to determine with certainty whether these patients inherited the mutation from their mother through autosomal dominant inheritance, or if the mother is mosaic and carries germline mutations, taking into account that the probability of two sporadic familial cases is very low. Nevertheless, an inherited autosomal dominant mutation from the mother is the most probable origin; as the fathers of both patients are apparently healthy men.

To sum up, FOP is a devastating disease for all affected individuals; it is a therapeutic challenge for the medical team in charge because it requires an intimate collaboration between physicians, physiotherapists, respiratory therapists, psychologists and occupational therapists, and a strong support network. Although there is no available effective medication that cures FOP, the ‘flare-ups’ of soft tissues can be ameliorated with intravenous steroids and analgesics (opioids, non-steroidal anti-

inflammatory drugs, COX-2 inhibitors and muscle relaxants).^{2 3} In conclusion, there are still many questions unanswered regarding the pathogenesis of this disease and how it can be prevented. There is still a long way to go but, hopefully, in a short time, many of these answers will be available in order to offer patients with FOP a better life.

Learning points

- ▶ Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease the prognosis of which depends on how early or late it is diagnosed.
- ▶ FOP is an autosomal dominant genetic disease secondary to a mutation in gene *ACVR1*; however, most cases are believed to be products of spontaneous individual mutations. Nevertheless, there are some documented cases of familial FOP, such as the case presented by Dr Shore *et al*⁶ in 2006, based on the DNA sampling of seven families, which illustrates inherited cases.
- ▶ This manuscript reports two half-brothers with 'classical' clinical FOP and genetic confirmation of an *ACVR1* mutation. It takes into account the fact that the probability of two sporadic cases is very low and, with the limitation of the progenitors not being accessible for genetic analysis, and the mental retardation in the mother, and mental retardation and osseous deformation in the maternal uncle, one can infer that this corresponds to a familial case of 'classical' FOP.
- ▶ There are no geographic, ethnic, gender or racial traits associated with the disease.
- ▶ The current medical treatment of this disease is primarily early detection to avoid trauma and aggravating factors, prophylactic measures against viral infections and respiratory decline, and symptomatic relief and physical therapy according to each patient's residual function; however, there is currently no cure for the disease.

Twitter Follow Andres Ramirez Botero at @aframirez

Funding Universidad ICESI 10.13039/501100002411.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Kaplan FS, Glaser DL, Shore EM, *et al*. The phenotype of fibrodysplasia ossificans progressiva. *Clin Rev Bone Miner Metab* 2005;3:183–8.
- 2 Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: clinical and genetic aspects. *Orphanet J Rare Dis* 2011;6:80.
- 3 Hüning I, Gillesen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. *Mol Syndromol* 2014;5:201–11.
- 4 Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. *Pediatr Endocrinol Rev* 2013;10 (Suppl 2):437–48.
- 5 Chakkalakal SA, Zhang D, Culbert AL, *et al*. An *Acr1* R206H knock-in mouse has fibrodysplasia ossificans progressiva. *J Bone Miner Res* 2012;27:1746–56.
- 6 Shore EM, Xu M, Feldman GJ, *et al*. A recurrent mutation in the BMP type I receptor *ACVR1* causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet* 2006;38:525–7.
- 7 Kaplan FS, Xu M, Seemann P, *et al*. Classic and atypical FOP phenotypes are caused by mutations in the BMP type I receptor *ACVR1*. *Hum Mutat* 2009;30:379–90.
- 8 Zhang W, Zhang K, Song L, *et al*. The phenotype and genotype of fibrodysplasia ossificans progressiva in China: a report of 72 cases. *Bone* 2013;57:386–91.
- 9 Stefanova I, Grünberg C, Gillesen-Kaesbach G. Fibrodysplasia ossificans progressiva. *Med Genet* 2012;24:20–32.
- 10 Carvalho DR, Navarro MM, Martins BJ, *et al*. Mutational screening of *ACVR1* gene in Brazilian fibrodysplasia ossificans progressiva patients. *Clin Genet* 2010;77:171–6.
- 11 Nakajima M, Haga N, Takikawa K, *et al*. The *ACVR1* 617G>A mutation is also recurrent in three Japanese patients with fibrodysplasia ossificans progressiva. *J Hum Genet* 2007;52:473–5.
- 12 Al-Haggar M, Ahmad N, Yahia S, *et al*. Sporadic fibrodysplasia ossificans progressiva in an Egyptian infant with c.617G>A mutation in *ACVR1* gene: a case report and review of literature. *Case Rep Genet* 2013;2013:834605.
- 13 Mishima K, Kitoh H, Haga N, *et al*. Radiographic characteristics of the hand and cervical spine in fibrodysplasia ossificans progressiva. *Intractable Rare Dis Res* 2014;3:46–51.
- 14 Kaplan FS, Chakkalakal SA, Shore EM. Fibrodysplasia ossificans progressiva: mechanisms and models of skeletal metamorphosis. *Dis Model Mech* 2012;5:756–62.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow