

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

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Biology 423L 2006

Date

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Abstract

Fibrodysplasia ossificans progressive (FOP) is a rare autosomal dominant disorder of connective tissue that results in heterotopic osteogenesis in humans and results in the postnatal formation of an ectopic skeleton. It affects about 1 in 2 million people (Mahboubi *et al*, 2001). FOP was first described by Patin in 1648 as “the woman who turned into wood”. The term “FOP” was introduced by Bauer and Bode in 1800 and since then over 700 cases of the disorder have been reported. This disorder usually arises from a spontaneous mutation in a gene that gets passed down to future generations and since reproductive fitness is low (Kaplan *et al*, 1993) the rarity of this disorder increases making traditional positional cloning and linkage analysis difficult.

There are very distinct clinical features for FOP. One of these features is the Congenital malformation of the great toes, with shortening of the first metatarsal and proximal phalanx which is the earliest phenotypic feature of FOP and is present in nearly all affected individuals at birth. (Meij *et al*, 2005). Another feature is the heterotopic ossification of soft tissue (Feldmen *et al*. 2000) and the third feature is the temporal progression of osteogenesis in characteristic anatomic patterns (Mahoubi *et al*, 2001). A person afflicted with FOP has basically 2 skeletons, one that was formed during embryogenesis called normatopic and a second skeleton that is formed around the first skeleton postnatally called a heterotopic skeleton. Spinal deformity is a variable feature of FOP.

In a study researchers reviewed clinical records in order to characterize the spinal deformity in forty patients who have established diagnosis of FOP. 65% had scoliosis, present since childhood. 88% of those who had scoliosis had unbalanced c-shaped curves, while 12% of them had s-shaped curves (Shah *et al*, 1994). Scoliosis is seen as the result of asymmetric bars of heterotopic bone connecting the rib cage to the pelvis (Mahboubi *et al*, 2001)

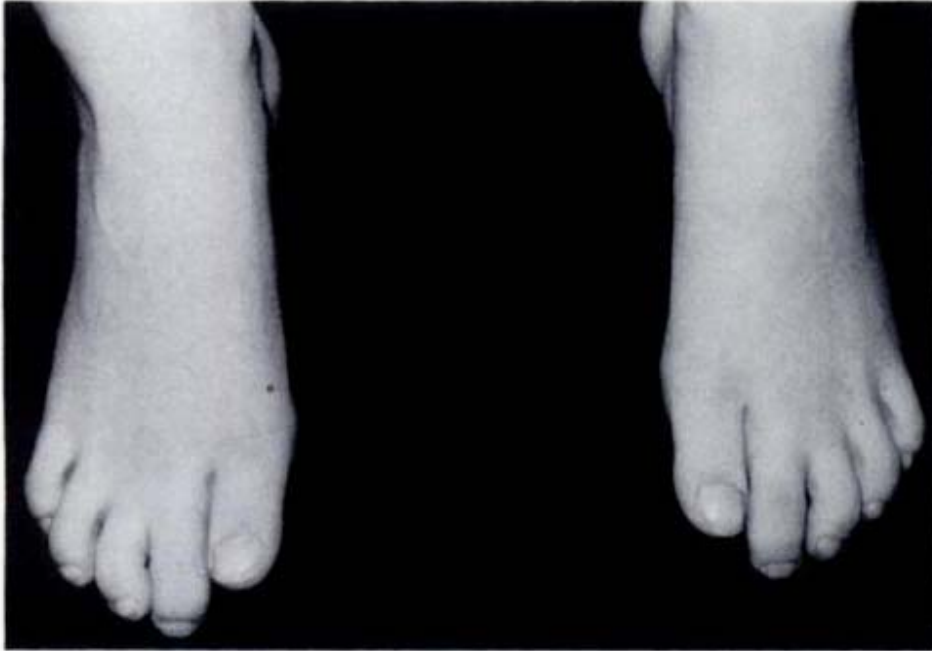


Figure 1: FOP patients are characterized by malformed big toes. (Conner *et al*, 1982)

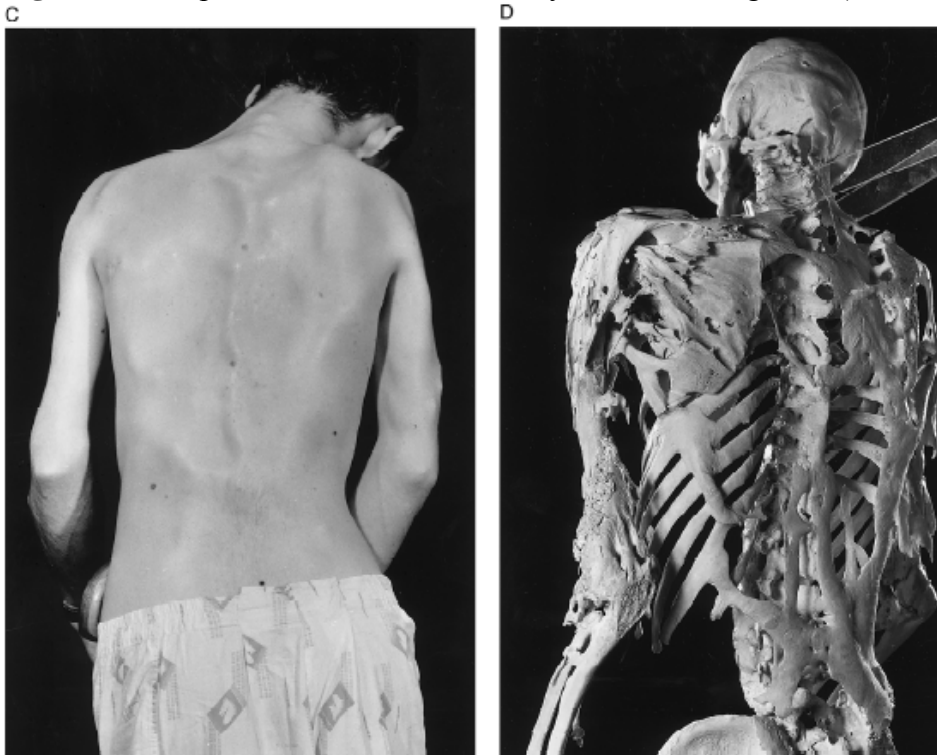


Figure 2: On the left is a 25 year old man afflicted with FOP. On the right is the skeleton of that man at the age of 40 after he died of pneumonia. The picture on the right clearly shows how this man's muscles around his shoulders and throughout his arms have been turned into bone and have become a part of his skeleton. (Feldmen *et al*, 2000)



Figure 3: Spinal deformity is common in FOP patients. This is a figure of an 8 year old girl with an unbalanced c-shaped lumbar scoliosis. (Shah *et al*, 1994)

FOP is a Progressive disorder. Although the rate of disease progression is variable, most patients are confined to a wheelchair by their early twenties. Mobility of the person with FOP becomes more rigid and disabled with age. Any injury to soft tissue can increase the progression of its transformation into bone and is usually the case, but can occur without detectable trauma. (Feldman *et al*, 2000). Mahboubi and fellow researchers observed that the ossification of the affected site are recognized by the spontaneous appearance of large tumor-like swellings of highly vascular fibroproliferative tissue that arises after the death of muscle cells. These swelling occasionally regress but most often from bones. They are first identified by soft-tissue lesions. A biopsy of the lesion can not be taken, since the process of taking it would exacerbate the condition. The lesions progress through an expected course, in the first few weeks there is pain, swelling, warmth and tenderness, but after several weeks the swelling as well as the pain starts to subside as the intermediate lesion forms. Within three months the swelling disappears and the patient is left with a new bone created by heterotopic ossification. The bone formed in FOP is normal but is temporally and spatially inappropriate (Fiori *et al*, 2006).

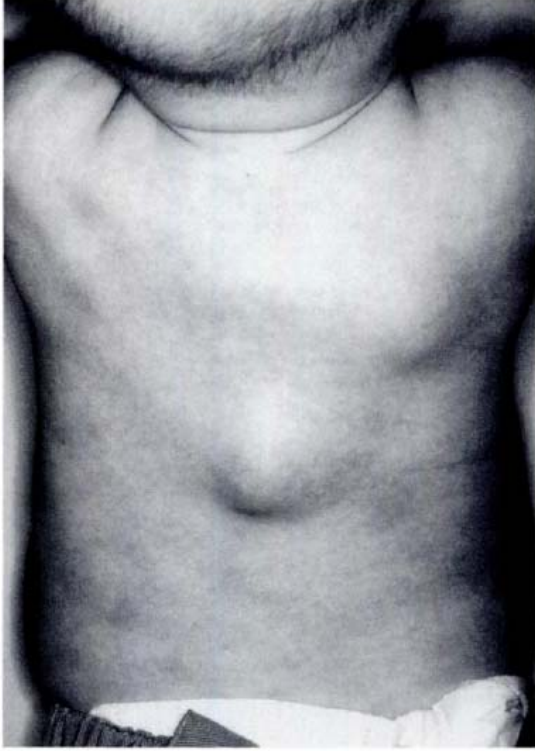


Figure 4: Infant showing soft tissue nodules on the back. These nodules are characteristically present in the earliest stages of FOP. (Kaplan *et al*, 1993)

In a study, researchers Connor and Evans found the progression of disability was erratic but severe restriction of movement of the shoulder and spine was usual by the age of 10 years and the hips were affected by the age of 20 years and confined to a wheelchair by the age of 30 years. Researchers have also observed that Permanent restriction of mandibular opening is seen in approximately 80% of the cases and occurs on the average age of 18 years (Meij *et al*, 2005).

Site	Age		
	10 or more years <i>n</i> = 29	20 or more years <i>n</i> = 25	30 or more years <i>n</i> = 15
Spine	93	100	100
L Shoulder	79	100	100
R Shoulder	79	96	100
L Elbow	10	40	53
R Elbow	3	36	73
L Wrist	0	4	20
R Wrist	0	16	27
L Hip	10	72	80
R Hip	0	60	93
L Knee	7	40	67
R Knee	7	44	73
L Ankle	3	28	40
R Ankle	0	32	47
Jaw	14	44	73

Figure 5: This table shows the progression of FOP in three age categories. It shows the distribution and percentage frequency of severe involvement of the joints related to age. With every increasing age column, the frequency of the joint involvement increases. (Conner *et al*, 1982)

Fibrodysplasia ossificans progressiva is genetically linked. In a study by Feldmen and fellow researches in 2000 they described a genome wide linkage analysis in four small families containing individuals affected with FOP and demonstrated locus homogeneity and linkage of the FOP gene at a 36-cM segment on the long arm of human chromosome 4.

To identify the chromosomal location of the FOP gene, they conducted a genome wide linkage analysis, using four affected families with a total of 14 informative meiosis events. These subjects were first genotyped. The researchers obtained peripheral blood from them and a set of highly polymorphic microsatellite markers covering all human autosomes were amplified by use of PCR. They were then denatured and separated by sized markers on gel and exposed to autoradiography film. A two point linkage analysis was performed and on the basis that penetrance of the FOP gene is 100%. They then constructed haplotypes from the genotype data.

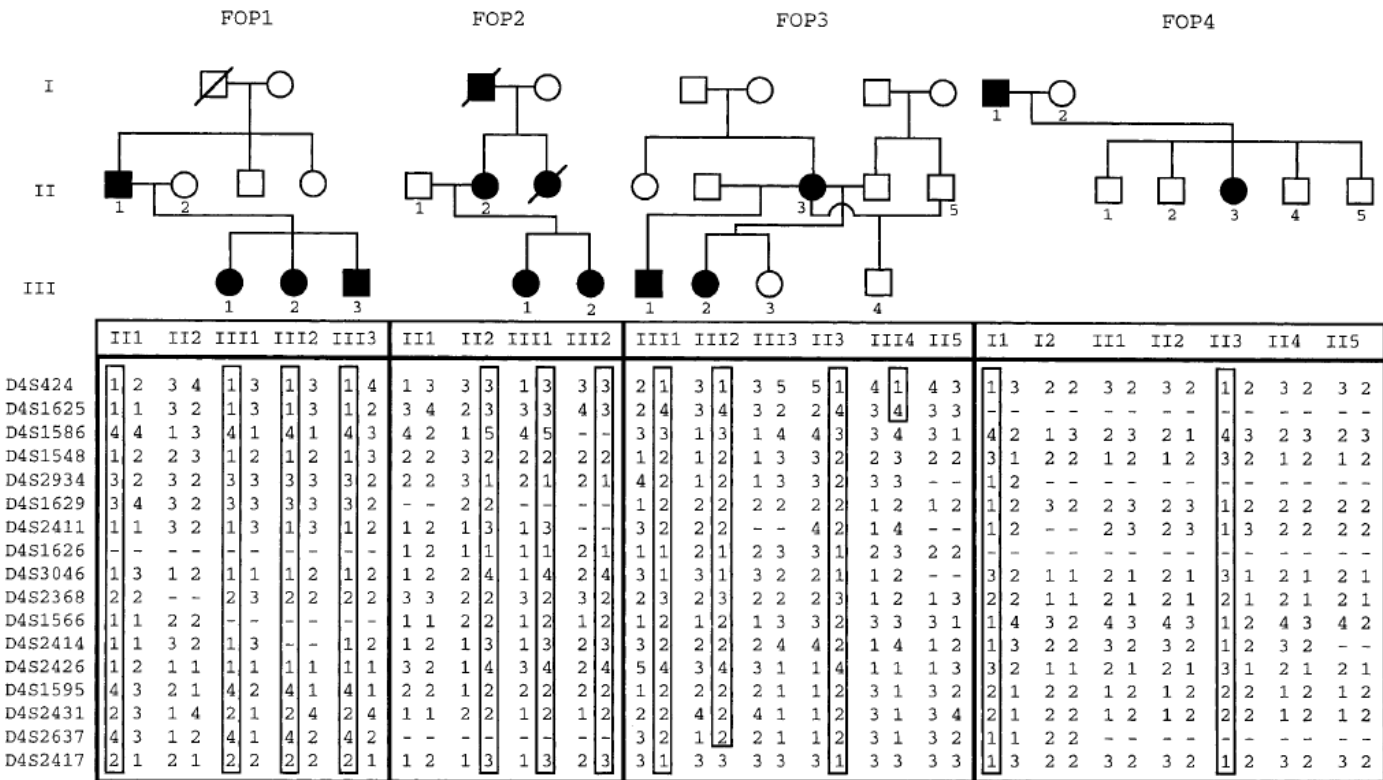


Figure 6: The pedigrees of 4 different families who have a history of FOP. They all have genotypes for markers from the chromosome 4q27-31. The haplotypes for the markers that are listed on the left of the table are listed below the symbols for the family members. For instance II1 in FOP1 is the afflicted male in the second generation. The haplotype that represents the people with the disorder are boxed. (Feldmen *et al*, 2000)

Based on their results they excluded X-linked inheritance since male-to-male transmission of the FOP phenotype was observed. In each family, penetrance was complete, and the inheritance pattern was consistent with autosomal-dominant transmission. They also used radiation-hybrid mapping to locate the gene, and based on that they were able to determine that the FOP phenotype is linked to markers located in the 4q27-31 region a 36-cM interval on human chromosome 4. The two-point LOD score calculation for the combined family data gave an LOD score of 3.31 with the markers D4S1548 and D4S2426 and with a recombination fraction of 0. Boundaries of the linked region were established by crossover events and showed to be bordered proximally by D4S1625 and distally by D4S2417. The interval contains at least one gene involved in the bone morphogenetic protein-signaling pathway. Linkage data from a genome wide screen support the localization of the gene that causes FOP to 4q27-31. Since there are more than a 100 anonymous transcripts in the 4q27-31 linked interval, the FOP gene may be a gene in the pathway that influences BMP activity.

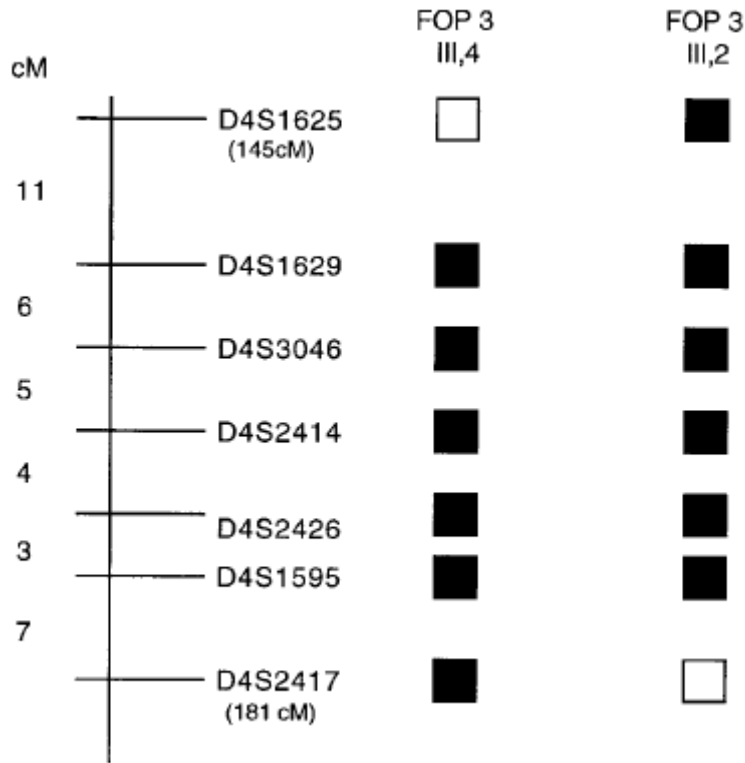


Figure 7: This shows the localization of the FOP-linked interval on the long arm of human chromosome 4. It represents the region of 4q27-31 with the markers used in the Feldmen genetic linkage analysis. The black boxes indicate regions of the allele that are shared by the people with FOP, the white boxes indicate crossovers. Therefore the gene must be within the region that is shared by all the FOP patients and between the markers that show crossovers, and this region is shown to be 36-cM long. (Feldmen *et al*, 2000)

BMP4 desregulation is found in all FOP patients. Little is known about the signals that initiate the differentiation of cells toward a chondrogenic or osteogenic pathway. The genetic defect in FOP is likely to be such an inductive signal (Feldmen *et al*, 2000). In a study by Fiori and fellow researchers they found that BMP4 mRNA and protein and BMP4 receptor type IA proteins are over expressed in cultured lymphocytes from FOP patients. In the search for candidate genes, they also discovered that, whereas BMP's are not mutated in FOP patients, the BMP signaling pathway is dysregulated in the FOP lymphoblastoid cell system. In another study by Kaplan and his fellow researchers they postulated that bone morphogenetic protein 4 (BMP-4) signaling was dysregulated in FOP cells and that a dysregulated BMP-4 signaling pathway could account for a congenital loss-of-function phenotype which causes malformed great toes. It could also account for the postnatal gain-of-function phenotype which results in progressive heterotopic ossification in an endochondral pattern. According to their studies bone morphogenetic proteins (BMPs), members of the transforming growth factor (TGF)- β super-family of proteins, act as gradient morphogens in a concentration-dependent manner to specify cell fate in embryogenesis and in post-natal bone regeneration. BMPs are both sufficient and necessary to induce the complete cellular

program of endochondral osteogenesis at heterotopic sites in vivo. BMP-4 is essential for the morphogenesis of the great toe and transgenic mice over expressing BMP-4 manifest an FOP-like phenotype of progressive heterotopic ossification. They concluded that the BMP-4 signal transduction pathway is dysregulated in FOP cells and predicts a BMP-4 loss-of-function phenotype developmentally and a BMP-4 gain of function phenotype post-natal.

There are no effective Treatments for FOP. Since surgical treatment exposes the patient to the risk of exacerbation it is not an option. In cases where surgery was attempted to fix this disorder there was a recurrence within 2 months and it triggered an accelerated progression of the disease. Although the bone can be removed surgically so that a fused joint may temporarily be more mobile, the bone is virtually guaranteed to reform, and often more abundantly than the original condition. Therefore elective surgery on the musculoskeletal system should be avoided (Meij *et al*, 2005). The lifespan of a person with FOP is greatly reduced by developing restrictive disease of the chest wall due to the attachment of the spine and rib cage (Kaplan *et al*. 1993). This would cause them the inability to expand their rib cages to expand their lungs, and inhale therefore they suffocate. The only treatment available is prevention. According to Goncalves and her fellow researchers, to prevent or rather not catalyze the disorder patients should try to prevent soft tissue injury or muscle damage. Damage by avoiding falls. Also intramuscular injections should be avoided, as well as overstretching the jaw during routine dental care. FOP patients may also have an increased likelihood of flare-ups after flu like illness. Therefore a flu vaccine should be considered especially FOP patients who already have a severe restrictive chest wall disease at which they have a greater chance of contracting respiratory infections. A treatment researchers are investigating is antiangiogenic therapy. Angiogenesis is a main histopathologic feature of FOP lesions, and by its therapy it can be used in heterotopic ossification to inhibit new blood vessel formation that would inhibit the production of a heterotopic bone since to form bone it needs blood vessels. (Kaplan *et al*, 2004)

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