Fibrodysplasia Ossifians Progressiva

Clinical overview and atypical course

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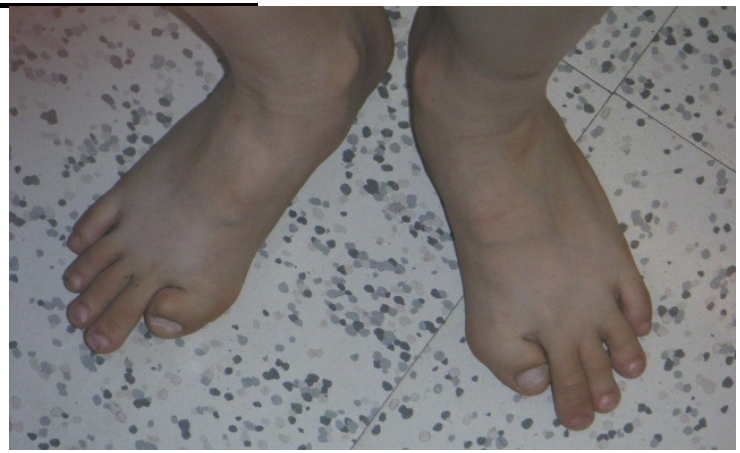
AM Kottler, Molecular biology, *CHU Caen*

FOP- Classical form

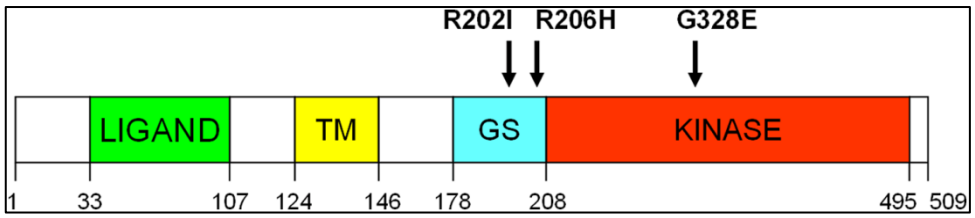
Multiple ectopic ossifications occuring after spontaneous flare up or following trauma as immunization, falls or viral illness *associated with malformative short first toes*



FOP –Molecular data

Shore et al , 2006

- *ACVR1* (Activin receptor type 1A) / ALK2
  - R206H, recurrent mutation, classical form
  - ACVR1 : BMP1 receptor



FOP phenotype spectrum

Hum Mutat. 2009 March ; 30(3): 379–390. doi:10.1002/humu.20868.

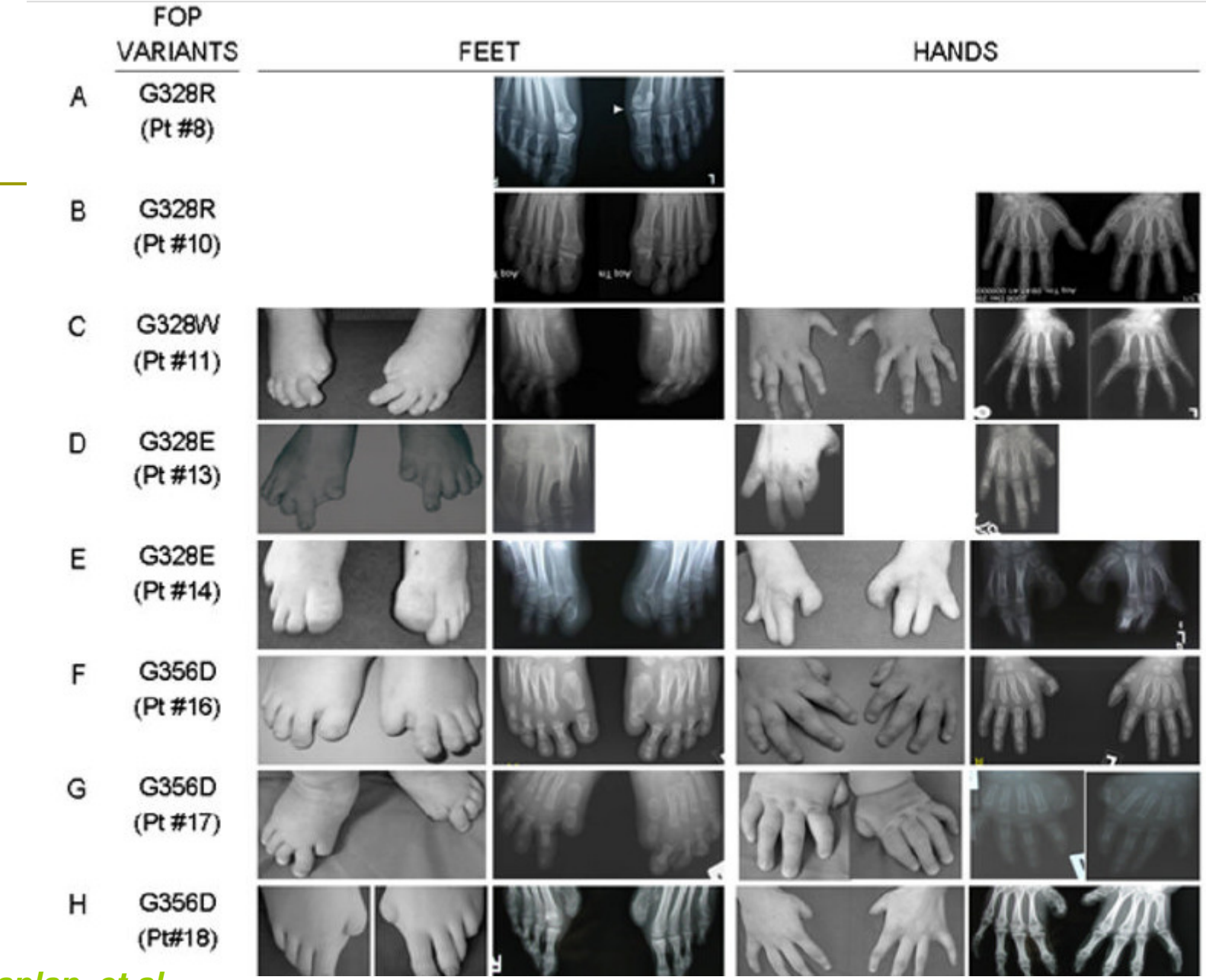
Classic and Atypical FOP Phenotypes are Caused by Mutations in the BMP Type I Receptor ACVR1

Frederick S. Kaplan[1,2], **Meiqi Xu**[1], **Petra Seemann**[4], **Michael Connor**[5], **David L. Glaser**[1], **Liam Carroll**[6], **Patricia Delai**[7], **Elisabeth Fastnacht-Urban**[8], **Stephen J. Forman**[9], **Gabriele Gillessen-Kaesbach**[10], **Julie Hoover-Fong**[11], **Bernhard Köster**[12], **Richard M. Pauli**[13], **William Reardon**[14], **Syed-Adeel Zaidi**[15], **Michael Zasloff**[1], **Rolf Morhart**[16], **Stefan Mundlos**[4,17], **Jay Groppe**[18], and **Eileen M. Shore**[1,3]

112 FOP	84 FOP classical Form	ACVR1 R206H
	8 FOP plus	R206H and several
	12 FOP Variants	
	7 families cases	ACVR1 R206H

FOP Phenotype spectrum- (Kaplan, 2009)

- FOP Classic
- FOP plus atypical features : aplastic anemia , polyostostic fibrous dysplasia, craniopharyngioma, glaucoma,retinopathy of prematurity…. Unlikely in relation with the disease
- Variants FOP: major variations in at least one classic feature associated or not with a unreported feature



Kaplan et al 2009

FOP -French experience

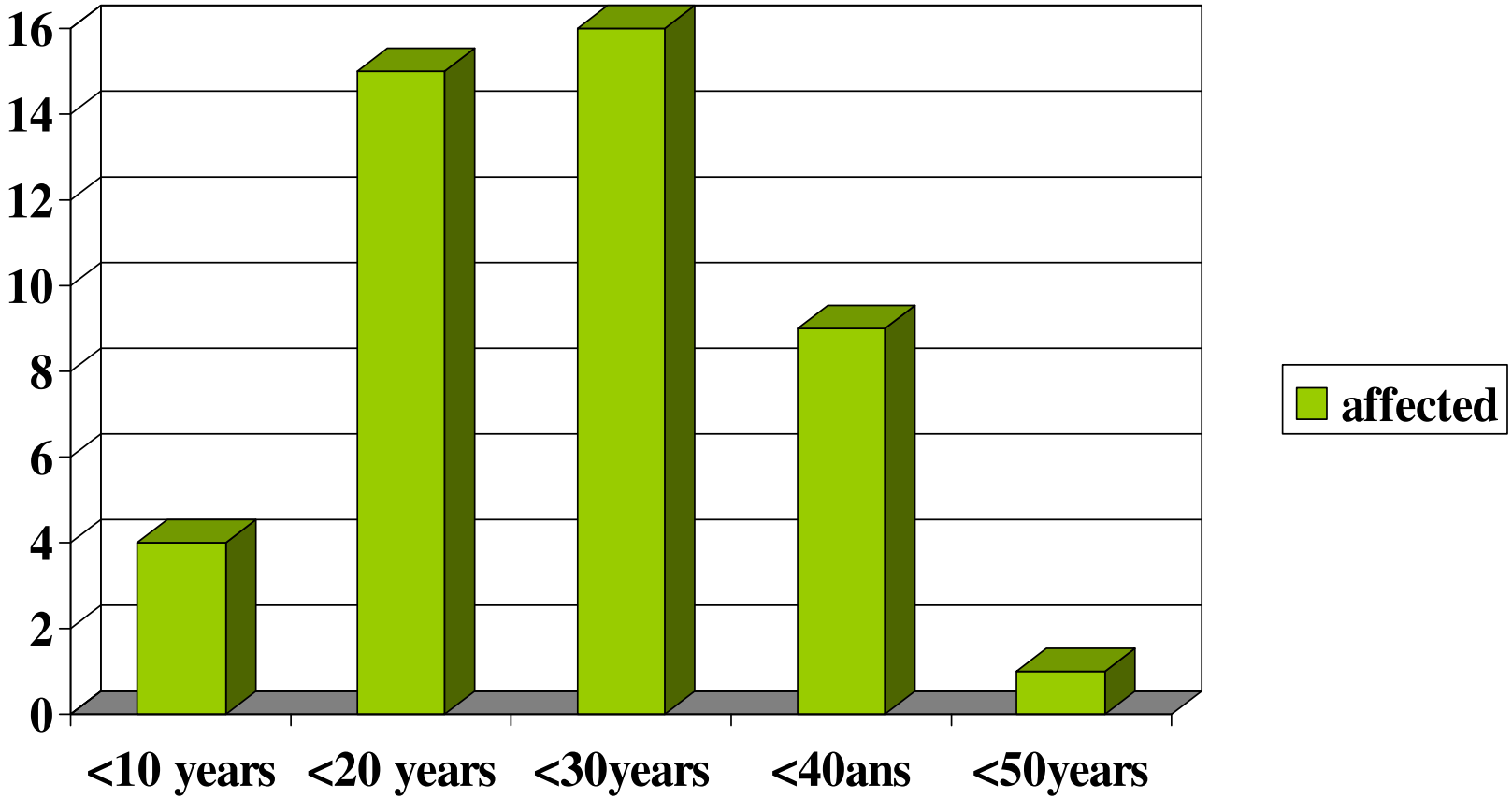
- **78 cases (1995-2011)**

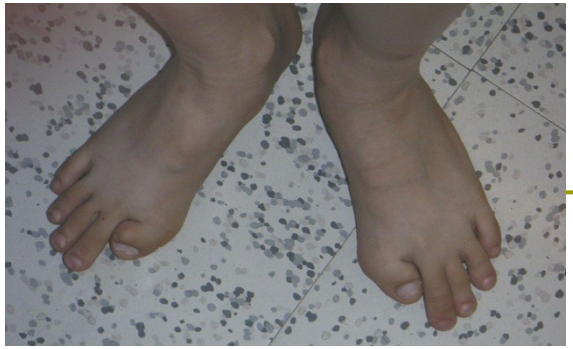
  Multifocal heterotopic ossification
  Microdactyly of the great toes (97.2)

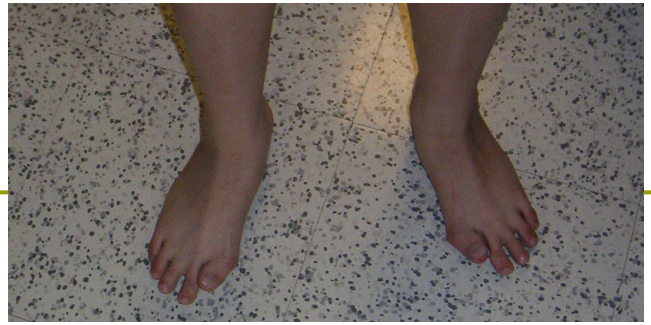
  - **Sex ratio: 0.9**
  - **Follow up : 56**
  - **Death: 8** (2 respiratory distress and 6 phlebitis)

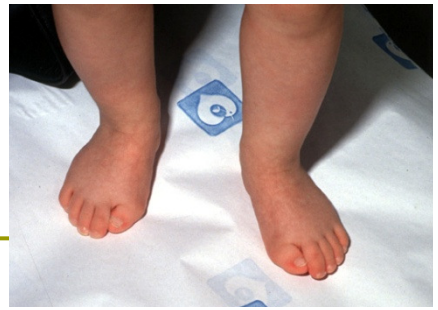
- **Genetics data**
  - **two families with FOP**
  - **75 sporadic cases**
  - **ACVR1 mutation screening : 51, all *R206H***

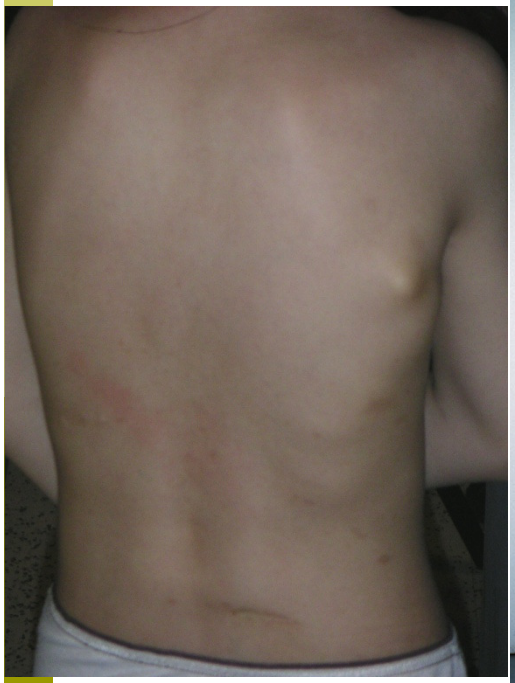
Age Distribution

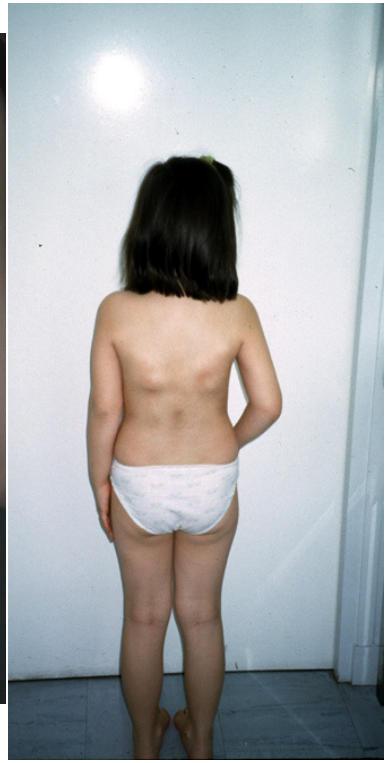


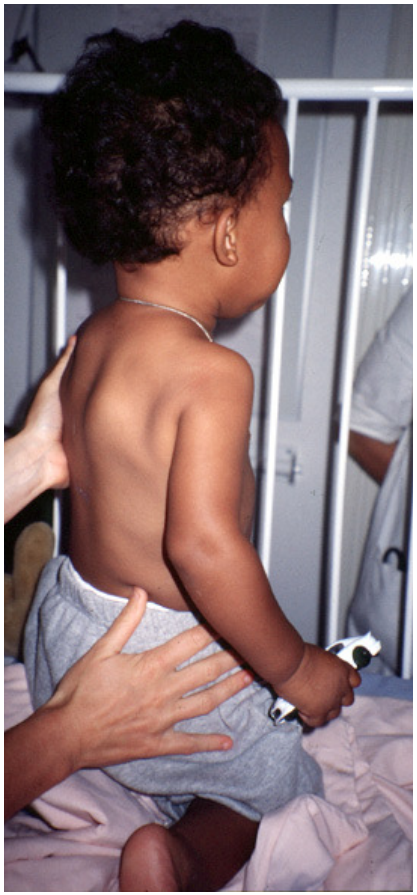


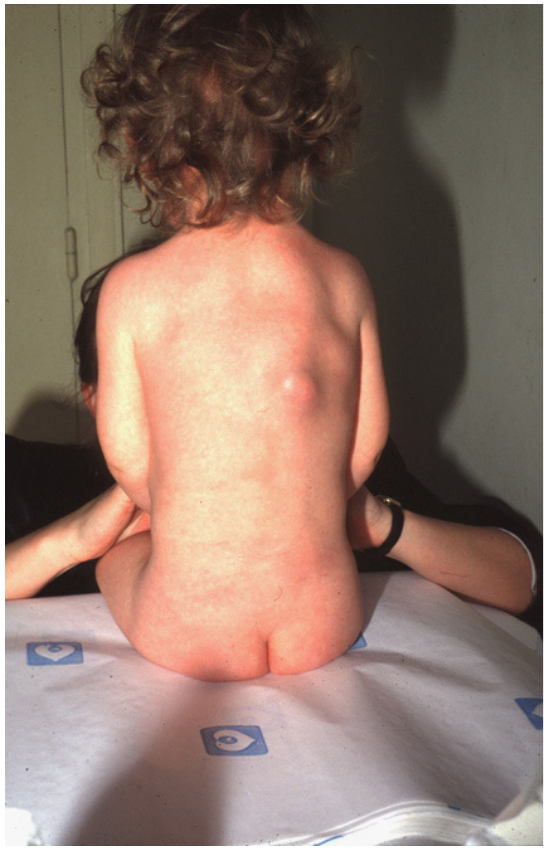


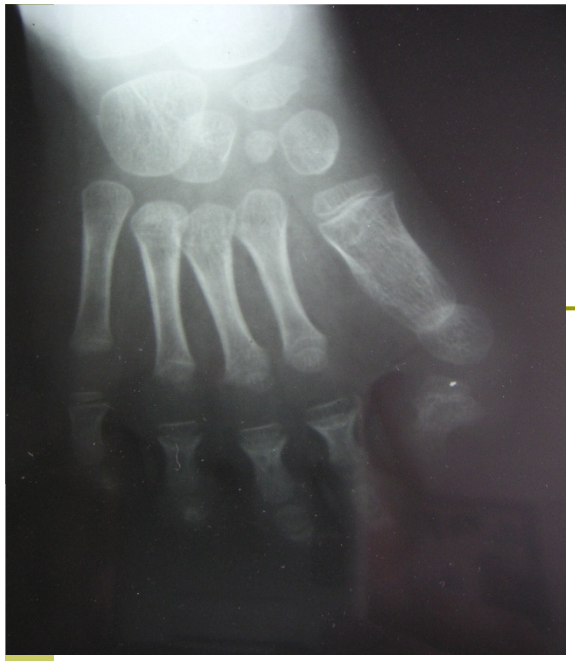


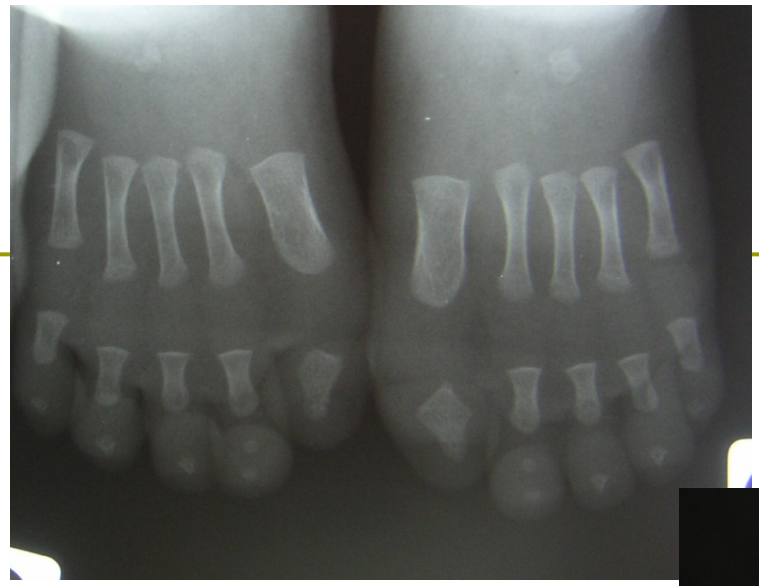


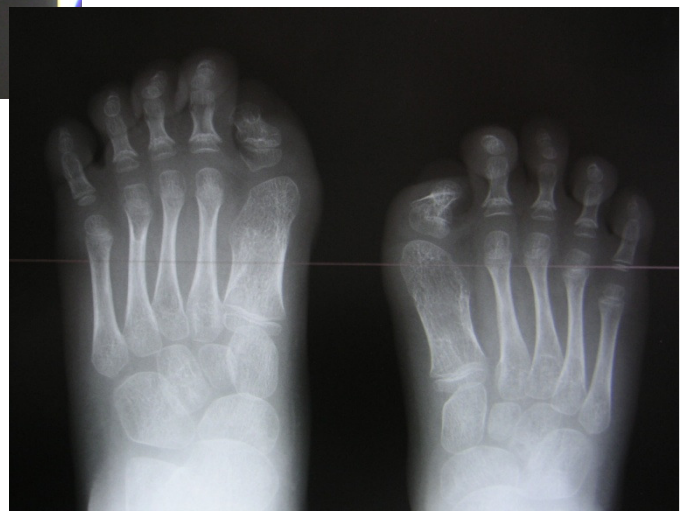


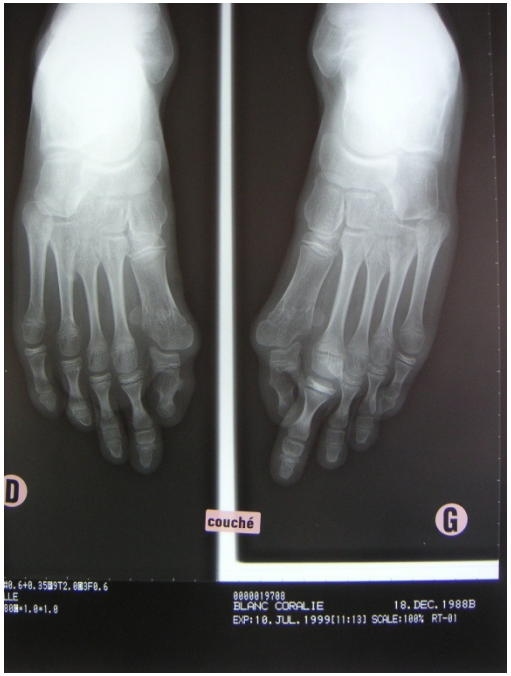








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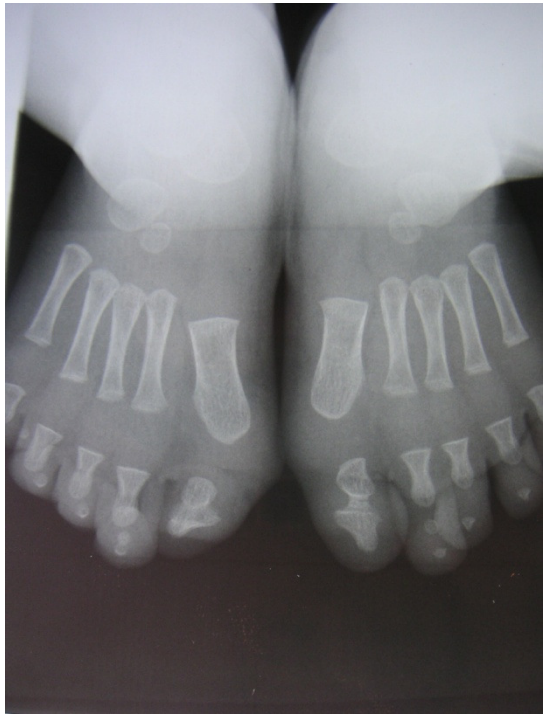

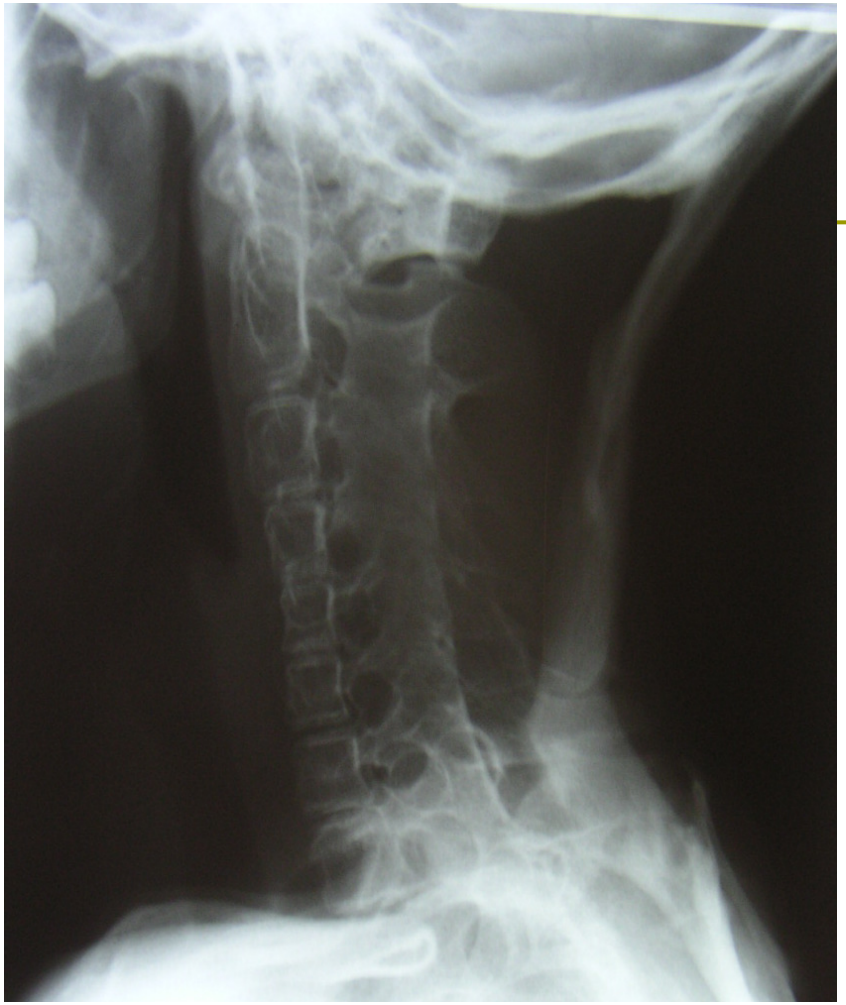

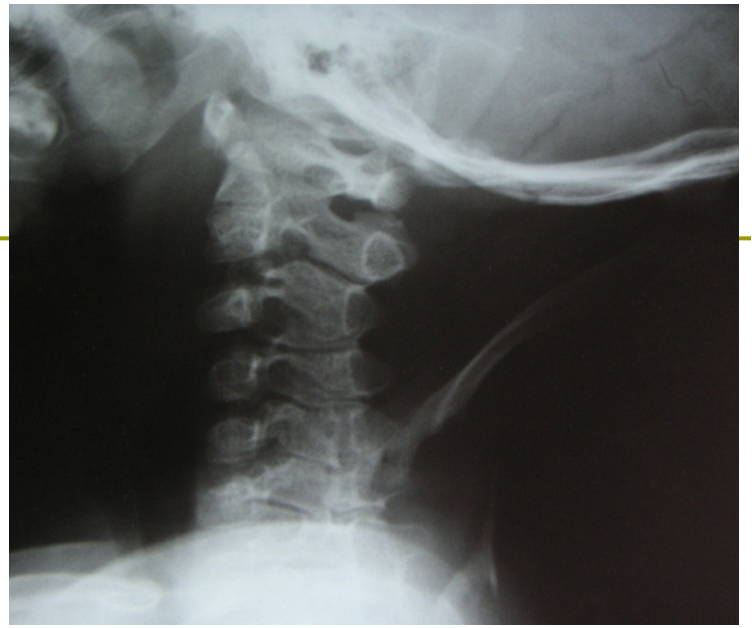

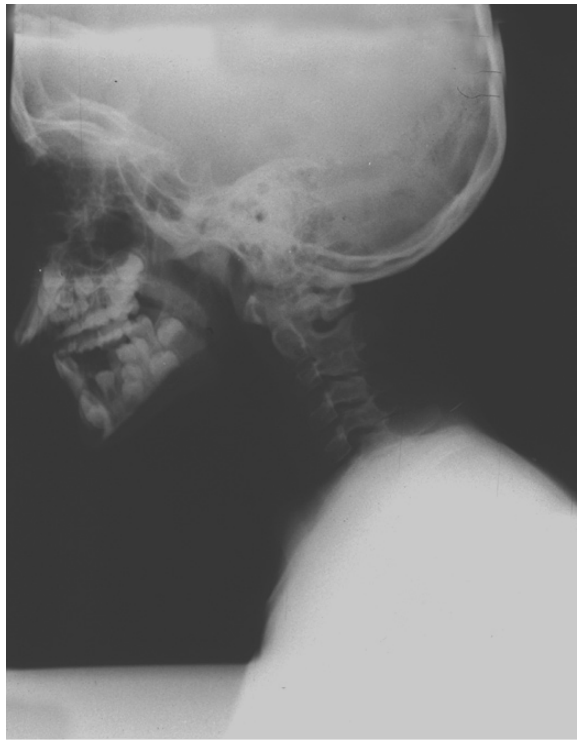

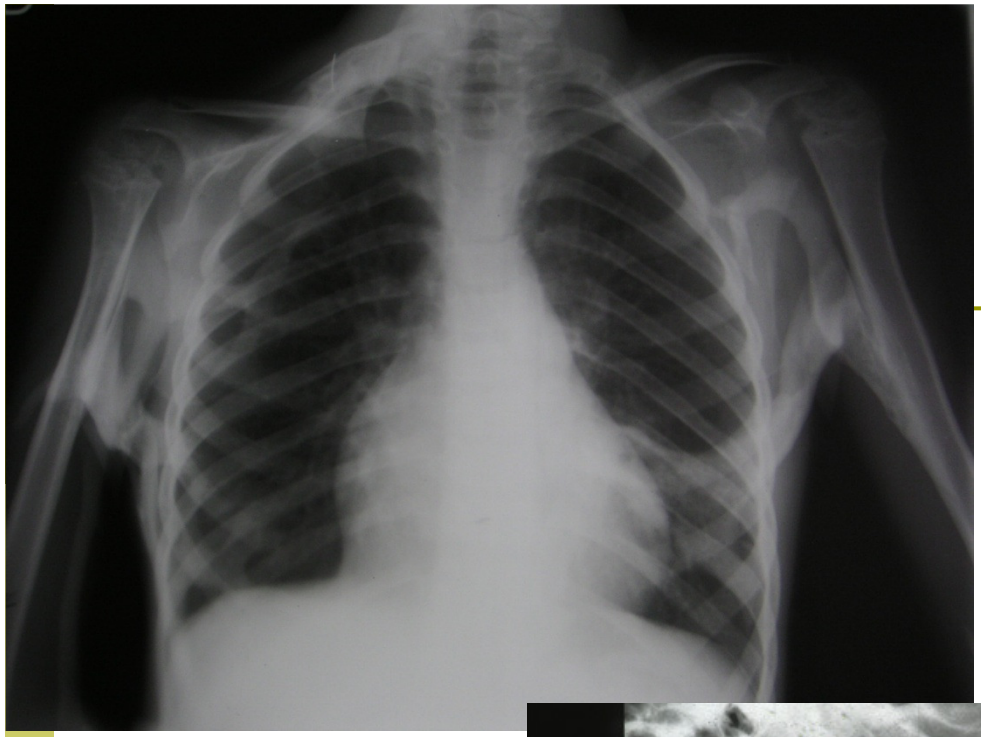

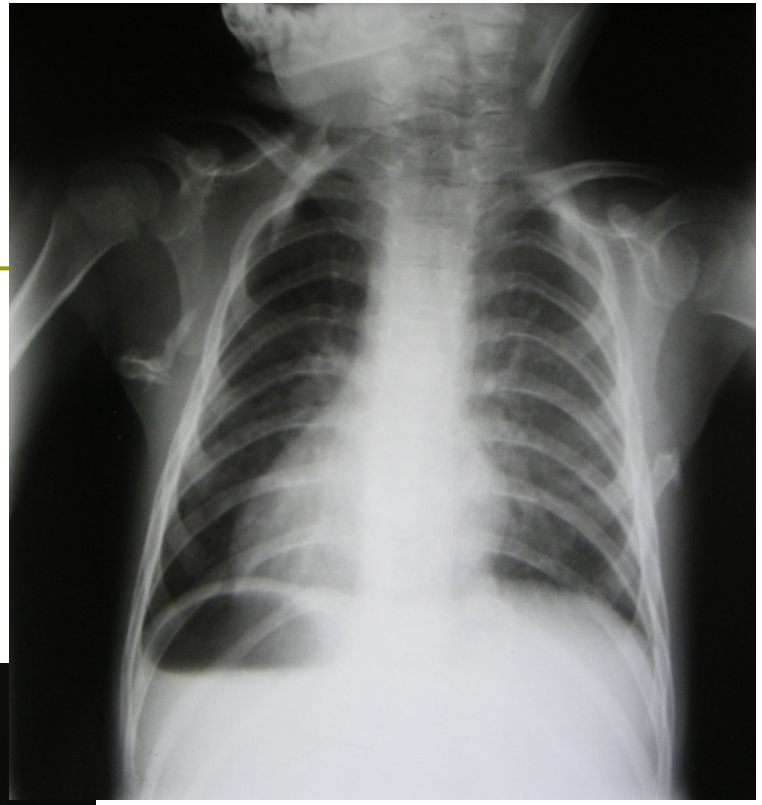

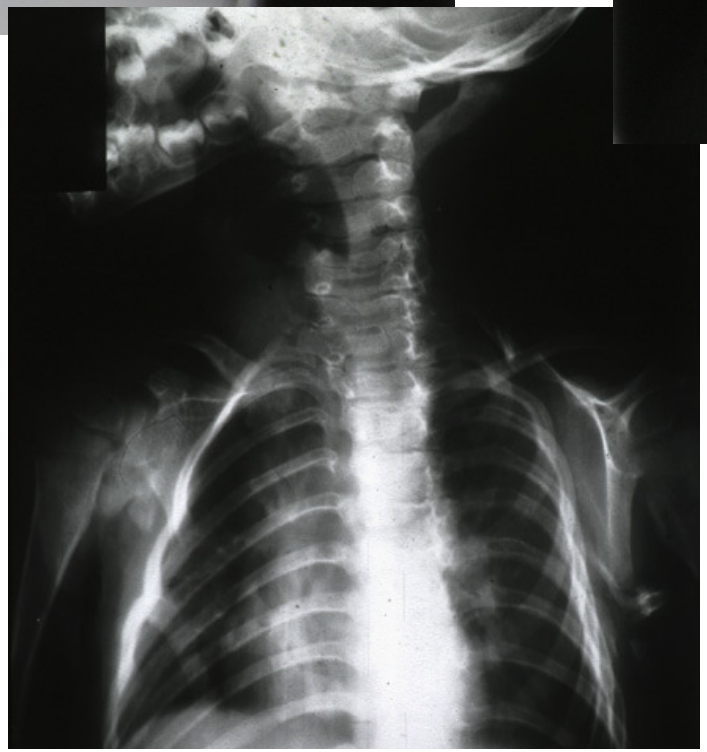

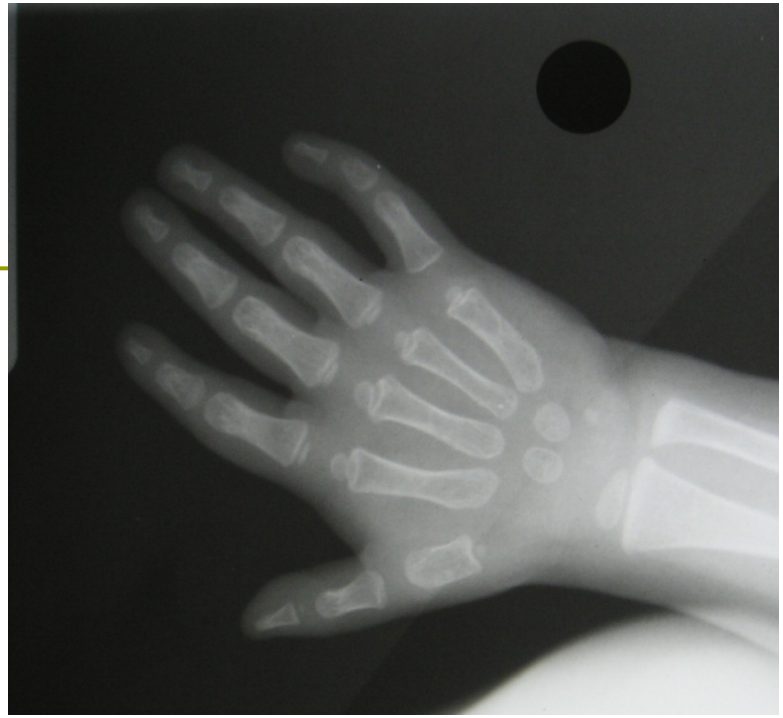

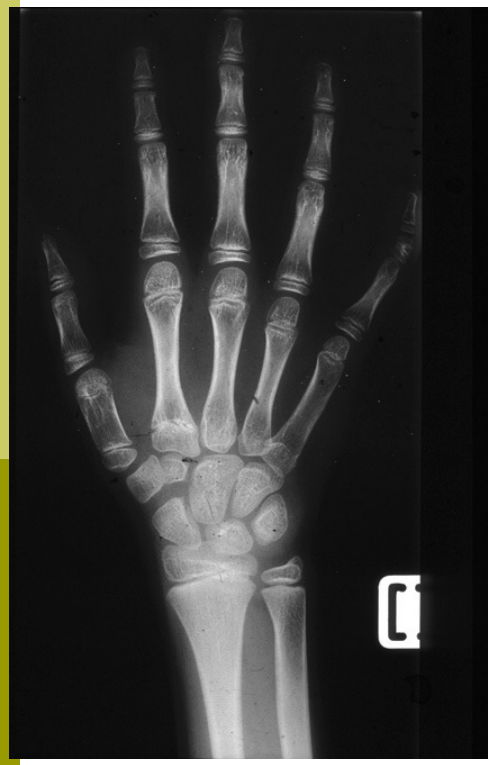

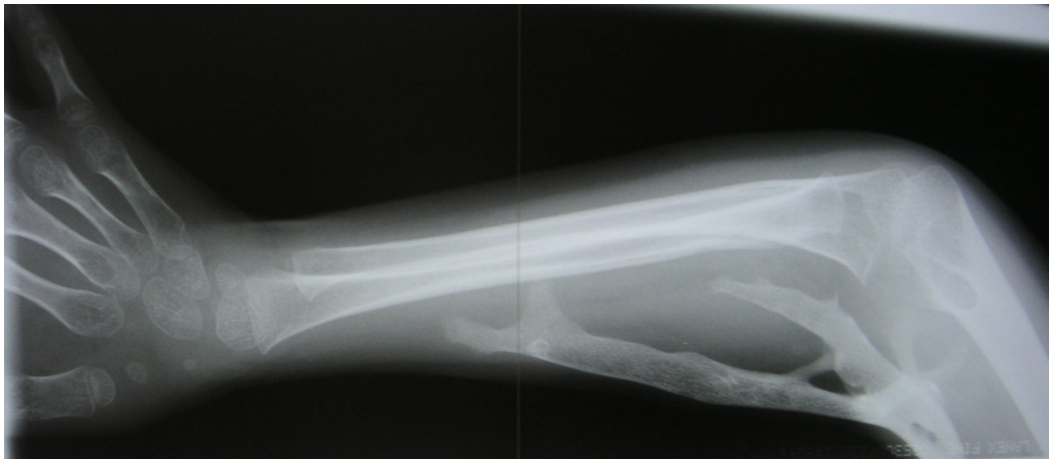

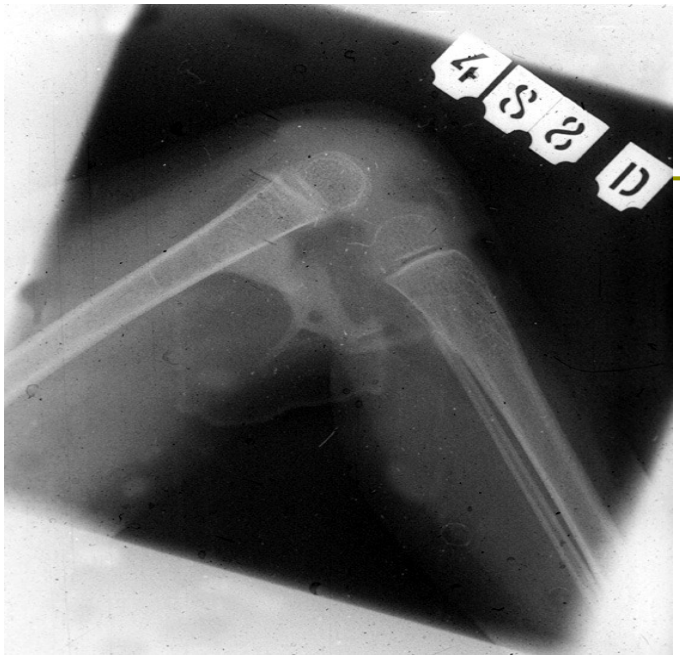
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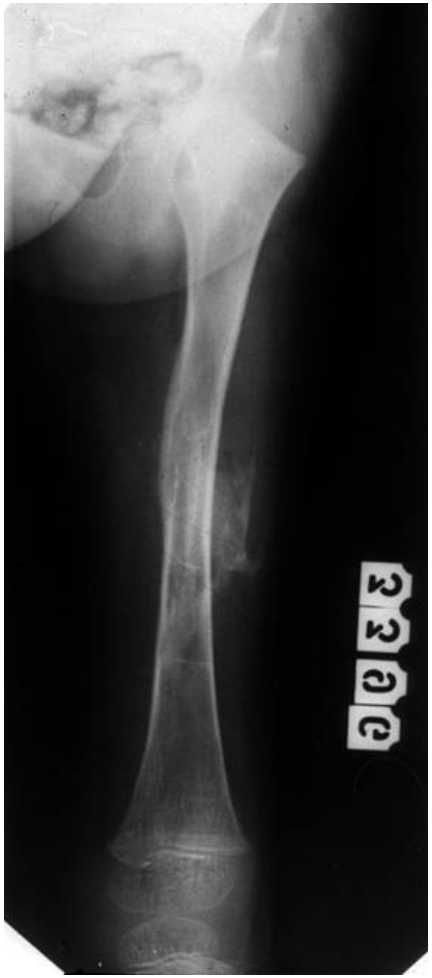
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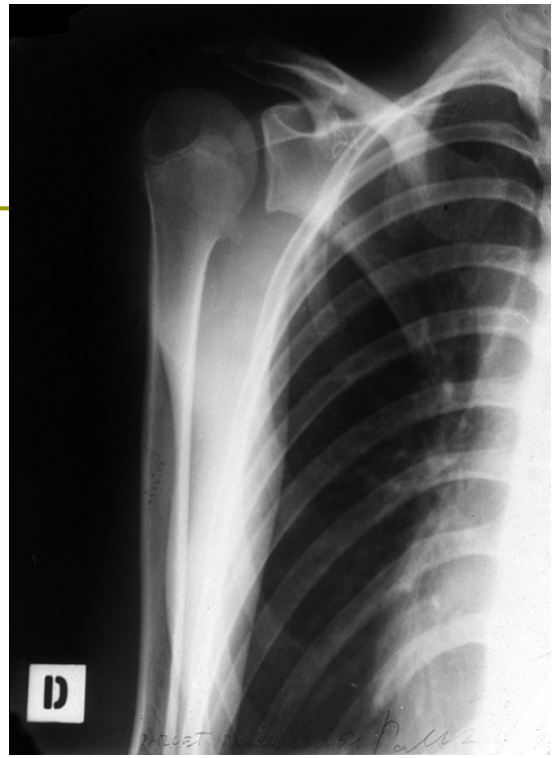
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FOP- Natural course

- Cranial to caudal, dorsal to ventral and proximal to distal ossification after to postinfectious or postraumatic flare up, maybe spontaneous
- Severity differs among patient, young patients could be yet in wheelchair during the teenage whereas some elderly are still walking
- The evolutivity of the disease is unexpected but there is an increase frequence of flare up during the adolescence
- There is a variability of the response to the viral infections

Is early onset synonym of severe course?

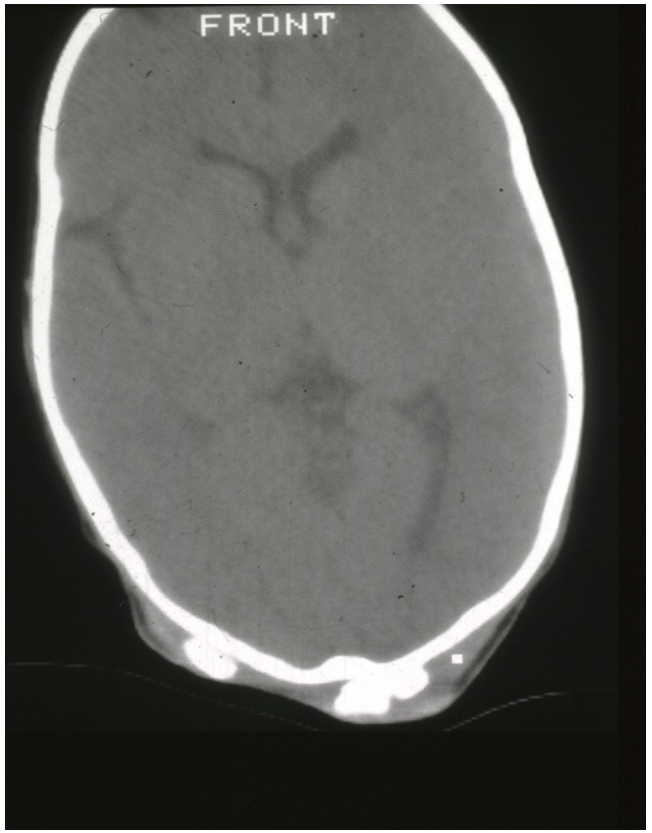
- Flare up early in the life (before 2 years)
  - After vaccination, on the neck or the back
  - Scalp nodules, at birth or before one year
  - Gradually craniocaudal ossification
- Series of flare up with progressive ankylosis before teenage
- Loss of walking at puberty
- Limitation of the jaw before puberty
- Congenital malformations, amputation, alopecia, vermis agenesis

Scalp nodules- dermatological point of view

Cranial fasciitis is a firm or elastic nodule of the scalp, which may be congenital or appear in children younger than 6 years with rapid enlargement in several weeks or months [Keyserling, AJNR 2003; 24: 1465-7.].

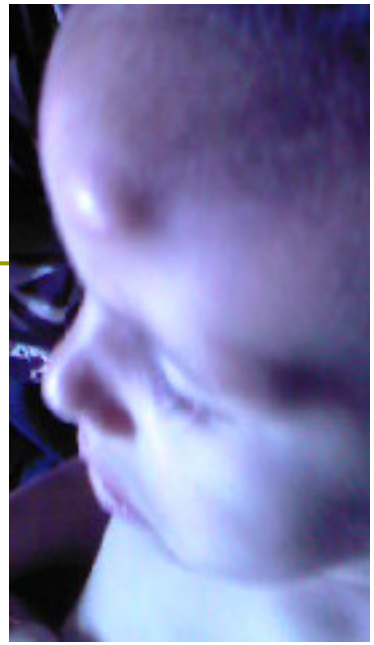
Histology and immunohistochemically examination show proliferation of fibroblasts and myofibroblasts in a myxoid stroma [Foureur, Ann Dermatol Venereol 2002; 129: 732-4].

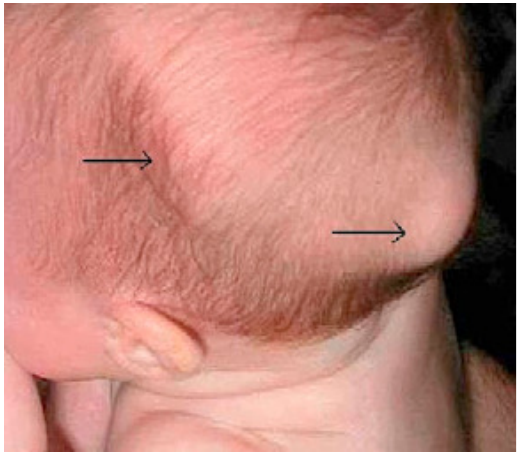
The prognosis is good and there is no recurrence after excision.



Scalp nodules

- 27 cases in the series
- mean age 2.4 years
- disappearing spontaneously
- often in severe cases





Scalp nodules as a presenting sign of fibrodysplasia ossificans progressiva: A register-based study

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Paris, France

Background: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder characterized by progressive ossification of soft tissues. Clinical diagnosis is important because trauma from lesional biopsies can exacerbate the disease.

Objective: We sought to evaluate the frequency of scalp nodules as the presenting manifestation of FOP.

Methods: We describe 3 infants with FOP who presented with multiple neonatal scalp nodules. We

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Scalp nodules – early feature of FOP ?

Associated to a microdactyly of the great toes, scalp nodules are the first symptoms of FOP

- French Study N=78

19/28 documented cases

  - Mean age=2.4, median=1.5, 17d-7y
  - 18/19 had a severe course
  - 19/19 ACVR1 R206H

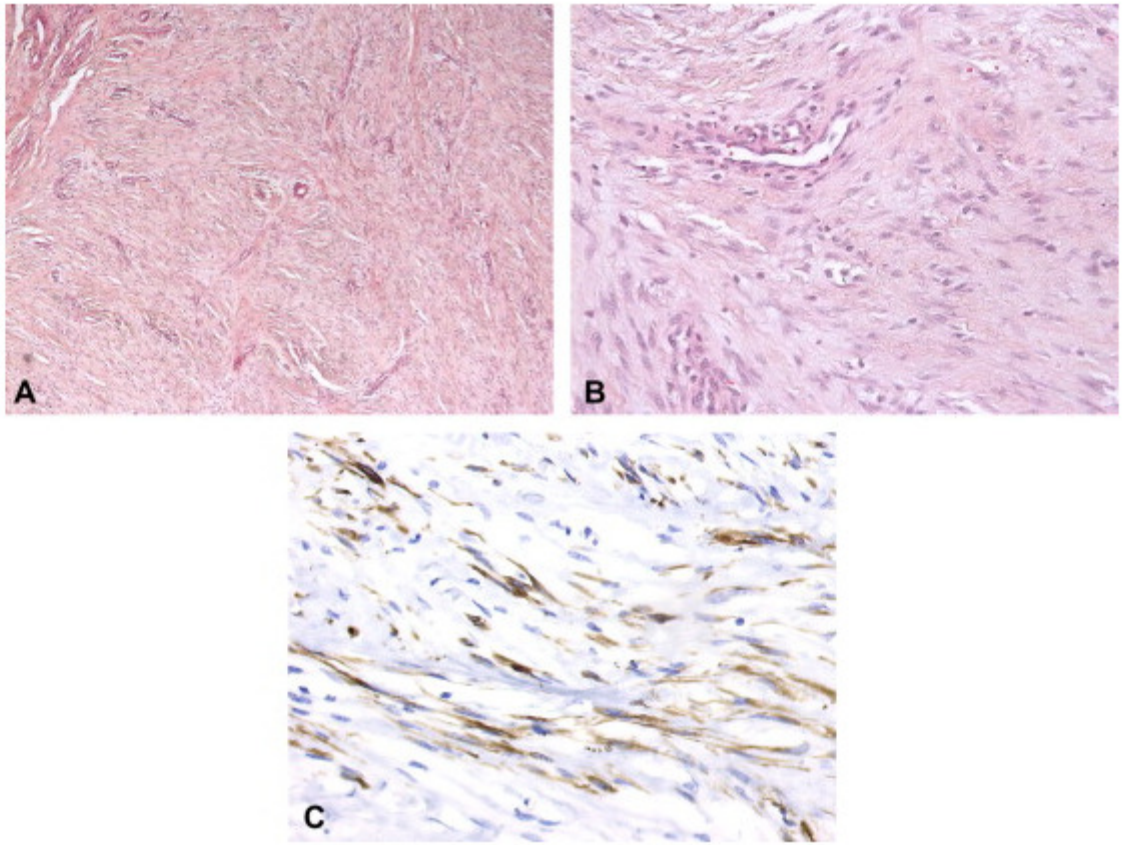
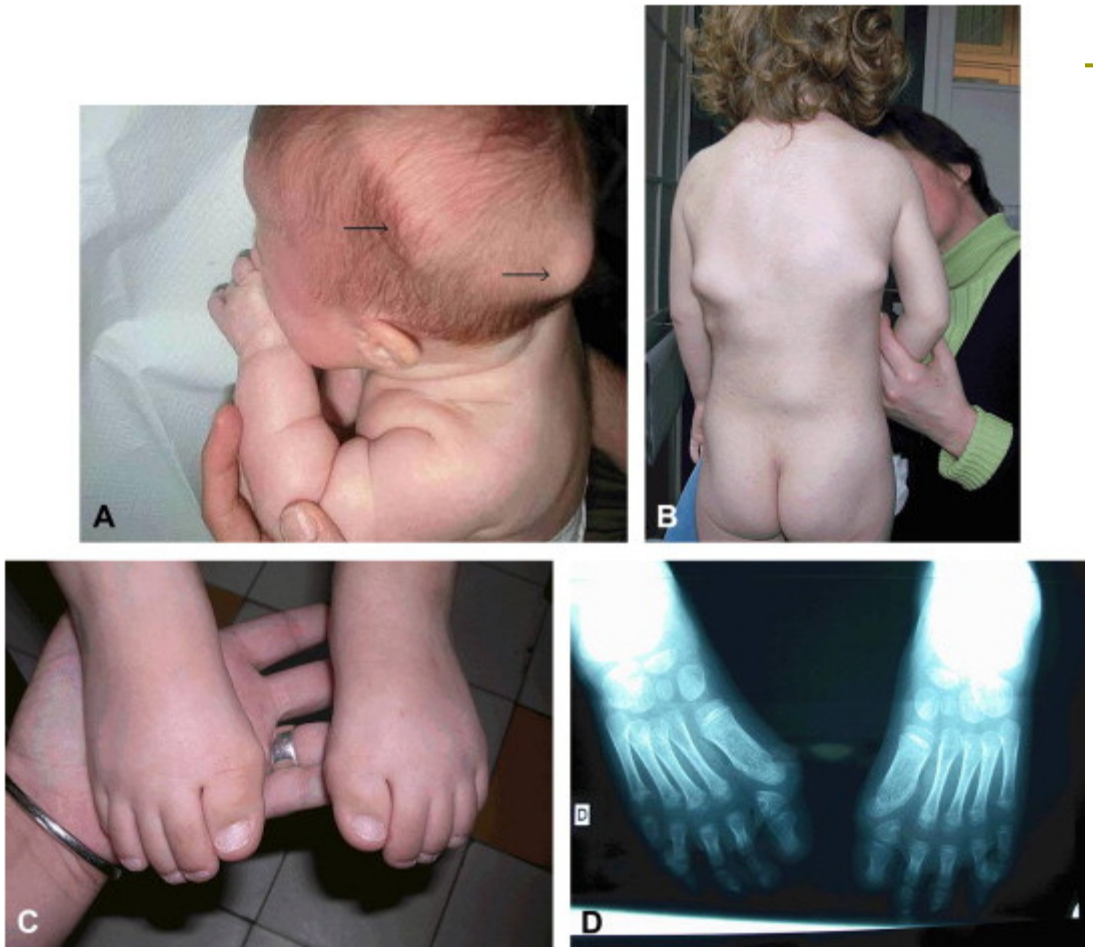


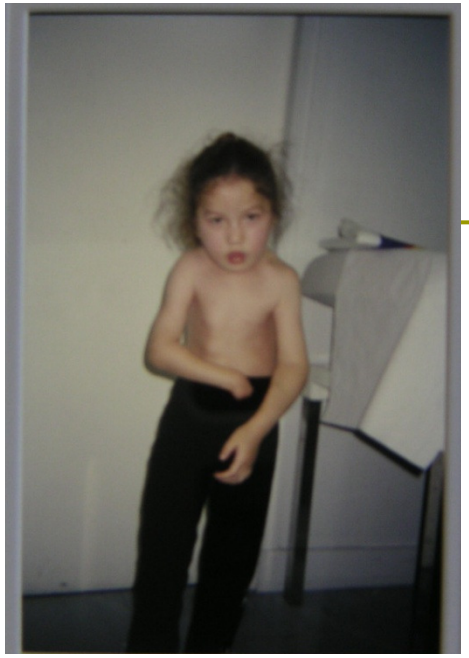
Fig 2

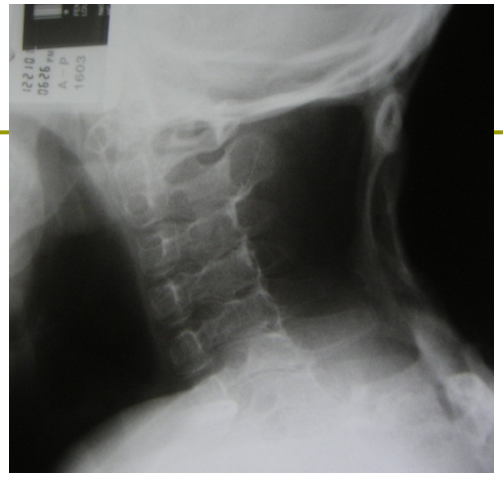
Patient 1, histopathologic analysis of nodule. **A**, Spindle-cell proliferation in deep subcutaneous tissue associated with abundant well-vascularized stroma. **B**, Short spindle-shaped cells randomly arranged in collagenous stroma. Numerous capillaries sometimes associated with mononuclear inflammatory cells arranged around these vessels. **C**, Positive staining for smooth muscle actin. (**A** to **C**,

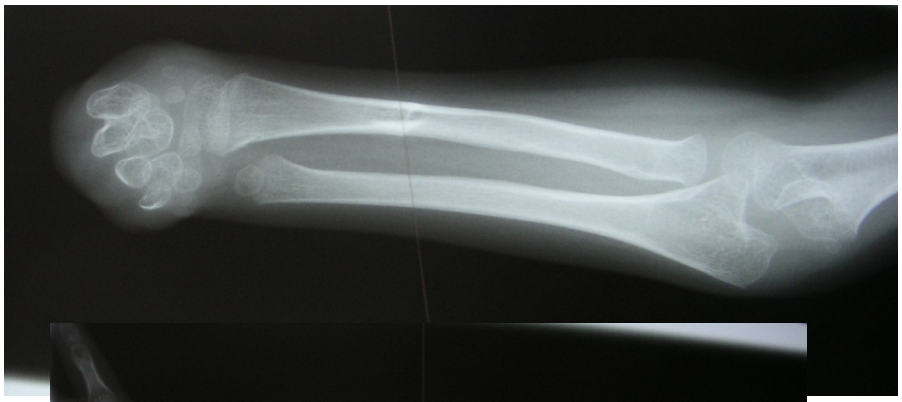

A
B
C
D

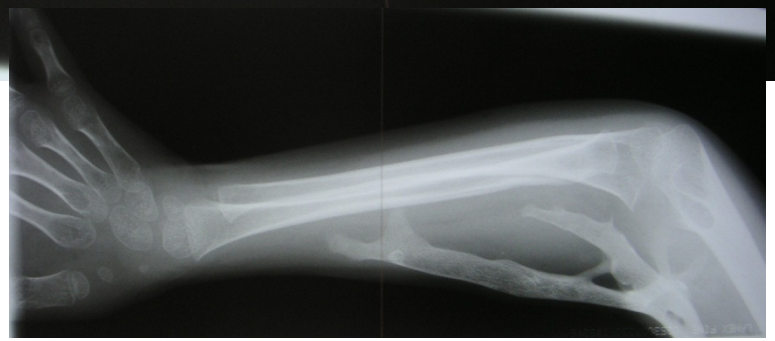
FOP –Variant forms Associated defects

	French study n=9	Kaplan study n=14
Transverse amputation of the hand	2	7
Cardiac defect (ASD)	2	-
Hip luxation/osteoenchondroma	2	3
Normal /minimal changes of great toes	2	3
Corpus callosum agenesis and vermis hypoplasia	1	2
Alopecia	4	6
Osteoma osteoid	1	-
Desmoid proliferation of the deltoid	1	-









5 years old, algerian

Transverse congenital defect of the right hand

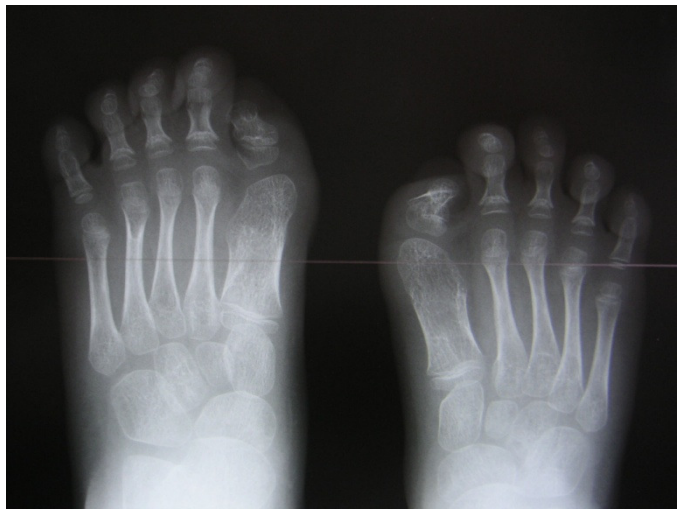
Swelling of the skull at birth

Cerebellar Vermis agenesis

Ankylosis of the jaw at 4 y

Karyotype 46 XX

ACVR1 R206H

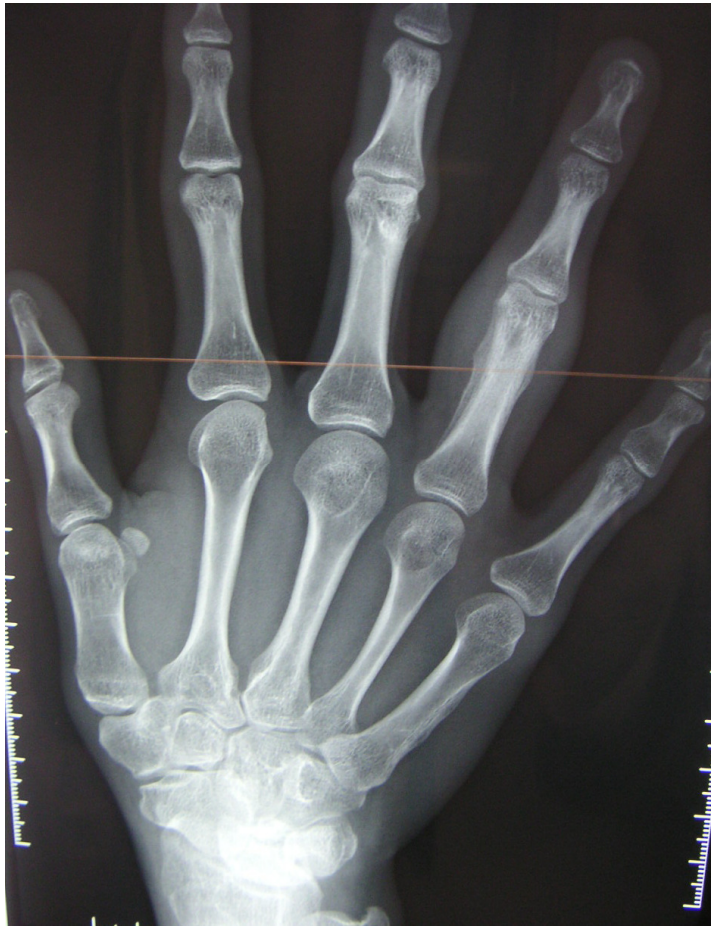


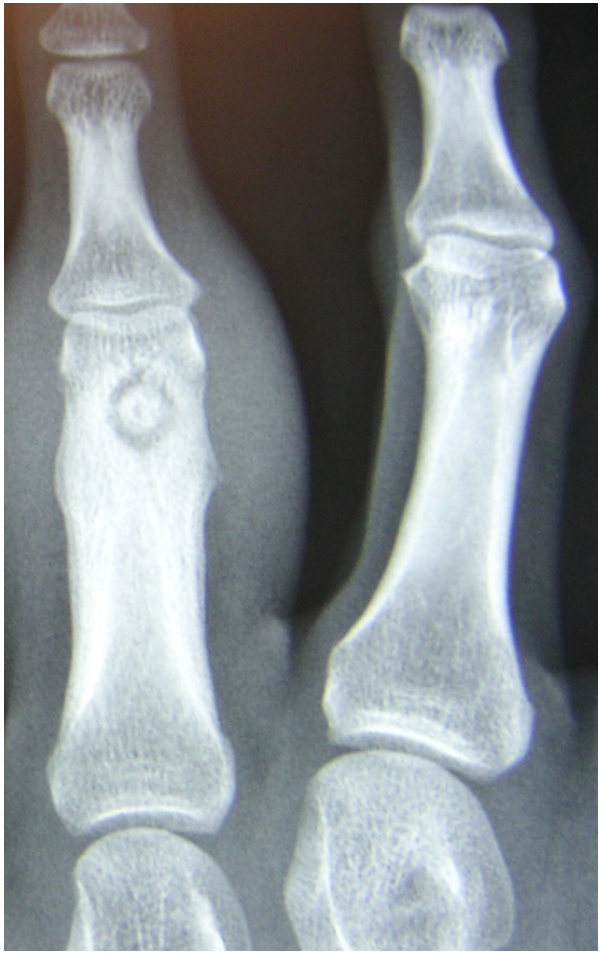
Coralie, 18 years

Pain +++ and swelling of the 4th digit

Osteoma osteoid

Surgery without problem





ACVR1 R206H

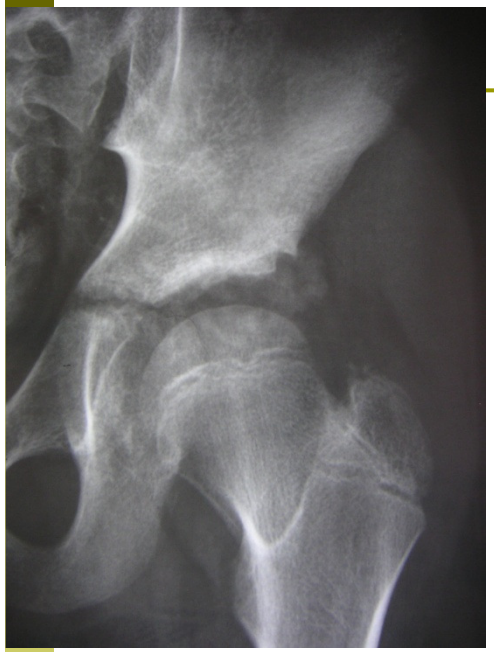
Is a late onset suggest a mild course?

- First flare up late in chilhood, teenage, or adult with mild abnormalities of the great toes
- Localisation of the flare up and the ectopic ossification not classical : lower back, hips lower limbs

→ Silent and progressive ossification

Mild and progressive disabilities for a long time

FOP or « localized ossificans myositis » ?

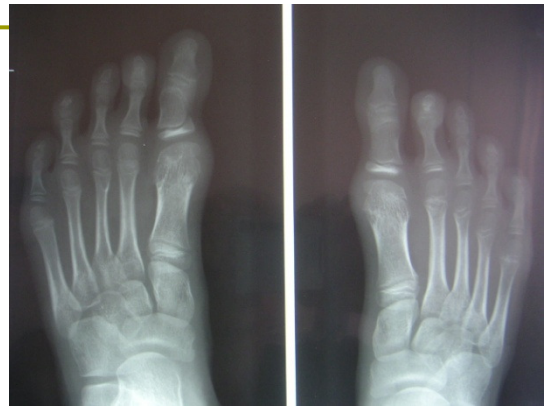


10 years , girl

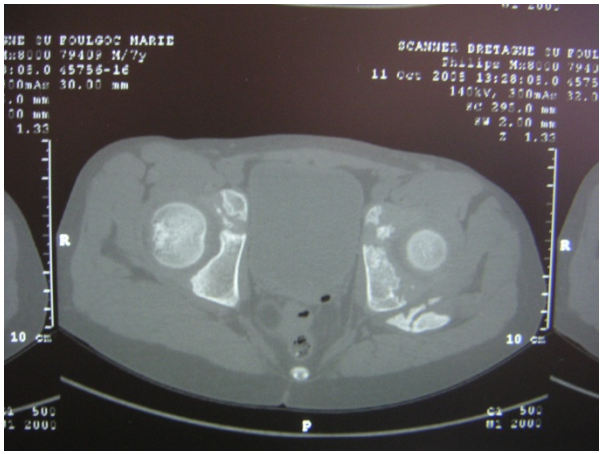
Pain and stiffness of the left hip

Normal neck

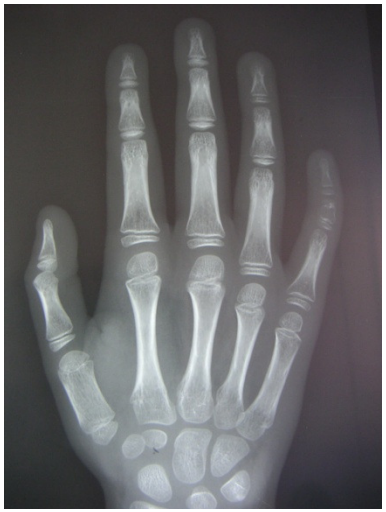
Xrays: Ossification



ACVR1 R206H

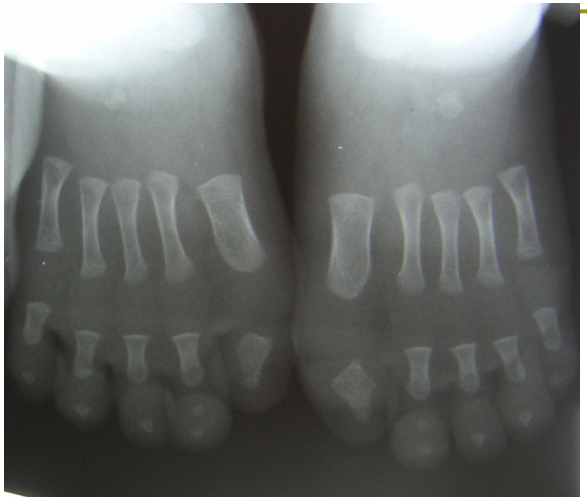


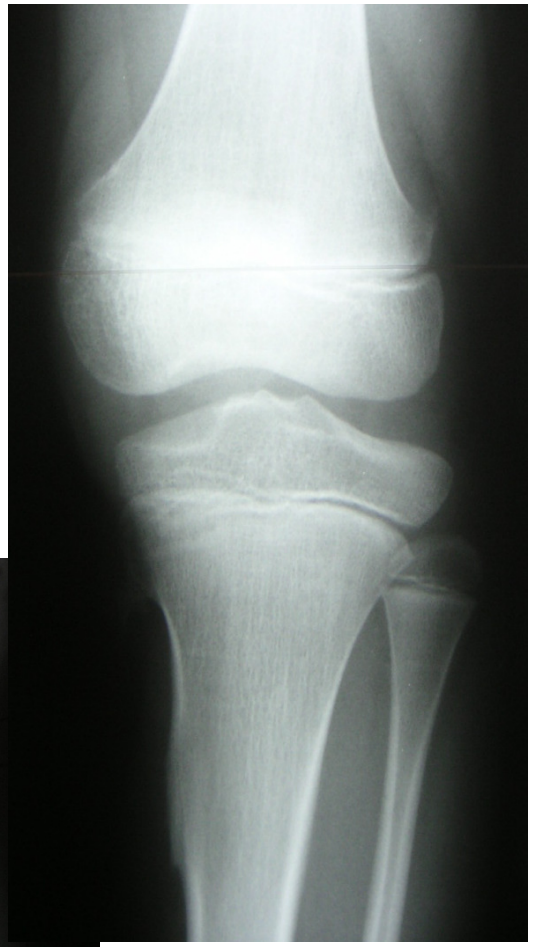
Mild Delta phalange of the great toes
Small first metacarpal and hypoplastic middle phalanges of the 5th

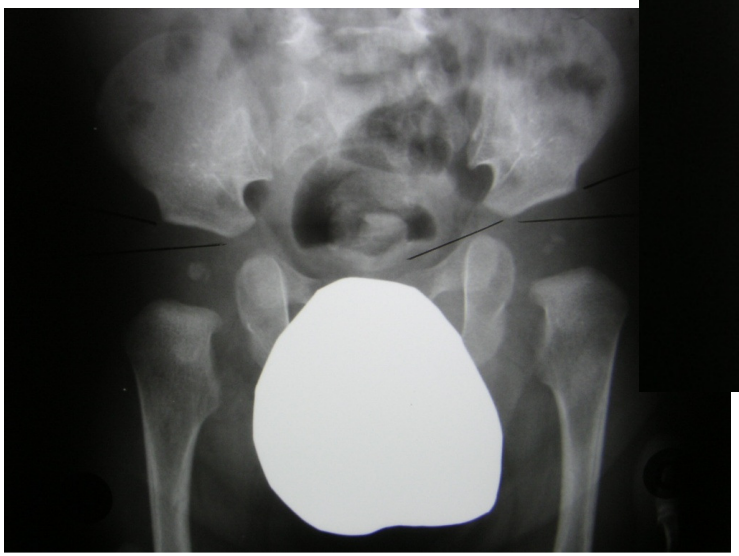


15 years, ossification in left quadriceps

Early diagnosis, but slow ossification







Diagnosis suspected at 18 **month**s on short great toes

Two years:

-stiff left hip

-normal neck mobility

Stability until **19 years** :

-Progressive retraction of the left lower limb with equinovarus

-Tall stature

ACVR1 R206H

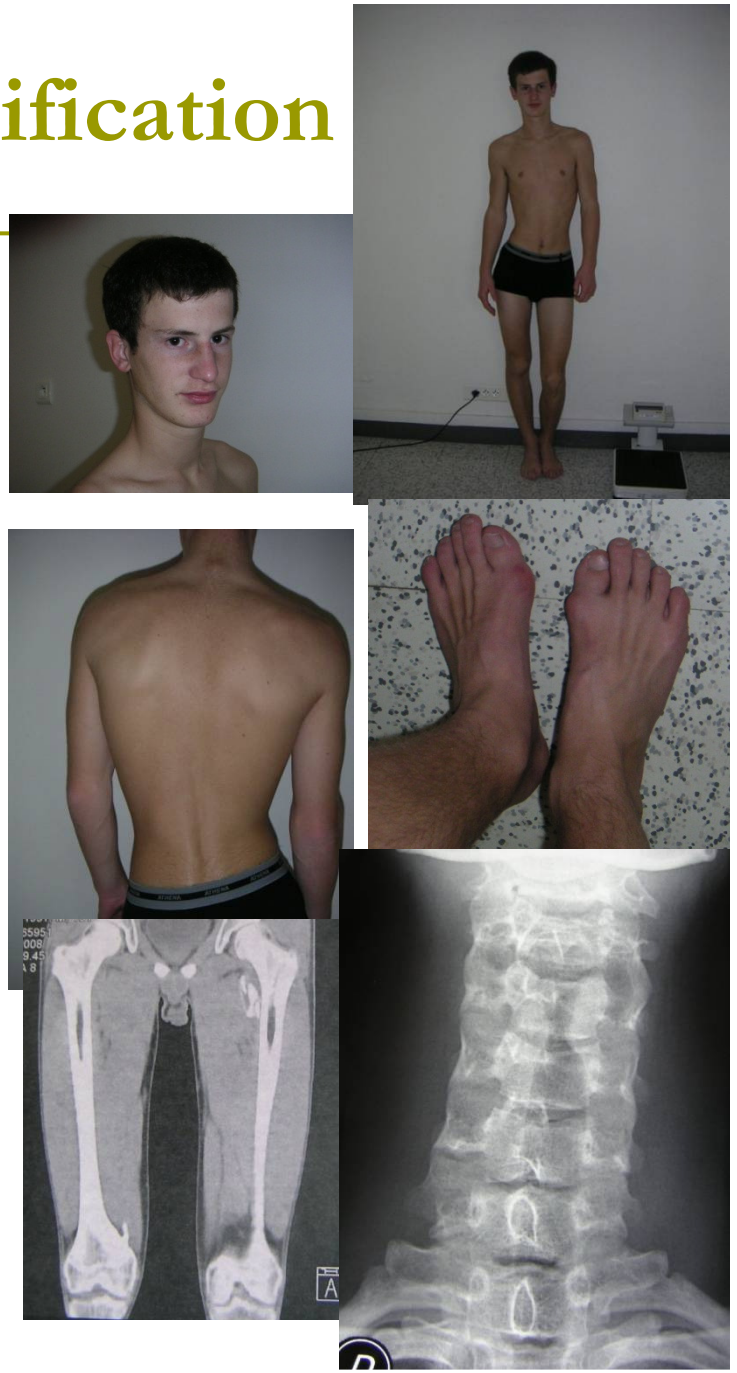
Early symptoms….late ossification

- Young man playing football
- Flare up of the skull during the first year
- Short first toes
- Stiffness of the neck and back without ossification during the childhood considered as « torticolli »

No diagnosis

- Ossification in the lumbar region at 15
- Ossification of the adductor at 17

ACVR1 R206H



FOP- Classical form

4 years

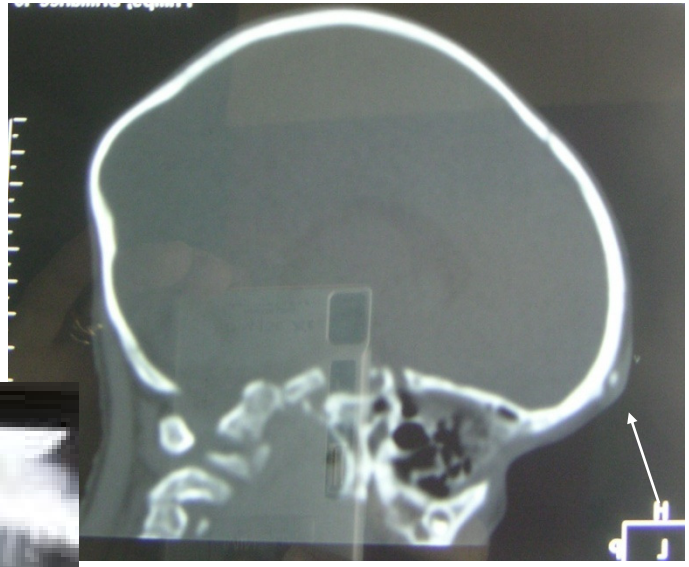
Short first toes

Scalp nodule

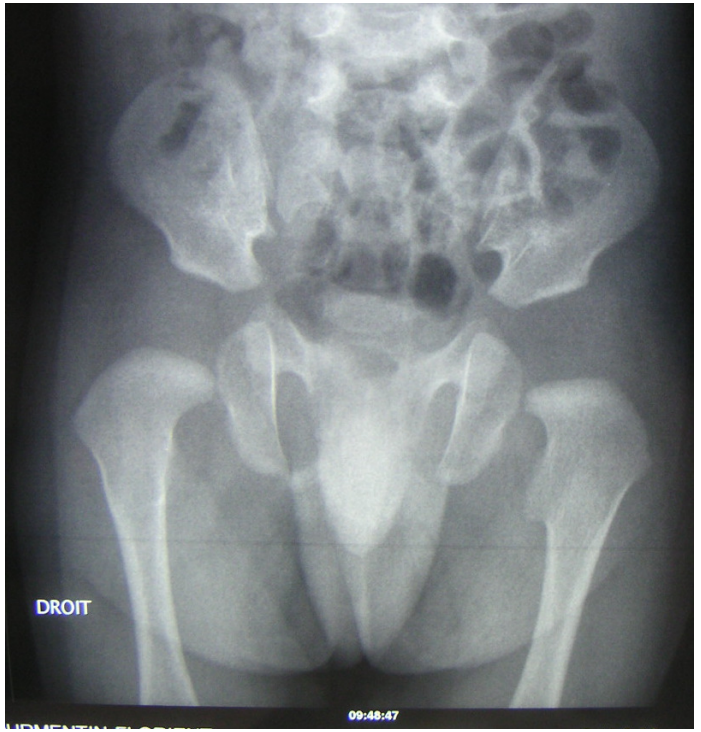
Normal mobility of the neck

Right hip limitation

The cranio caudal pattern could be absent !!



ACVR1 R206H



Worse versus moderate ?

Severe form: flare up and ossification during chilhood

54/78

Mild form: flare up after puberty

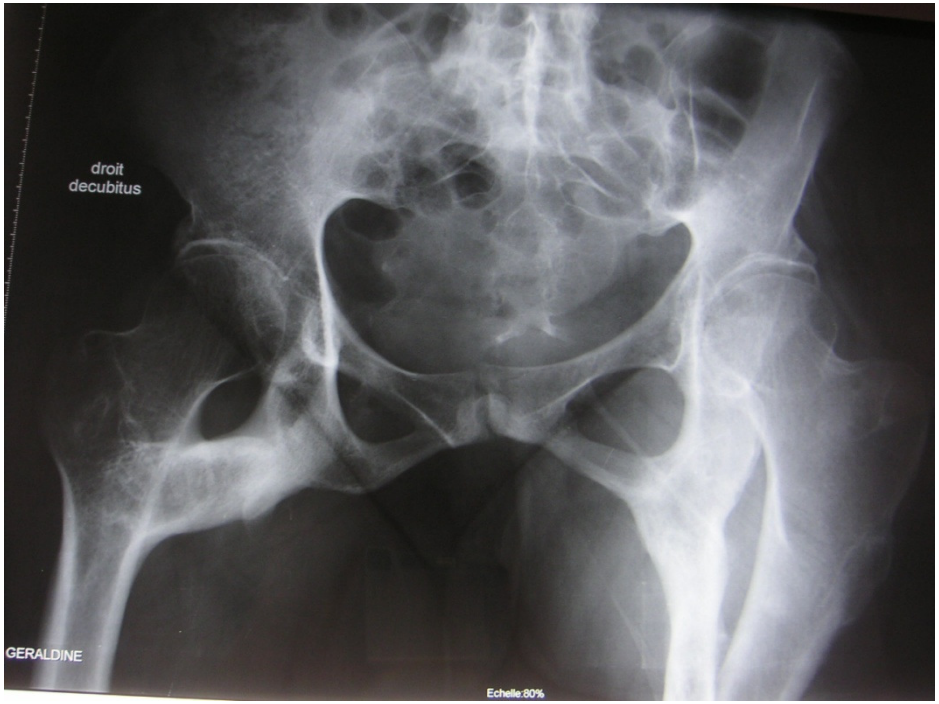
19/78

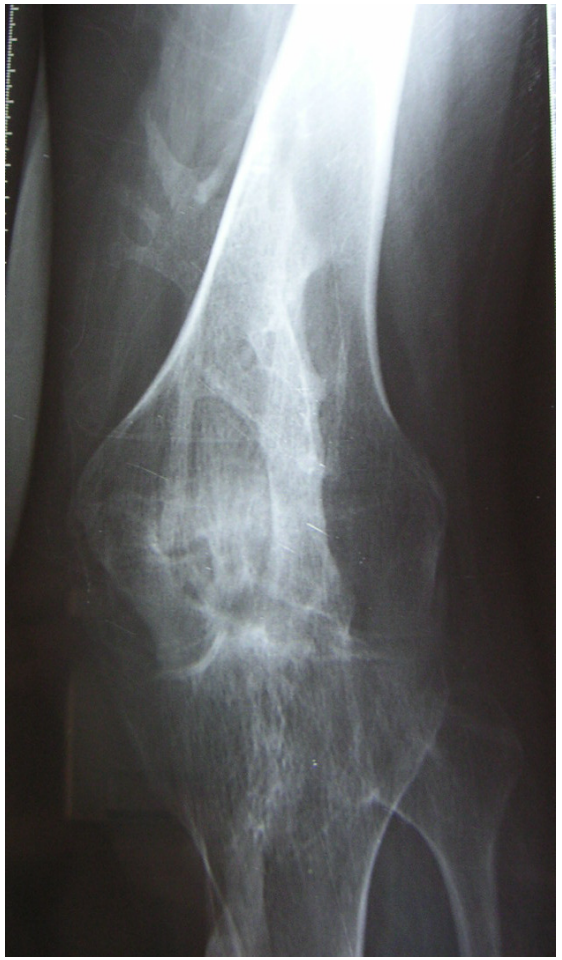
*But **rapid progression** of the lesions are frequent with ossification of the jaw*

FOP – late onset

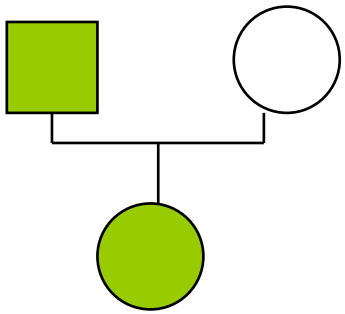
45 years

Frist symptoms at 25 years





Mild Familial case



Father

15 y : Short big toes

Back ossification

35y: still walking

Recent jaw ossification

Daughter :

Short big toes at birth

13y: no ossification

Genotype –phenotype correlation

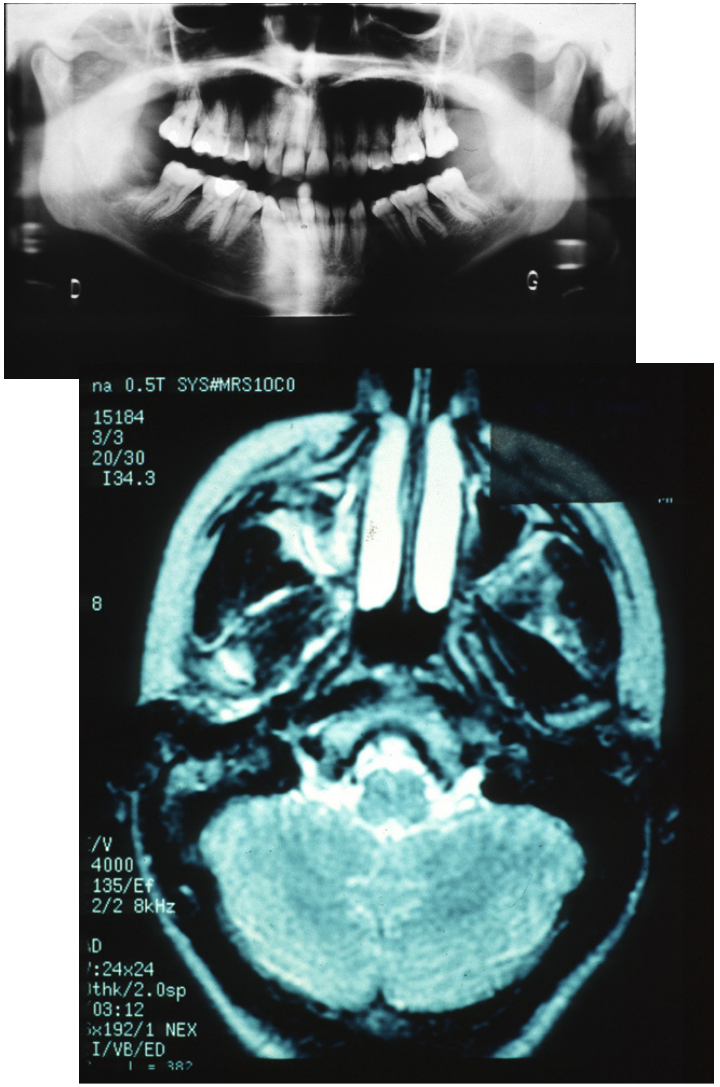
- Activin receptor type 1A
  - a recurrent mutation, R206H, for a large clinical spectrum
  - Several other mutations associated with variant phenotype but not found in french data (but all the patients are not screened)
  - Are there Families which do not fit with ACVR1 gene ? It seems no
  - Is there distinctive phenotype for another localisation and another Gene?

Mandibular form

M Le Merrer C Debeney Bruyère Andoni Urtizberrera

- First symptoms after teeth care or cervical trauma
- Stiffness of the cervical region
- oedema ,then progressive trismus
- Ossification of Pterygoid then temporal and masseter muscles

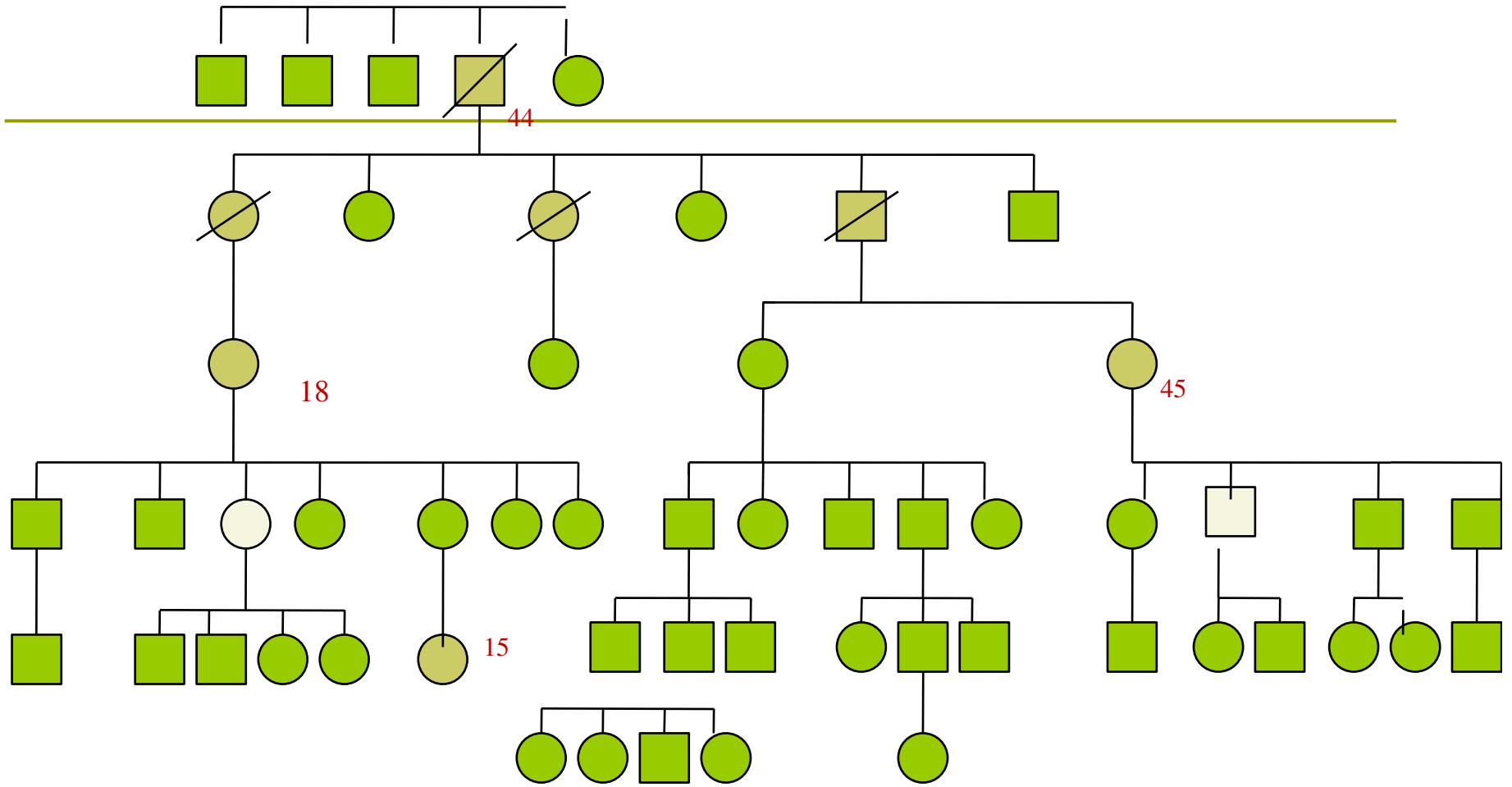
- Age of onset: 15- 45 y



FOP-Mandibular form

- Complete trismus in few weeks
- Surgery and medical treatment failed
- No abnormal toes or extremities

- Ossification of muscles, limbs or psoas after several years



FOP Mandibular

FOP mandibular and limb muscle

Mandibular form

- It is a an autosomal dominant phenotype with incomplete penetrance
- Negative ACVR1 screnning
- Not linked to ACVR1 locus

Other gene in the functionnal pathway??

Exome analysis is ongoing


This work was possible with the help of AFM, Association pour les myopathies, which gave assistance to recruite the patients through the country
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