BEST OF Meeting SOFFOET October, 15th 2021

Les Hôpitaux Universitaires de STRASBOURG

How a small fetus puzzled the fetal pathologist

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UF6349 Foetopathologie

SoFFœt
Société Française de Fœtopathologie

Patient's history and pregnancy follow up

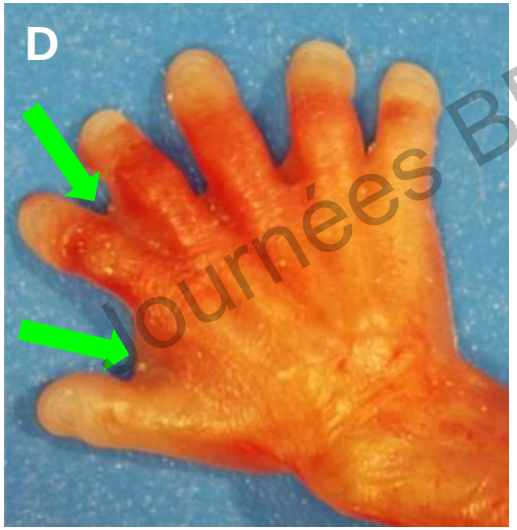
- Termination at 20 Weeks of Amenorrhea (WA) because of dwarfism. G3P1
- Unrelated couple
  - *Obstetrical history :*
    - 2013 : Fetal demise at 4 WA
    - 2014: C –section, male (3220 g)

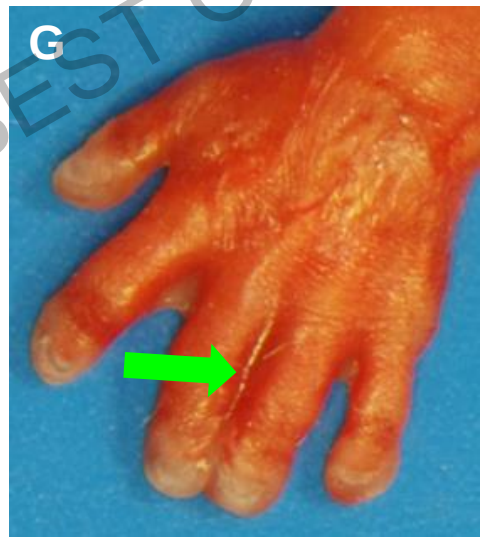
- **USS at 18 WA + 3 days**:
  - Micromelic dwarfism; femora <P5
  - Possible abnormality of the extremities
  - Normal amniotic fluid volume

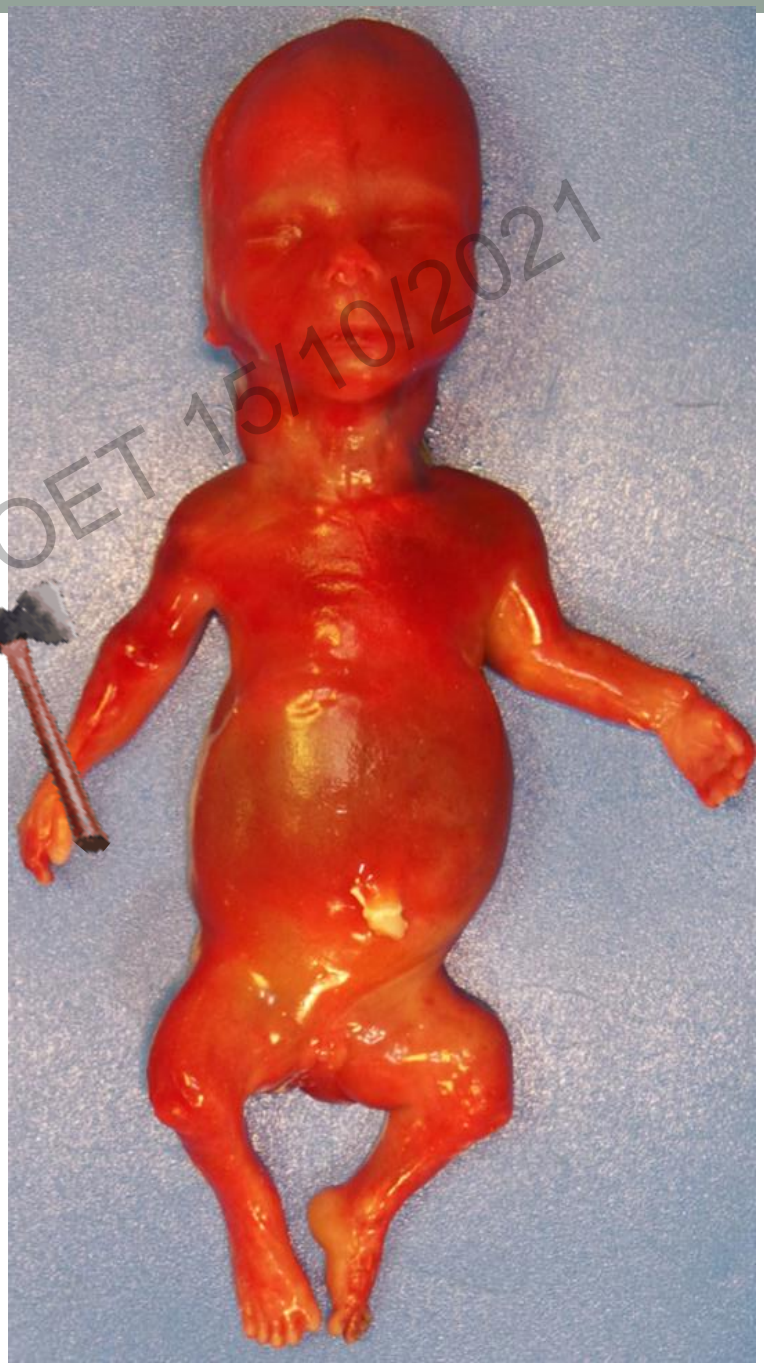
- **Lab screening**:
  - PCR for aneuploïdy : Usual profile
  - Prenatal a-CGH : arr(X,1-22)x2

External examination

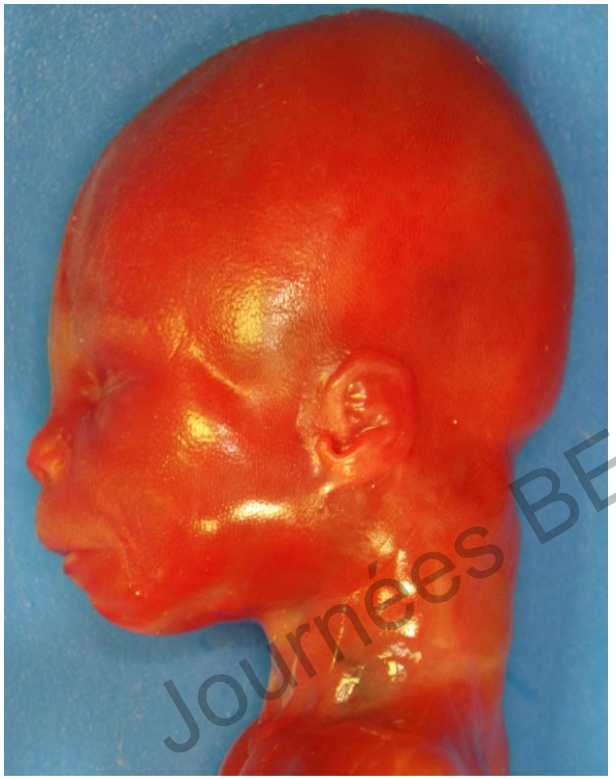
- Eutrophic
- **Vertex Heel < 5^{e} p**
- **Micromely**
- Femurs bowing
- Short and narrowed thorax with a protrusive abdomen

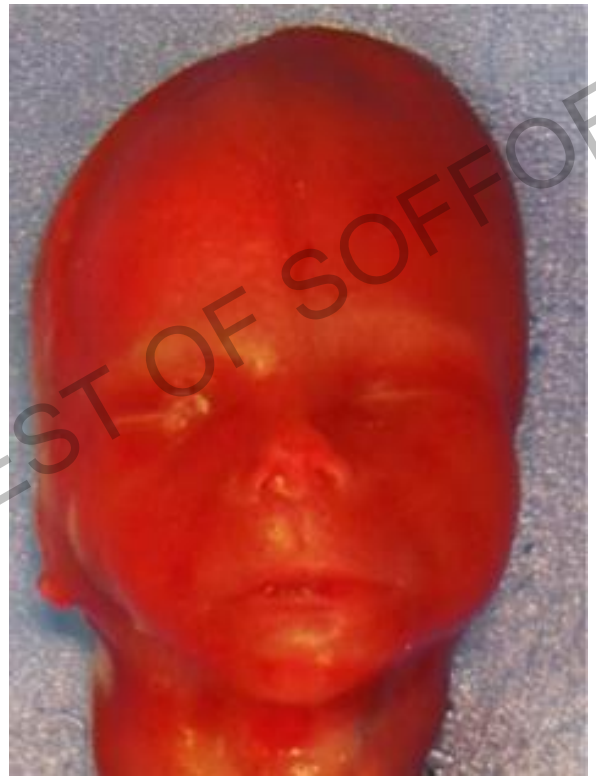


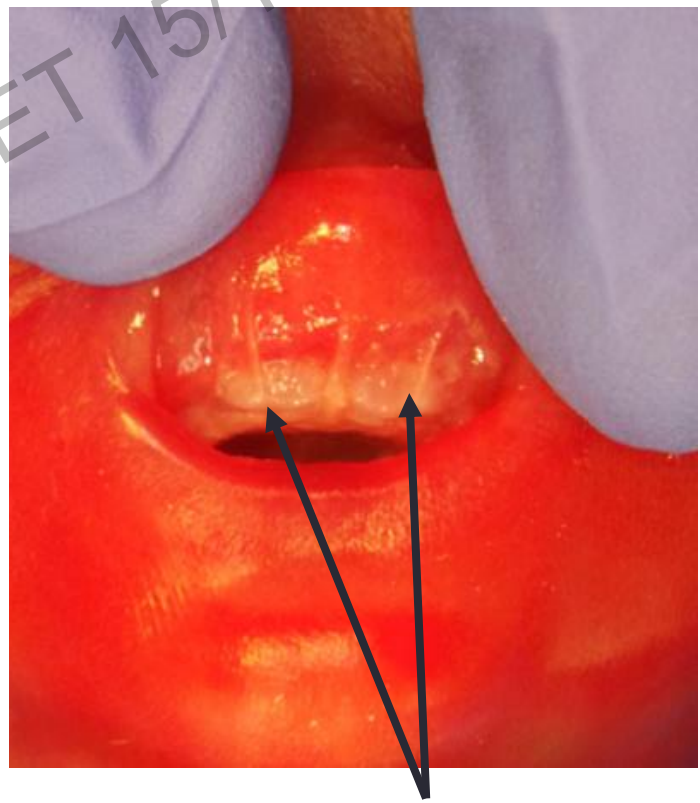




External examination







accessory labial frenuli

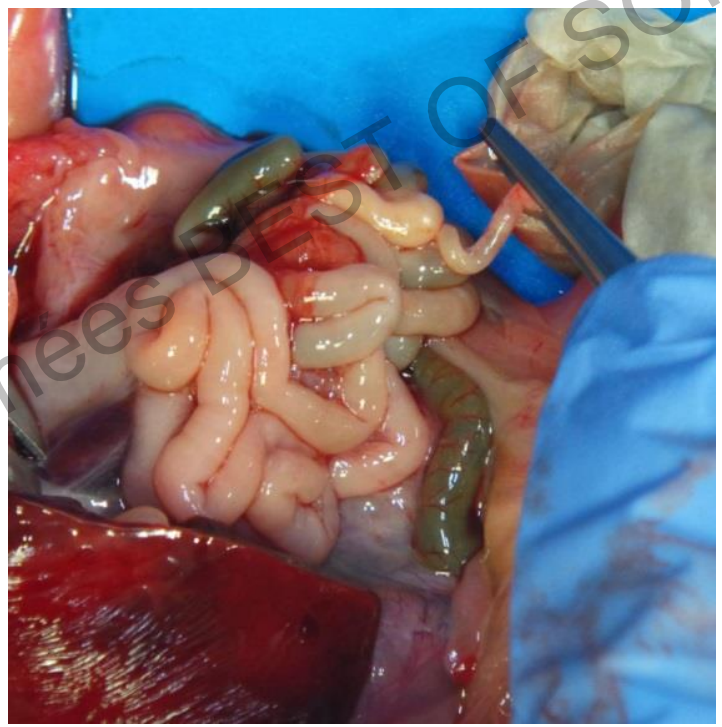
Autopsy

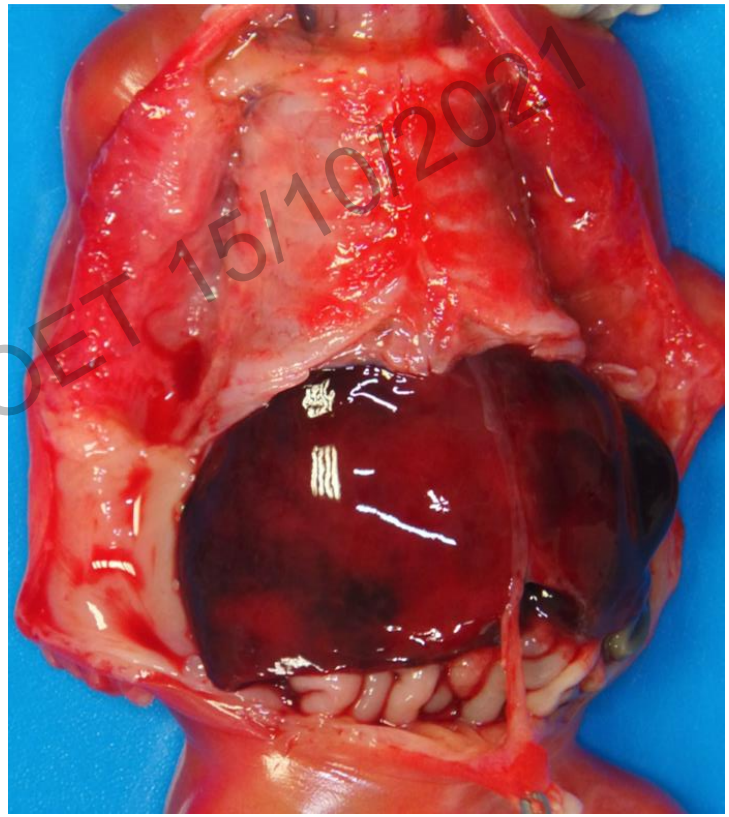
- Complete common mesentery
- **Short intestine**

47 cm (*N 20 WA : 125 cm)*

  - *(= 18,5 inches, 49 inches for normal length)*

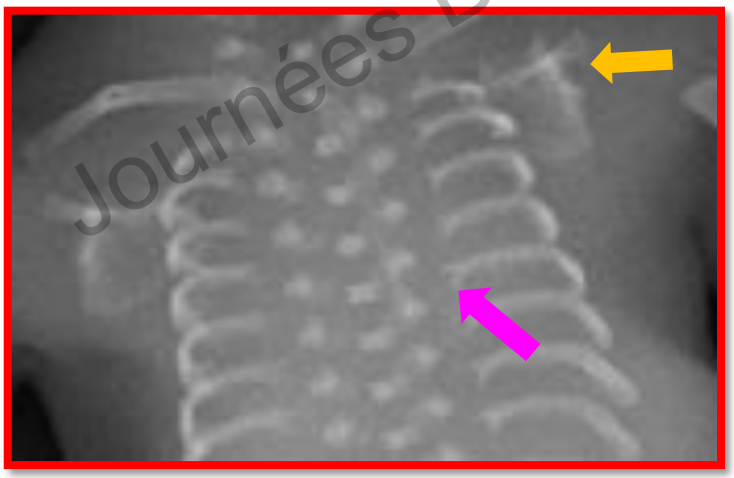
- Incomplete right lung minor fissure

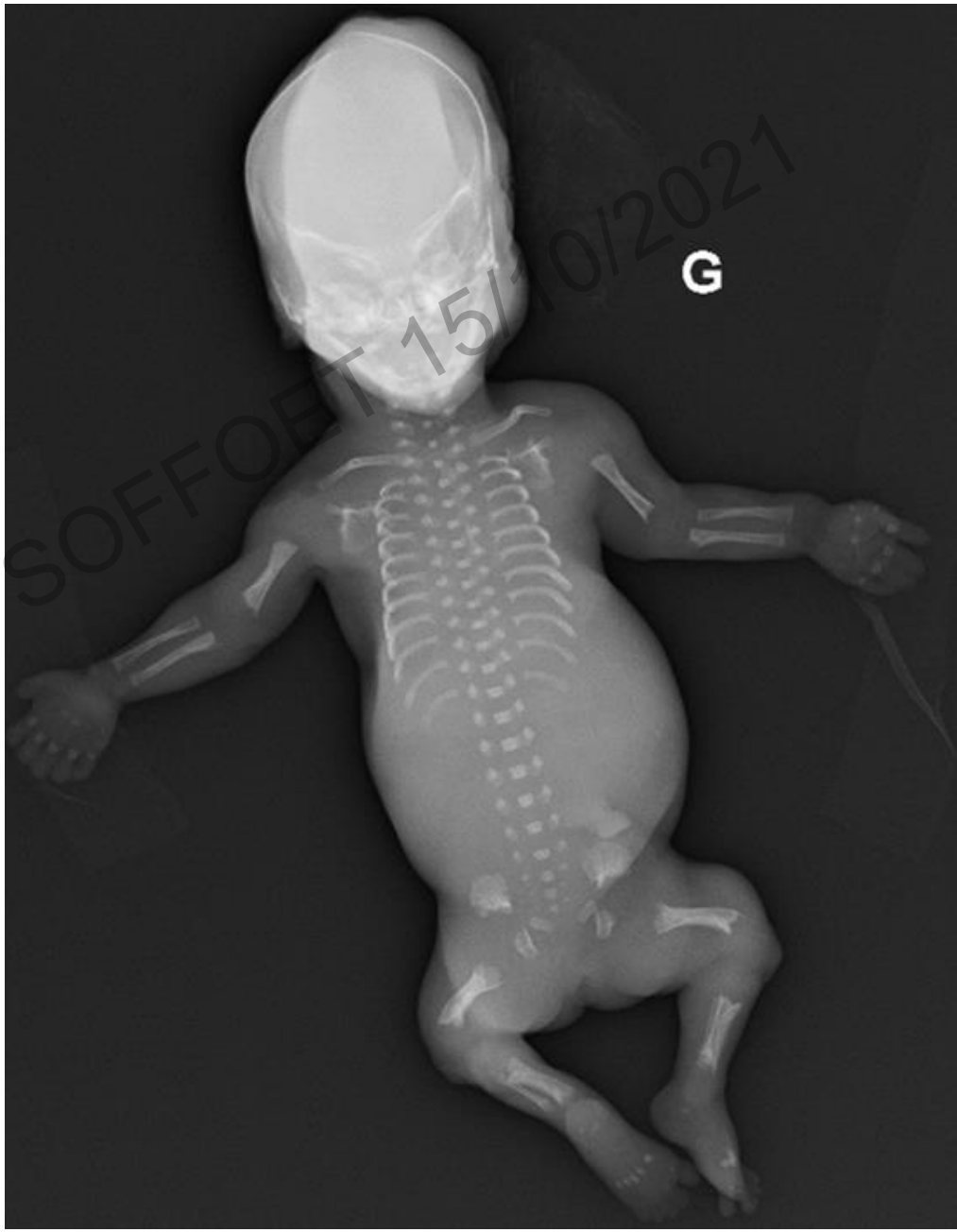




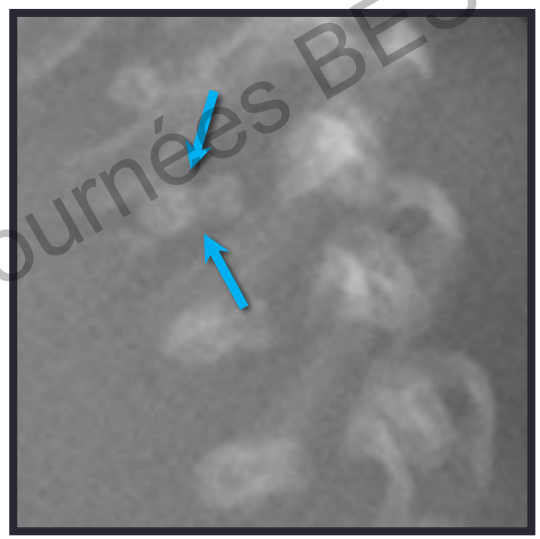
- Increased bone translucency
- Bone dysmaturation (calcanei, 23WA)
- Short femora (<P3, -8 DS)

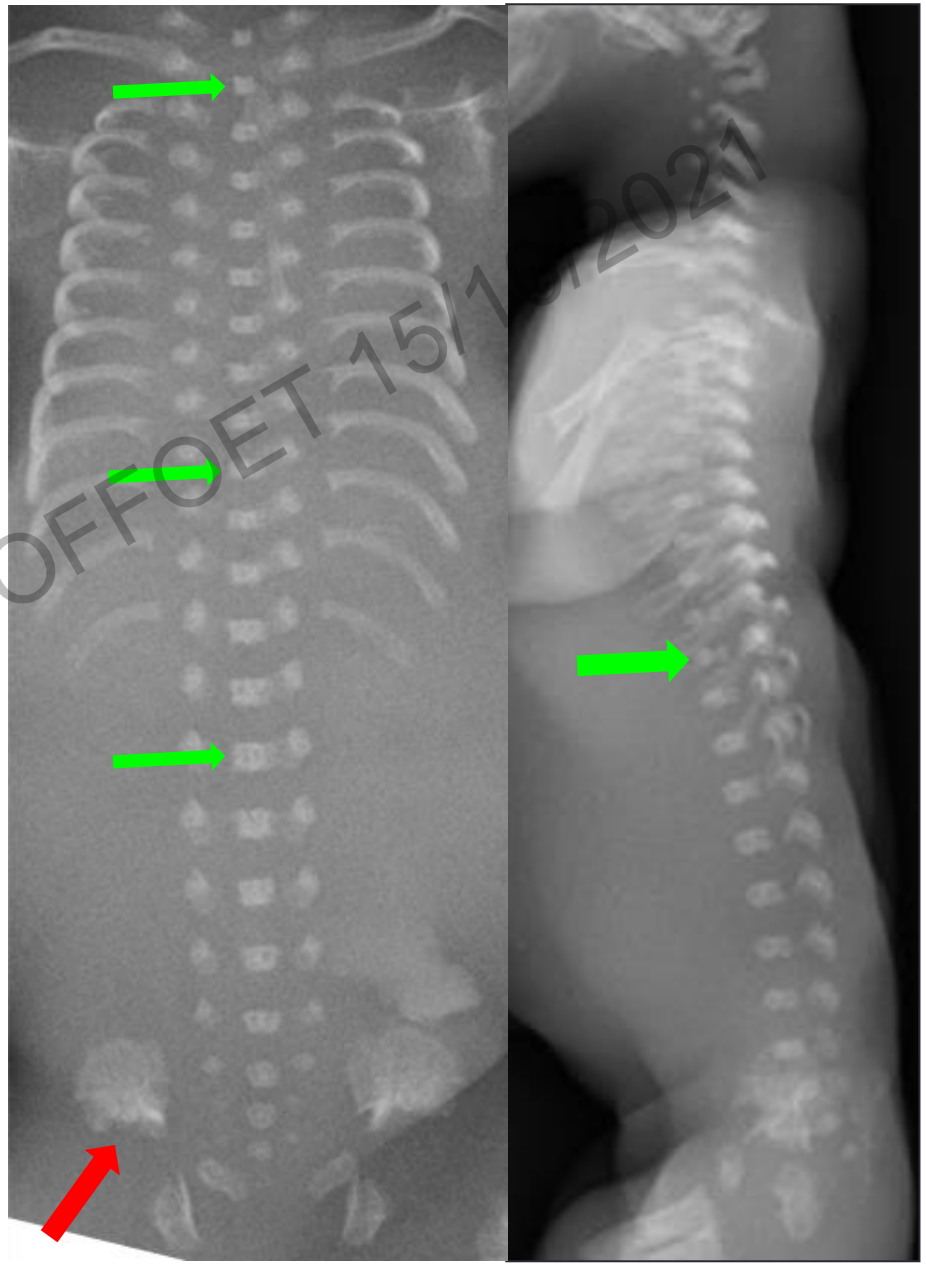
- Dysplasia of scapulae
- 11 pairs of short ribs with cupuliform extremities





- Abnormal vertebral ossification
  - ✔ Reduced transverse and antero-postériror diameters
  - ✔ Central depression of the upper and lower plateaus
  - ✔ Platyspondyly
- Hypoplasia of the acetabular roof and acetabulum





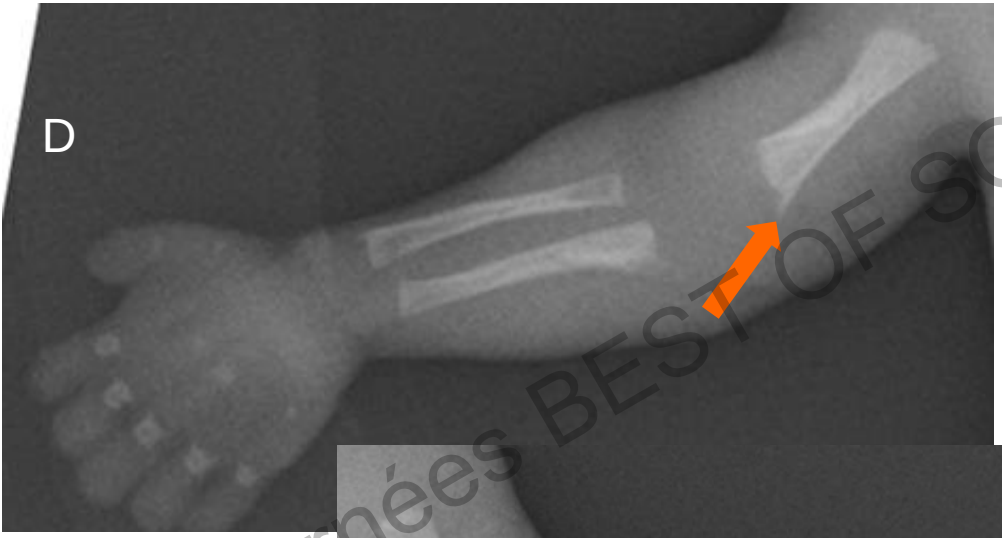
Short long bones

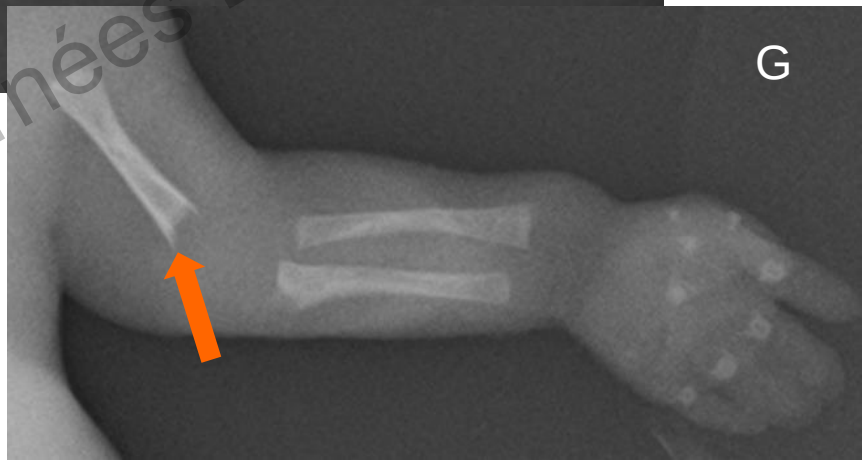
Upper limb :

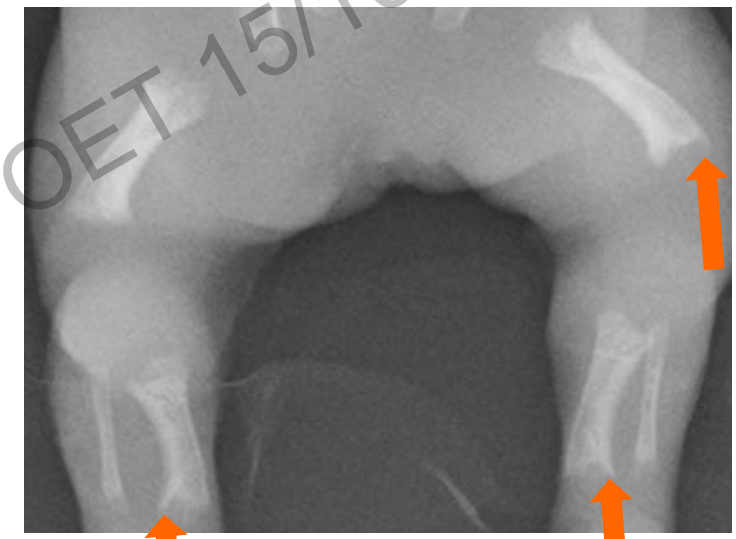
- **Delayed ossification** carpes, métacarpes and phalanges
- **Metaphyseal Spurs**

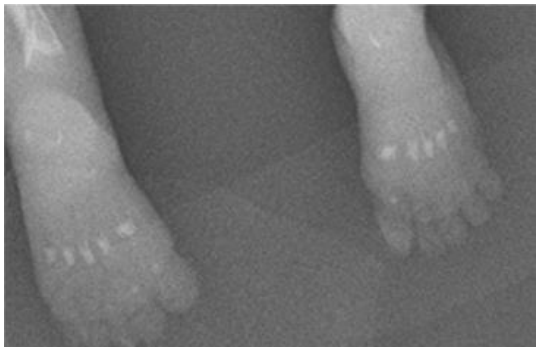
Lower limb :

- **Delayed ossification** proximal phalanges
- **Metaphyseal Spurs**



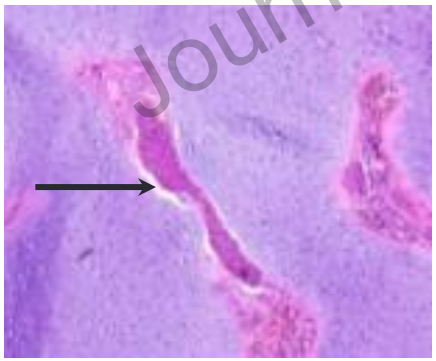


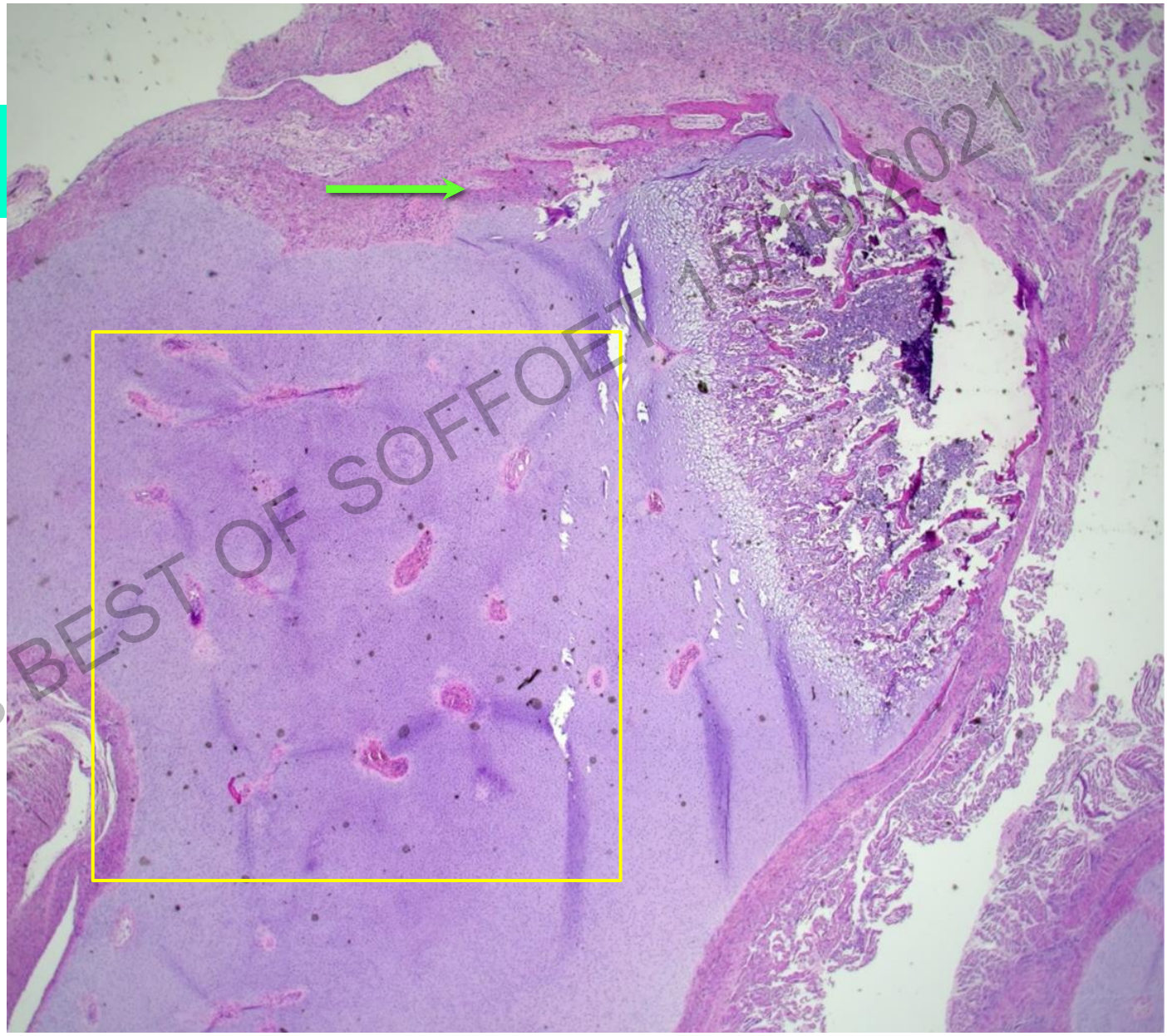




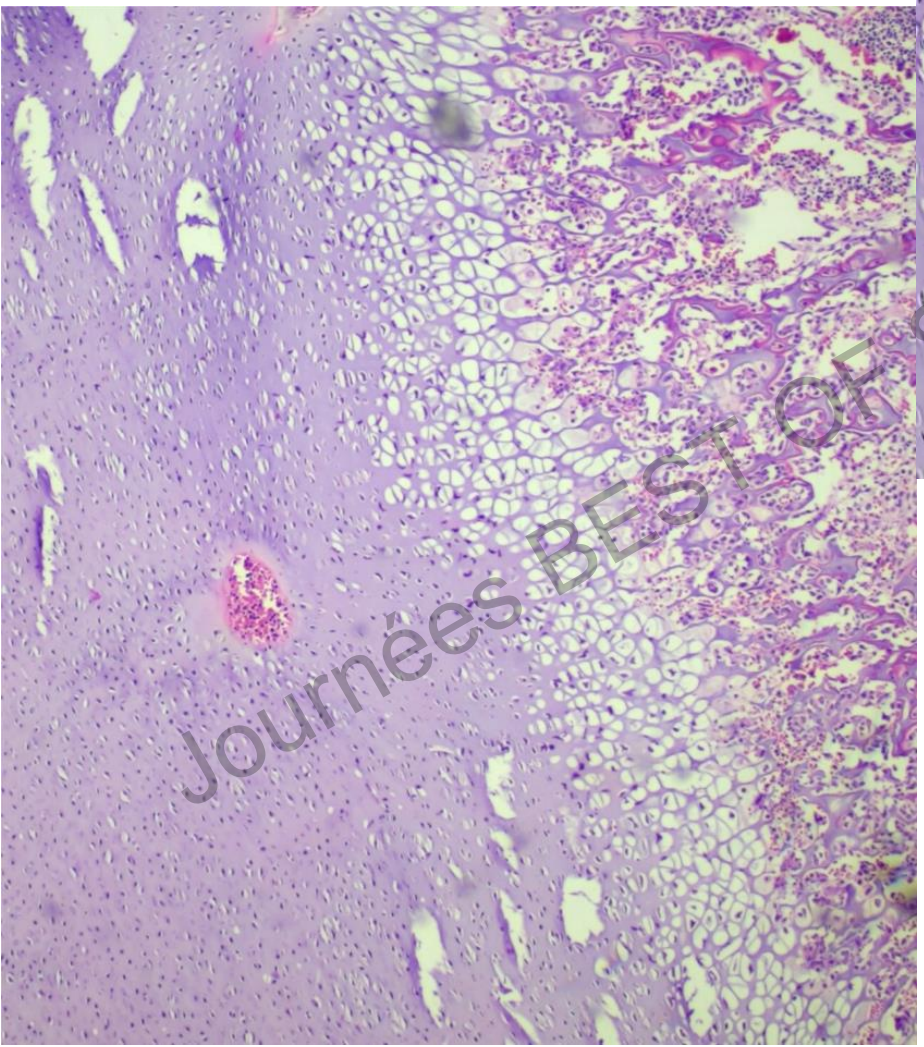
Long Bone epiphysis (femur)

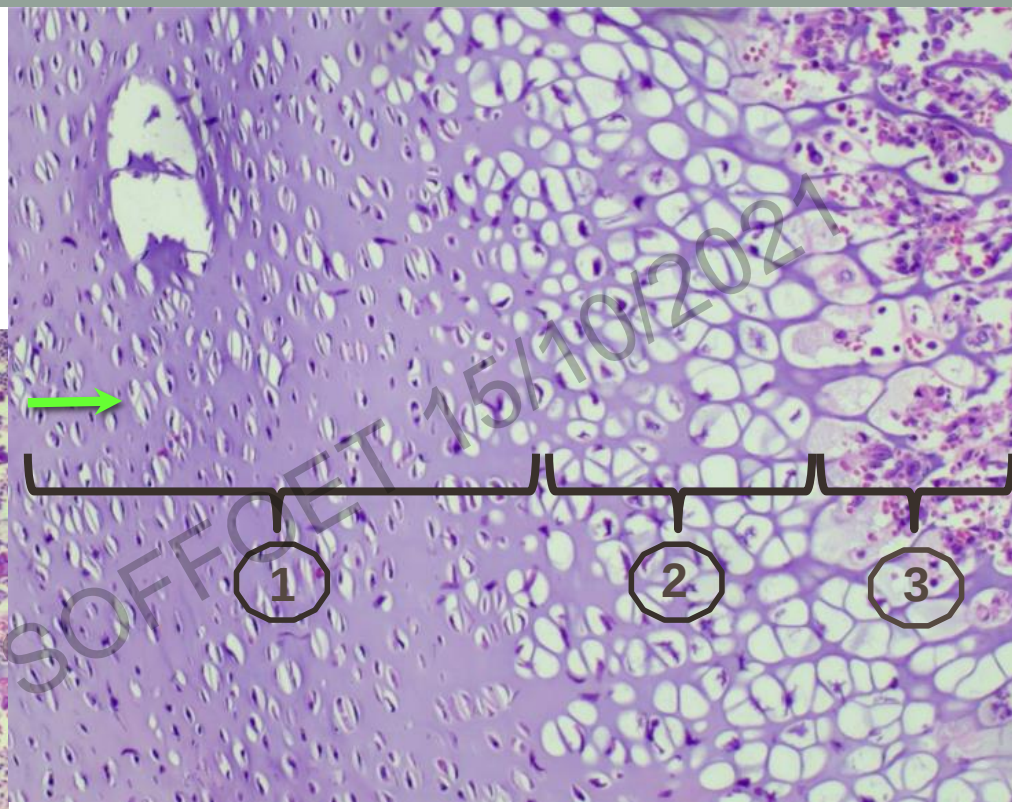
- Increased number of vascular channels
- Exuberrant ossificatuion of perichondral bone (*spur on Rx*)
- Aberrant ossification points (*not visible on the radio)*





Long Bone Metaphysis (femur)

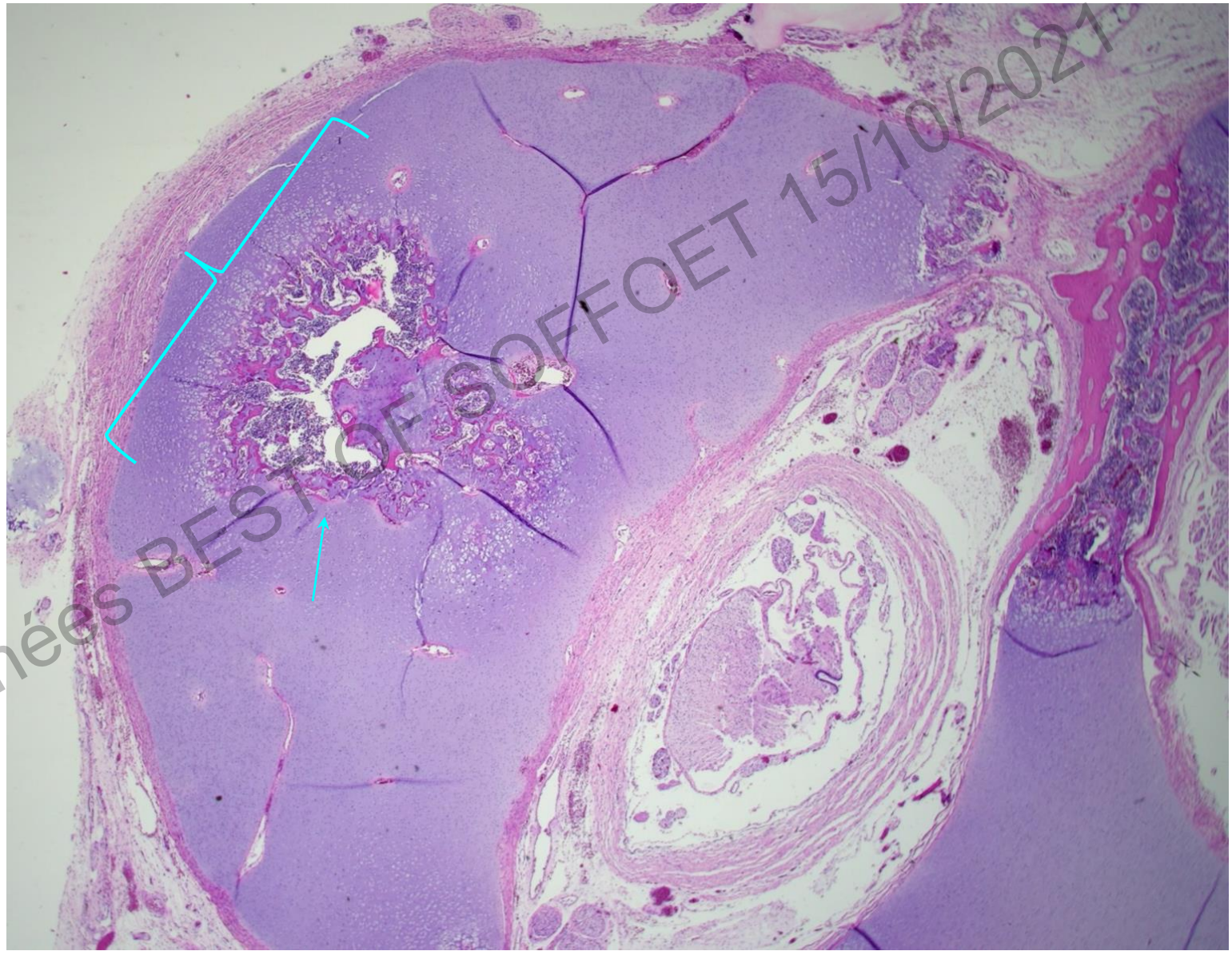




Linear metaphysis

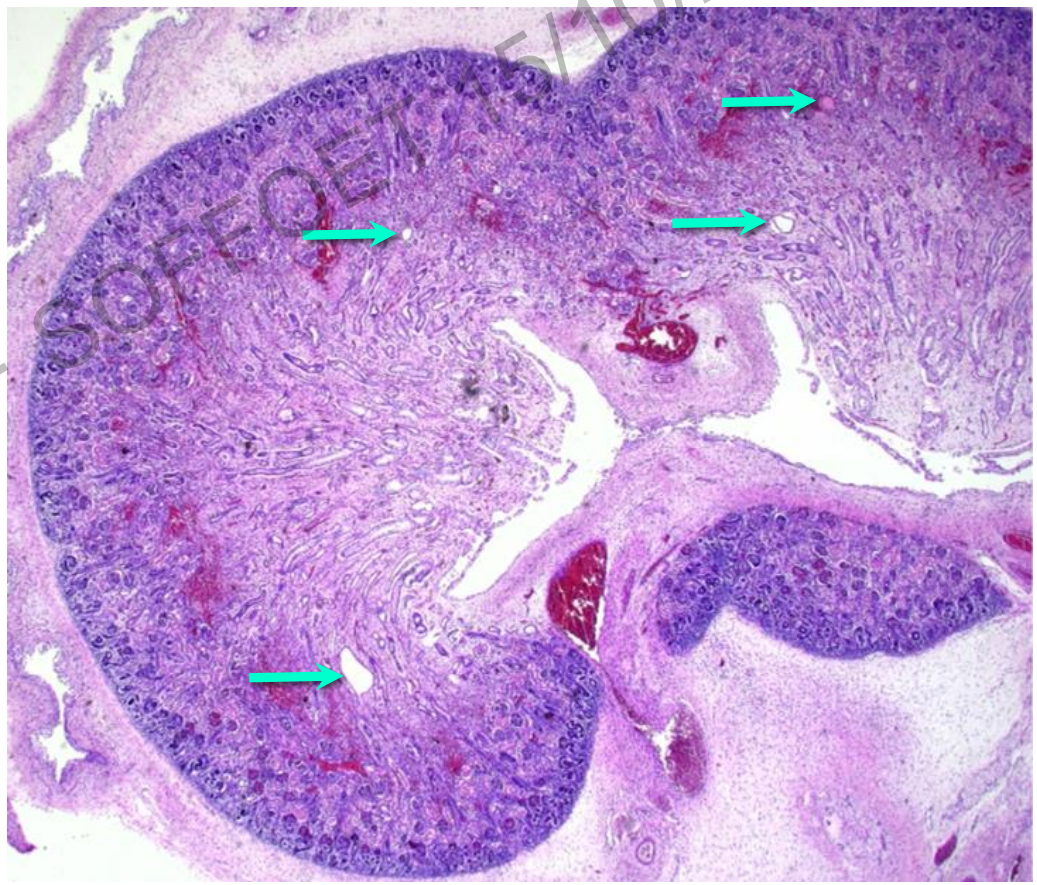
1. Proliferation area: :
   - ✔ Axial isogenic clusters of small size, not aligned
2. Hypoplastic hypertrophic zone
3. Erosion line: :
   - ✔ Normal density and uniformly distributed guiding trabeculae and normal mineralization

Vertebra



Organs

- Normal maturation



Kidneys

- rares dilatations *(concerning all the segments of the nephronic tube)*

Examination summary

Fœtus ♀ eutrophic

- Minor facial dysmorphism
- **Accessory labial frenuli**

- **Unilateral polydactyly, bilateral syndactylies**

- **Tetra-micromely more important in the rhizomelic part of the limbs**
- **Short ribs**
- **Anomalies of scapulae, vertebrae, ilia**

  enchondral ossification anomalies → disorder of proliferation and differentiation of the chondrocytes

- **Short intestine length and a commun mesentery**

- **Abnormality of the kidney *a minima***

Diagnostic Hypothesis

- Short ribs polydactyly syndromes
  - Type I : Saldino Noonan
  - Type II : Majewski
  - Type III : Verma Naumoff
  - Type IV : Beemer

→

- Micromely – short long bones
- Short ribs
- Abnormality of the pelvis (trident)
- +/-polydactyly
- +/-visceral malformations
- +/-brain malformations

→ Severe part of the skeletal ciliopathy spectrum but what type ???

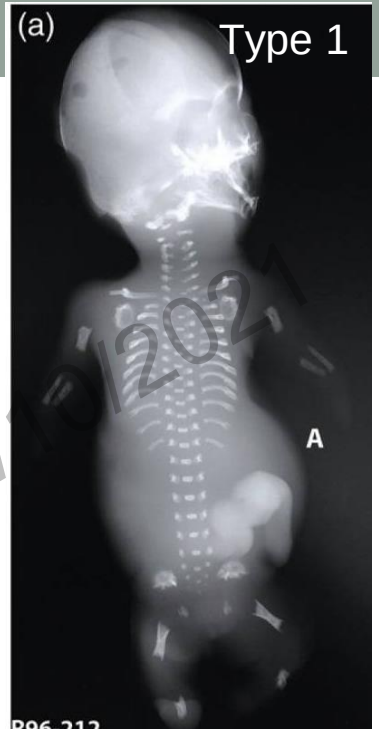
→ clinical and genetic diversity +++

→ mostly **Autosomal Recessive**

Severity gradient

- Saldino Noonan (type 1)
  - Anasarque
  - Postaxial polydactyly
  - Metaphyseal dysplasia of longs bones (flame-shaped)
  - Skeletal anomalies (pelvis-vertebrae-scapula)
  - Visceral anomalies

→ genes *WDR35, WDR34, WDR60, DYNC2H1, IFT80*



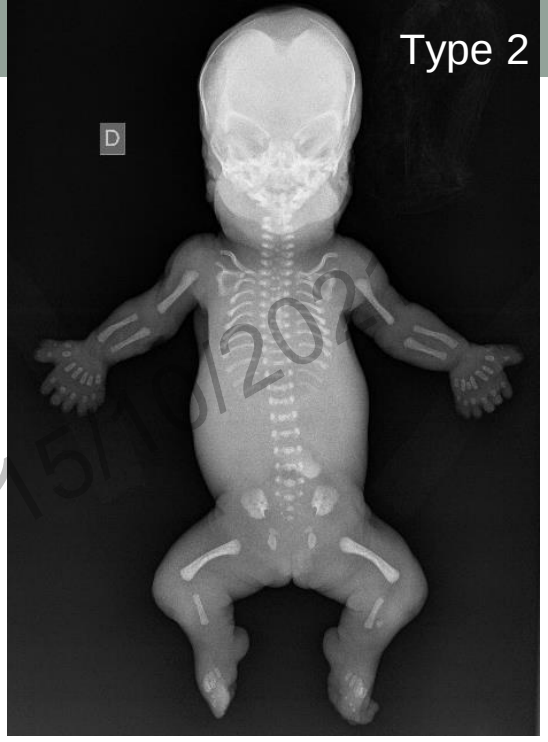
- Verma Naumoff (type 3)
  - Polydactyly
  - Metaphyseal spicules
  - Rachis anomalies (platyspondyly)
  - Pelvic anomalies
  - +/- visceral anomalies– cerebellar hypoplasia

→ genes *WDR35, WDR34, WDR60, DYNC2H1, IFT80*

SRPS

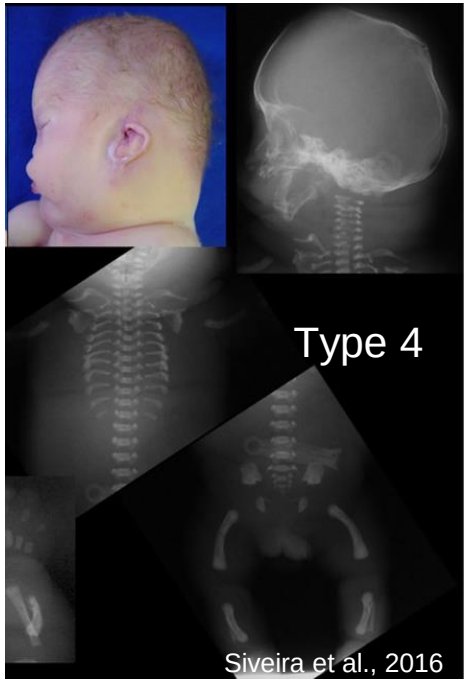
- Majewski (type 2)
  - Poly-syndactyly pre and post axial
  - Hypoplasia-Agenesia of tibias
  - +/- Pelvis normal
  - Oro facial anomalies (clefts)
  - Visceral anomalies
    - Renal cysts, pantreatic fibrosis, short little intestine with or without intestinal malrotation, cerebral anomalies (corpus callosum agenesia)

→ gènes *NEK1, IFT81, IFT122*

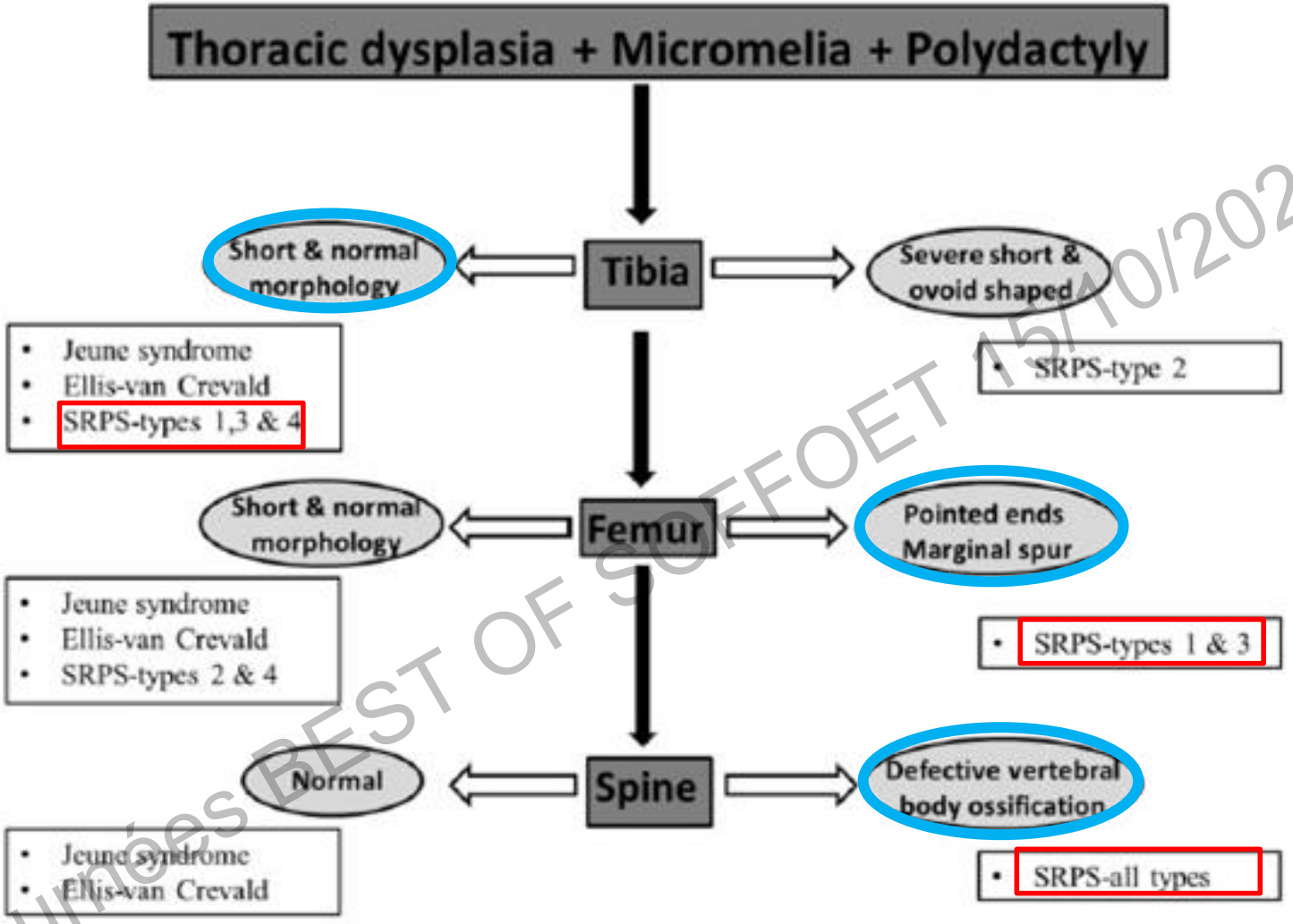


- Beemer (type 4)
  - Pre/post axial polydactyly (50%) + syndactyly
  - Round shaped
  - Radius/ulna bowing
  - Thick tibia
  - Moderate platyspondyly
  - Visceral anomalies
    - Renal cysts, intestinal malrotation, heart anomalies, omphalocele, neonatal teeth

→ gènes *IFT122, IFT80*



Diagnostic hypothesis



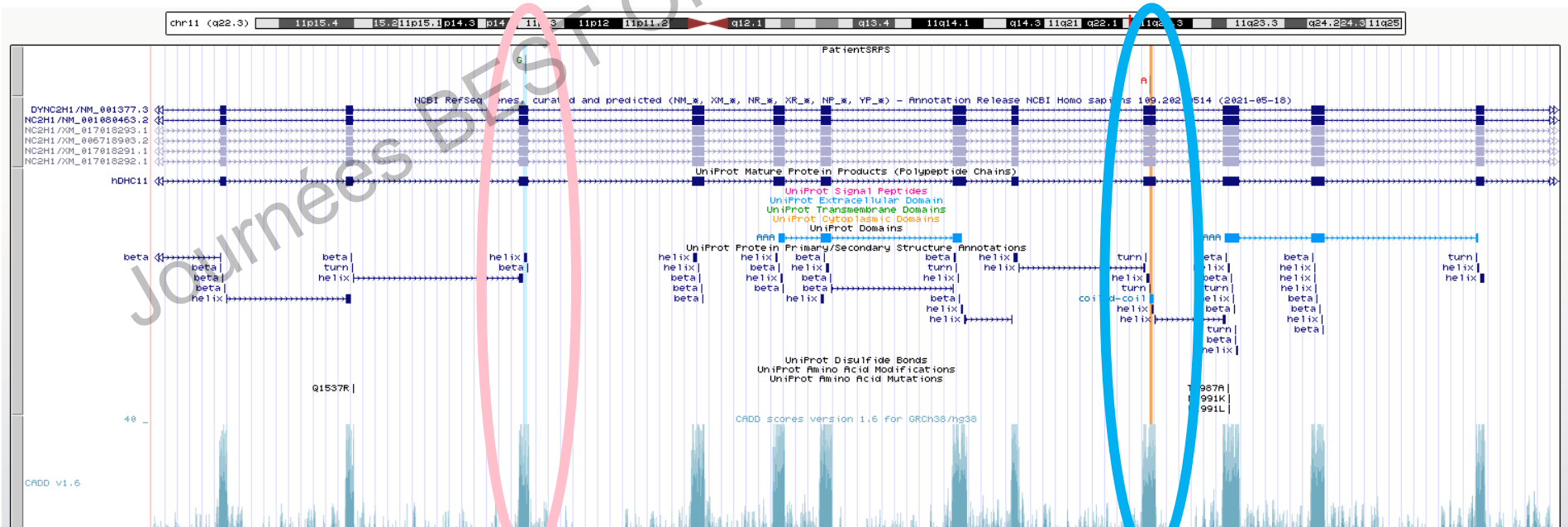
Agarwal et al., 2019

Type 1 **Saldino Noonan**
Type 2 **Majewski**
Type 3 **Verma Naumoff**
Type 4 **Beemer**

New Generation Sequencing :

- compound heterozygosity *DYNC2H1* (NM_001080463)

- (HG38)
- DYNC2H1:c.46999C>G, p.(Leu1567Val) mat
- DYNC2H1:c.5781G>A, p.(Pro1927=) pat



New Generation Sequencing :

- DYNC2H1:c.46999C>G, p.(Leu1567Val) mat
- Missense variation

(changes a Leucine for a Valine, very similar aminoacids)

- Mostly pathogenic computed scores
- Reported in a database of patients (Clinvar)

- DYNC2H1:c.5781G>A, p.(Pro1927=) pat
- Synonymous variation

(Does not change the aminoacid)

- Mostly benign computed scores (but may alter splicing)
- Reported in a database of variation in healthy individuals (Gnomad)

Autosomal Recessive disease

NGS, only a part of the answer

- Variations currently being investigated by Tania Attié-Bitach

- Could lead to more questions that it answers:

How helpfull is an inherited synonymous variant reported in Gnomad with discordant predicting splicing score for clinical classification ?

Thank you for your attention !