A RARE CASE OF OSTEOCHONDRODYSPLASIA

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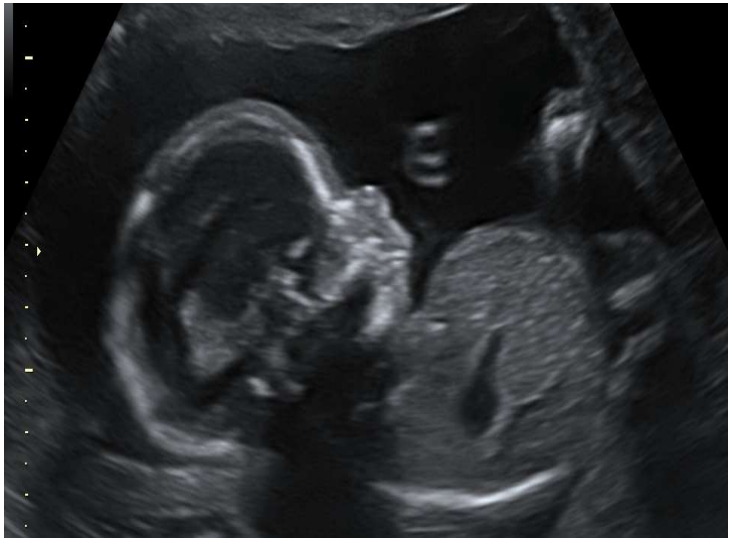
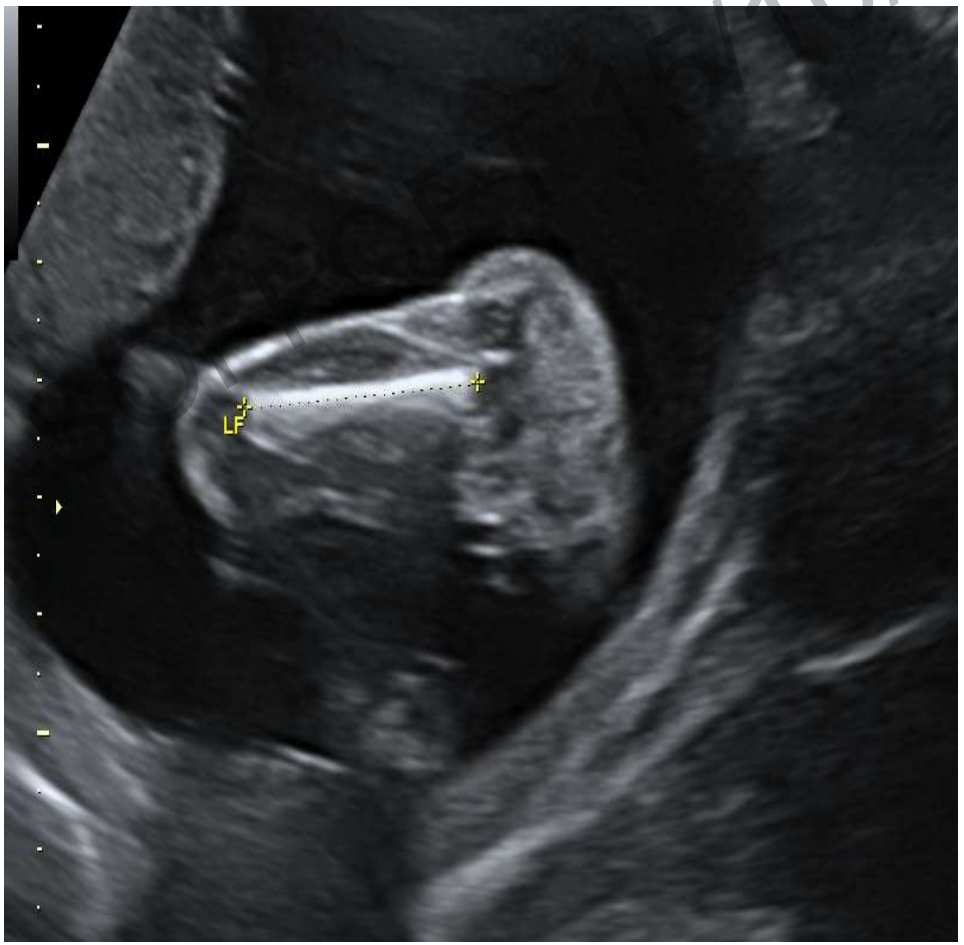
CHU ROUEN NORMANDIE

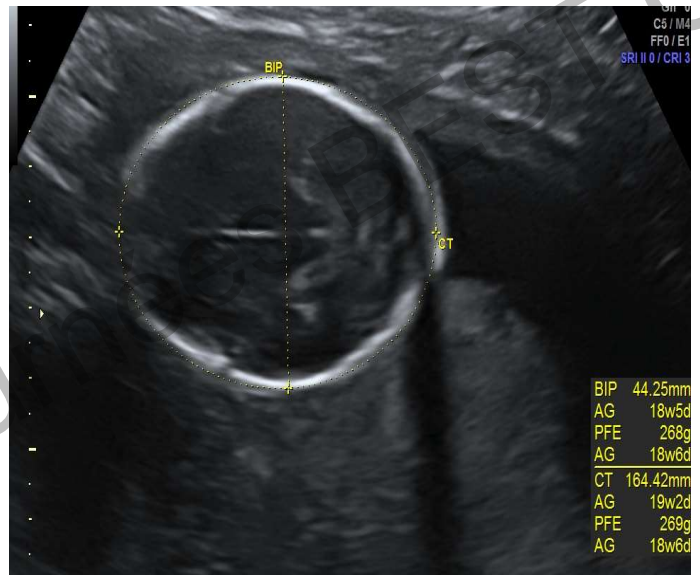
CLINICAL HISTORY

- Non consanguineous couple
- 35 yo G2P1 mother: 170 cm, 86 kgs BMI : 30
- Father : 170 cm 67 kgs
- First child born in 2014, 3 770 g, healthy.
- 1st trimester US showed increased nucal translucency at 3,4 mm
- Normal karyotype 46 XX
- Second trimester US :
  - Prominent forehead
  - Short bones
- CGH-array: normal
- No mutations in *FGFR3* gene

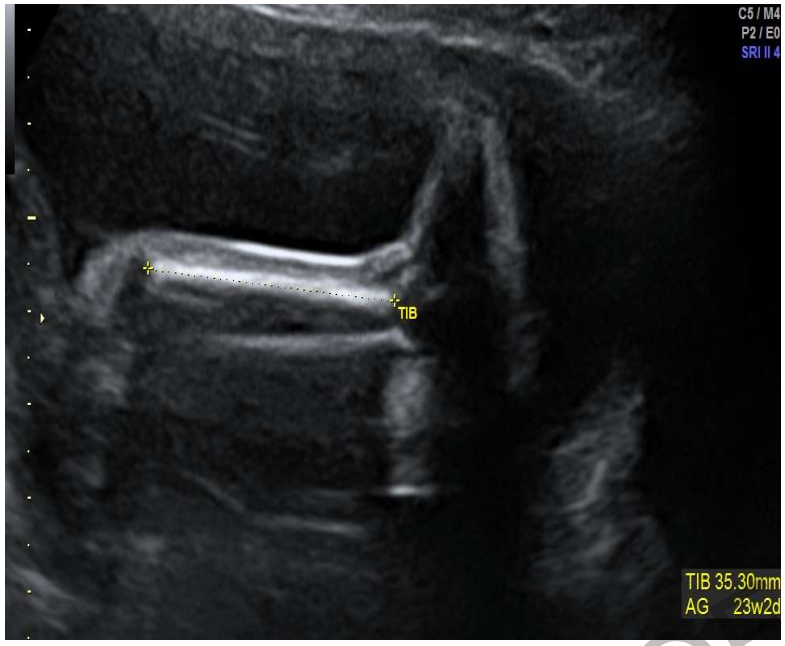


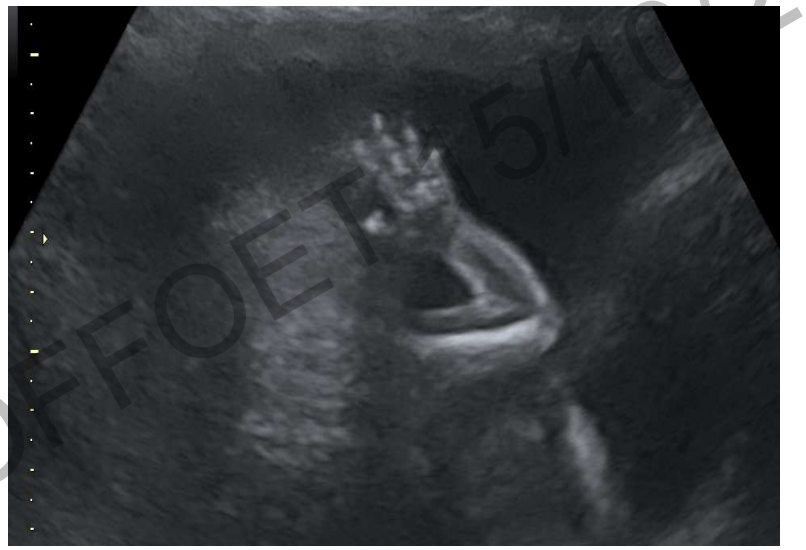
US 22 WG



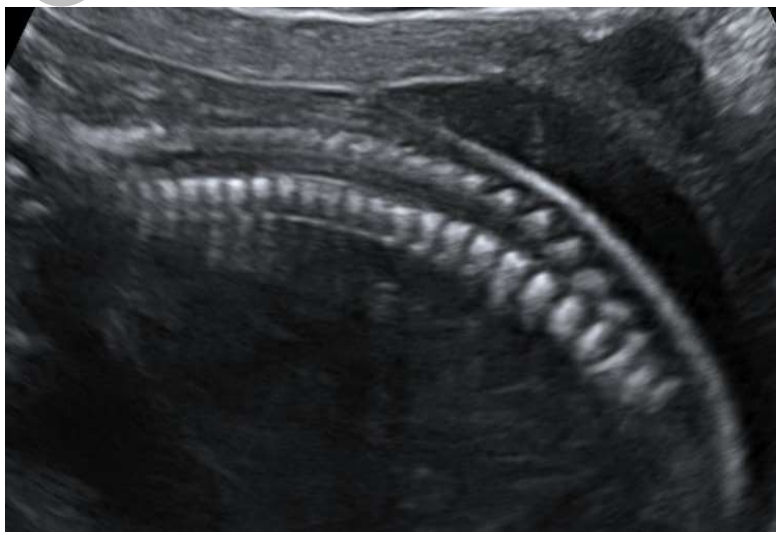


US at 27 WG

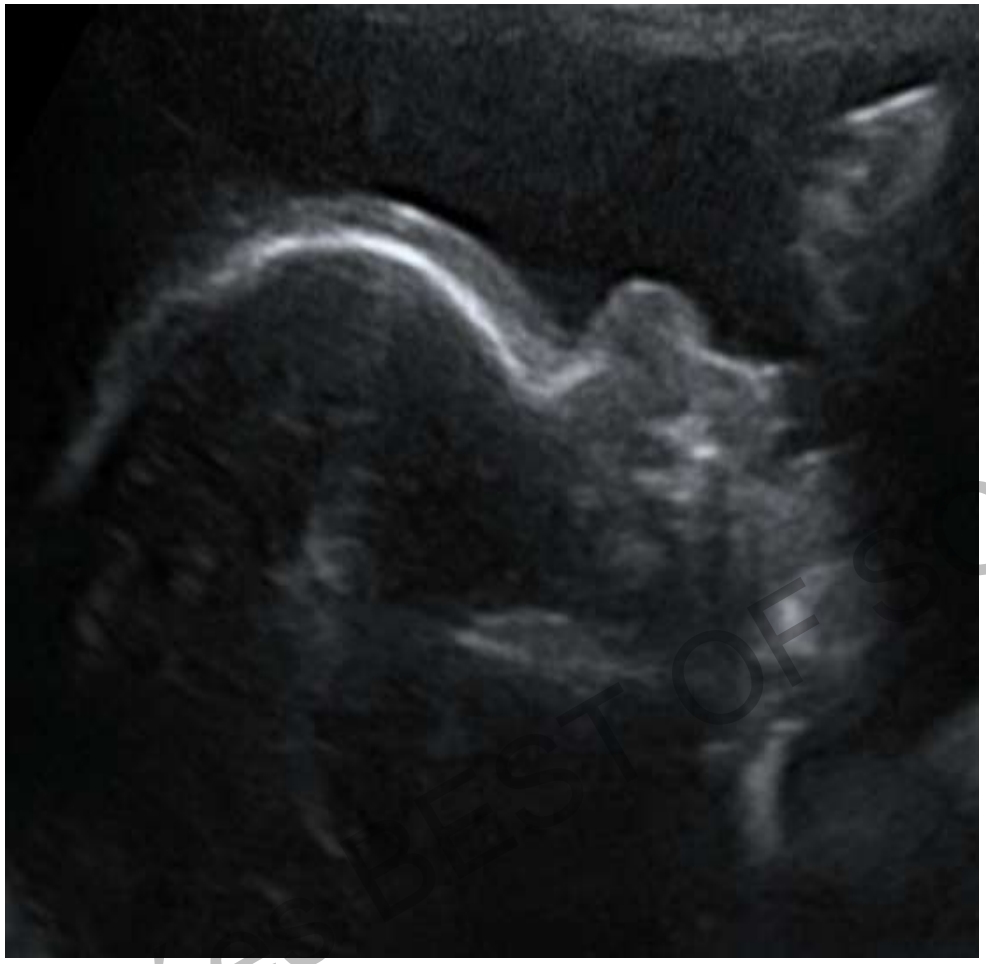


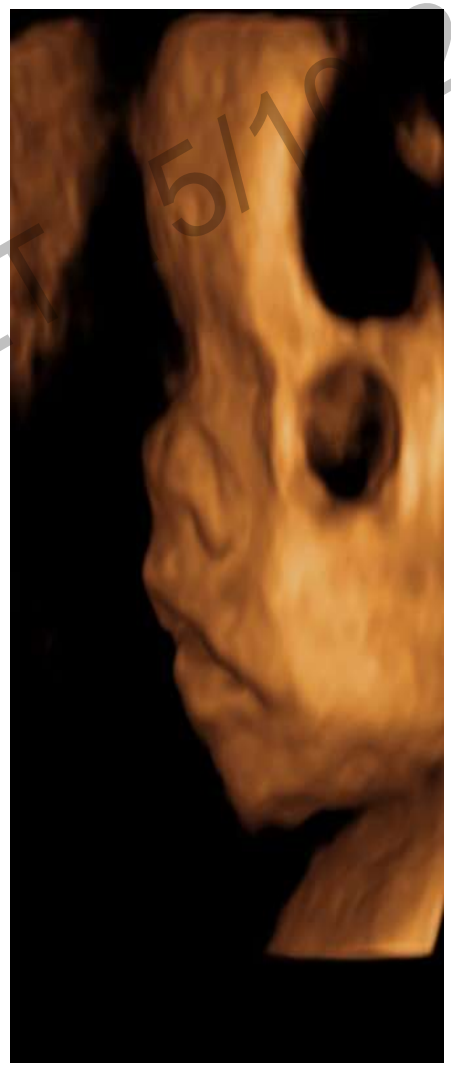


Thin and short bones
No angulations
No fractures



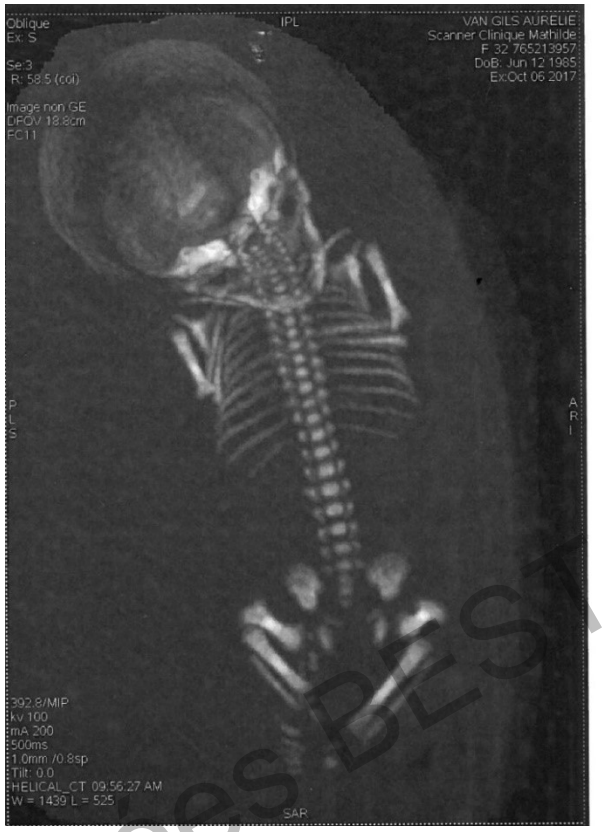
Tall vertebrae

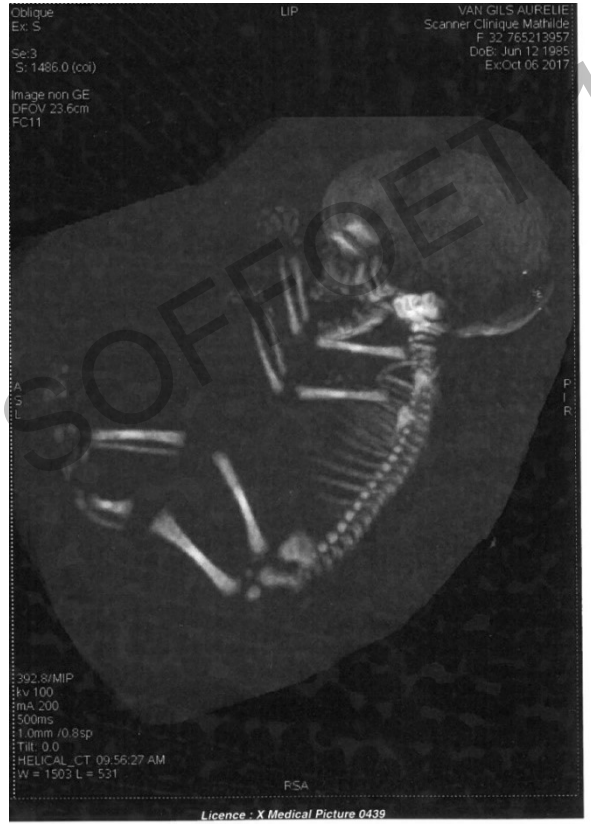




Frontal bossing
Depressed nasal root
Upturned nose
Prominent philtrum

CT AT 31 WG SUGGESTING SKELETAL DYSPLASIA (DR CAROLINE BLONDEL)



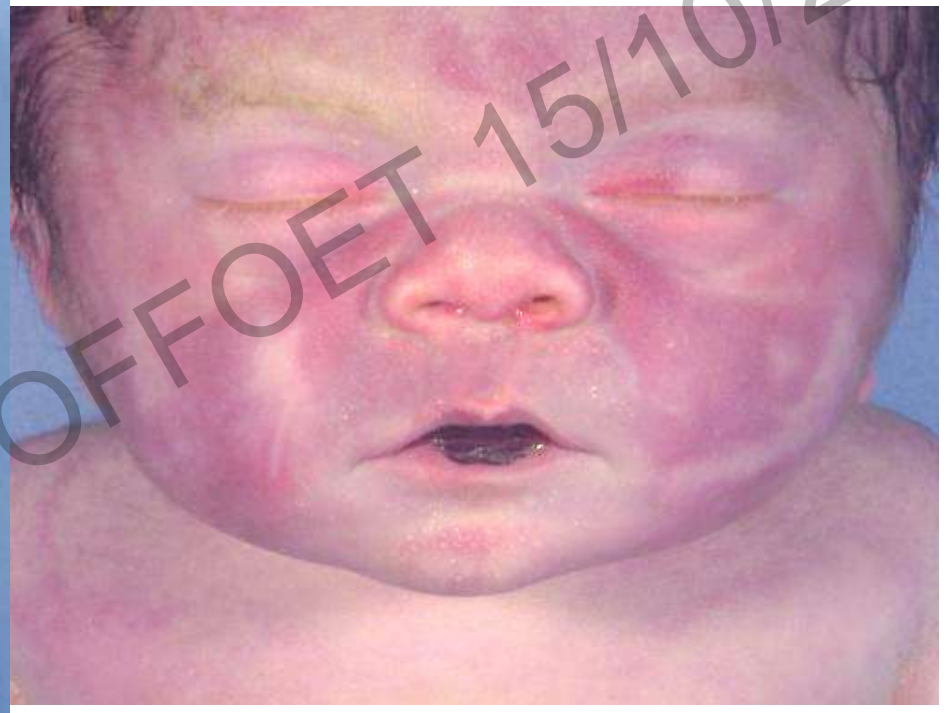


Short slender bones (specially upper limbs)< 3 percentile
Long bones measurements consistent with 25 WG
Head circumference 90 percentile

After counselling:
Uncertain prognosis
High risk of severe dwarfism
TOP at **34 WG**

Short stature
- Crown-heel like 28-29 WG
- Crown-rump: 29-30 WG

Macrocephaly like 38-39 WG
Normal weight: 2027 g
Short limbs
Craniofacial malformations



Large and high forehead

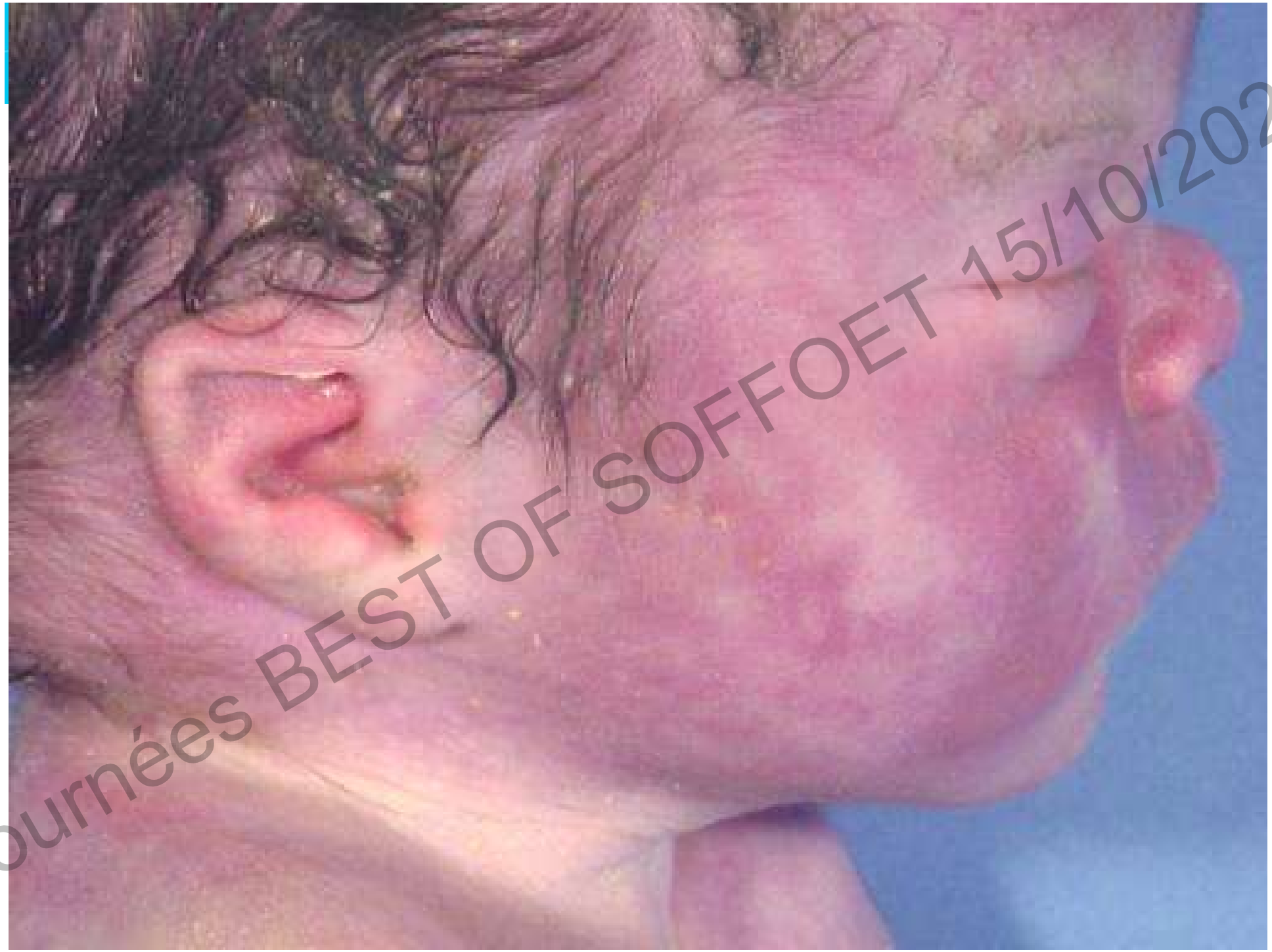
Triangular-shaped face with hypoplastic midface

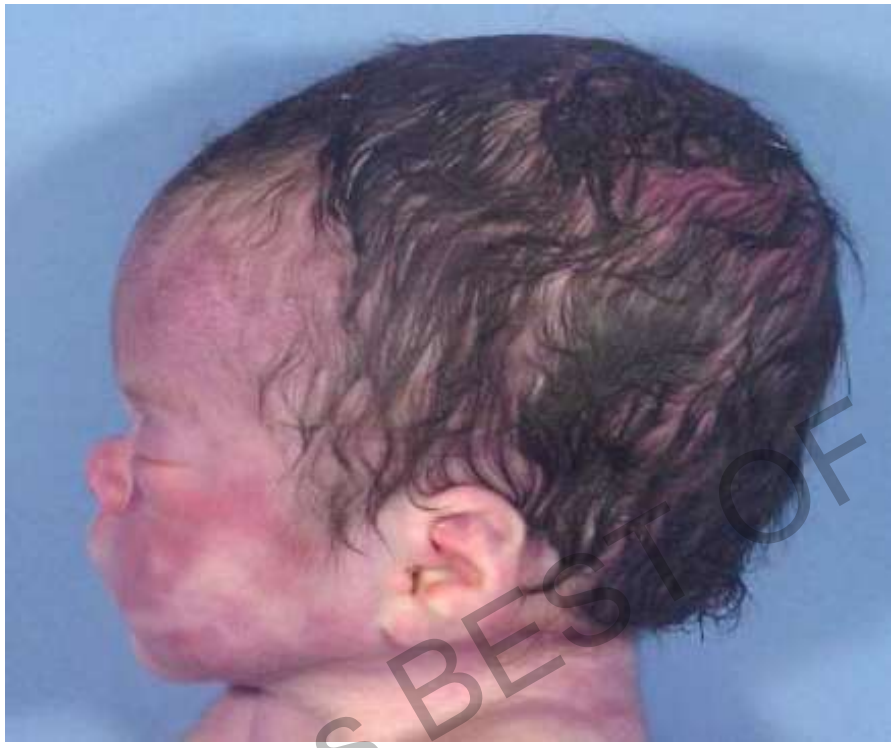
Pointed chin; small mouth

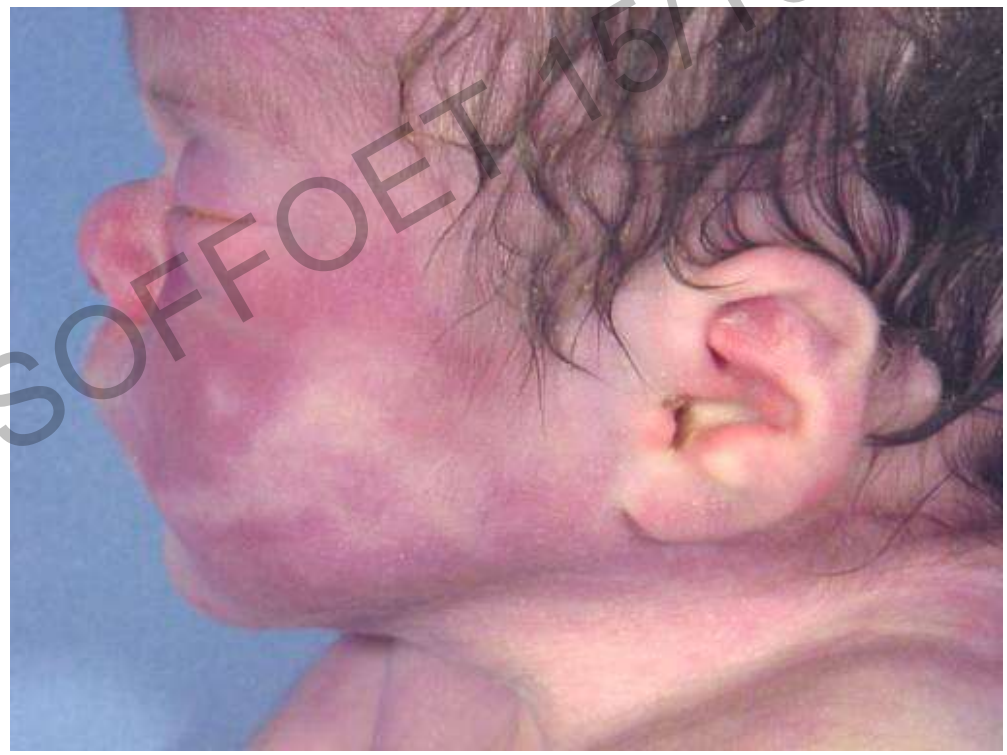
Flat cheeks

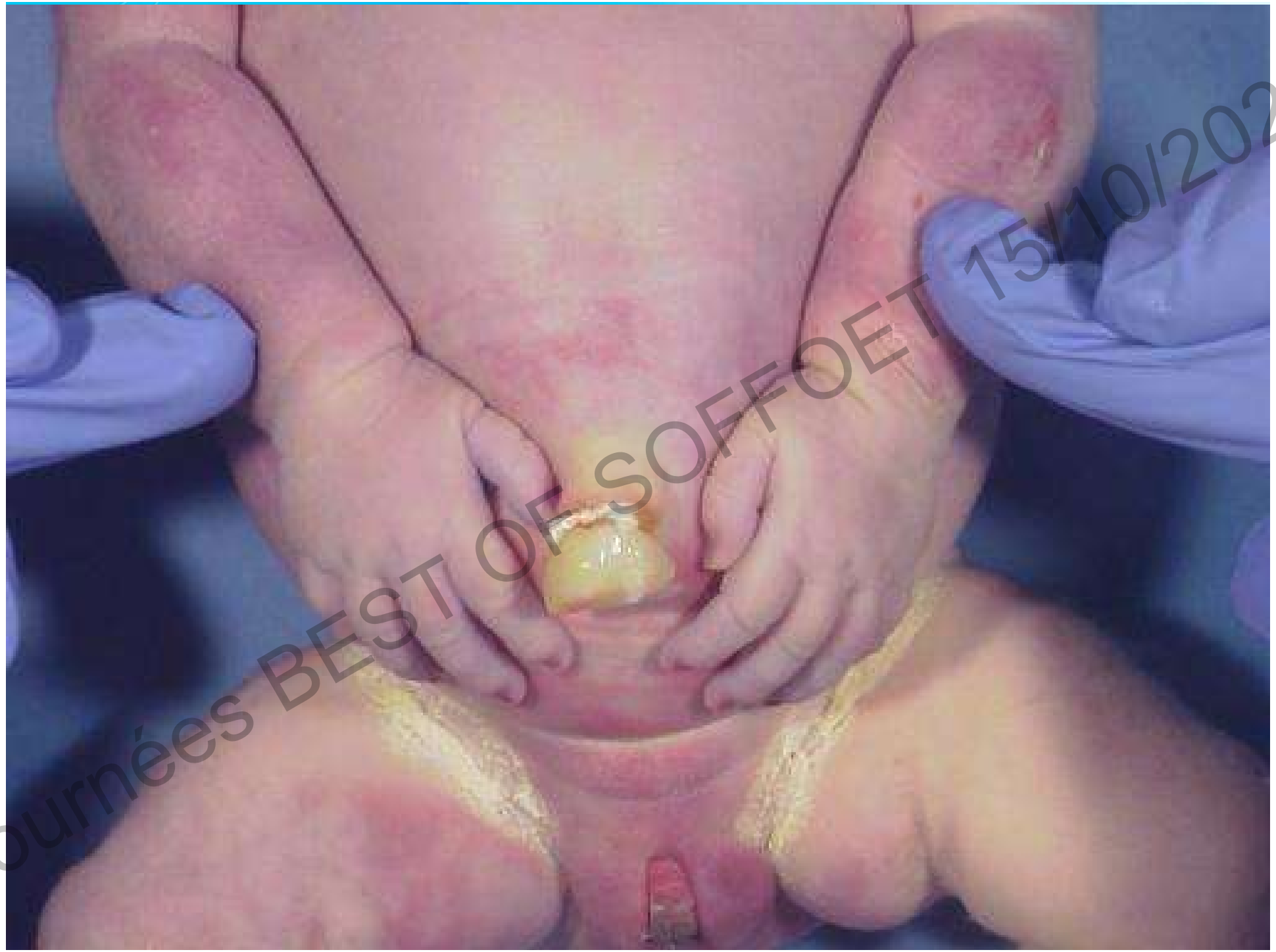
Dolichocephaly

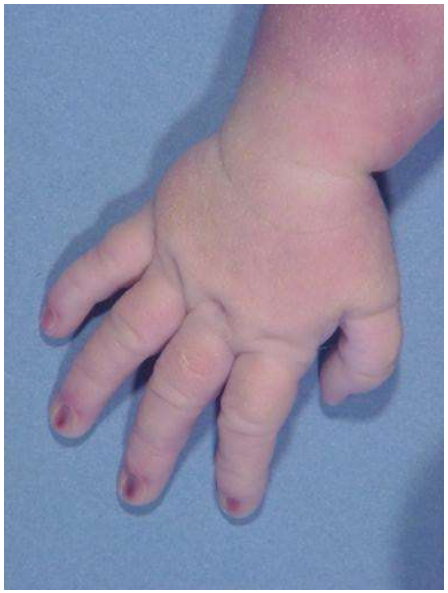
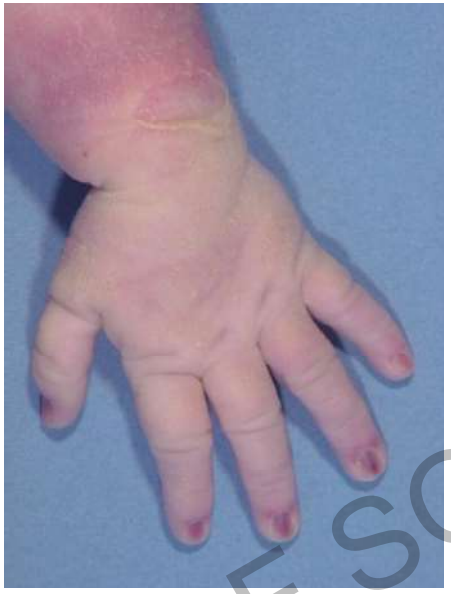
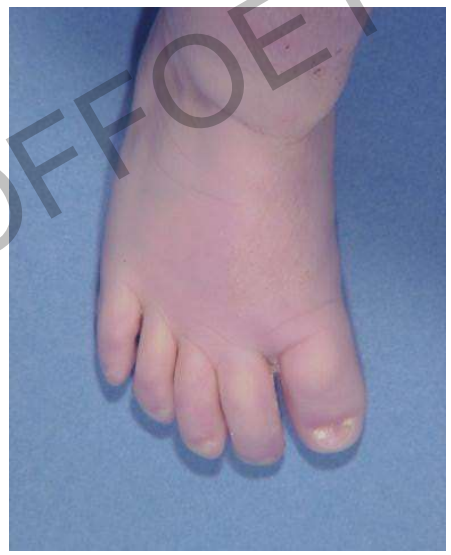
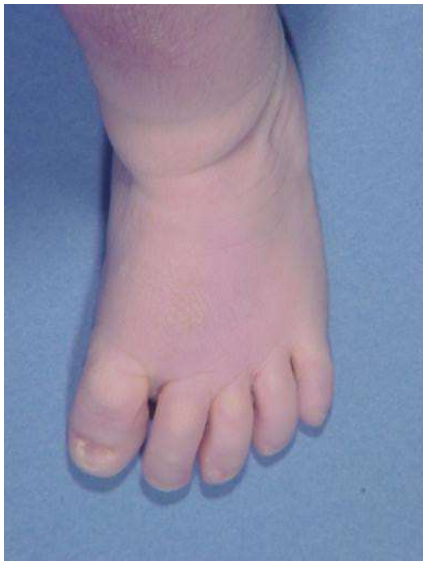
Depressed nasal root
Upturned nose
Anteverted nares

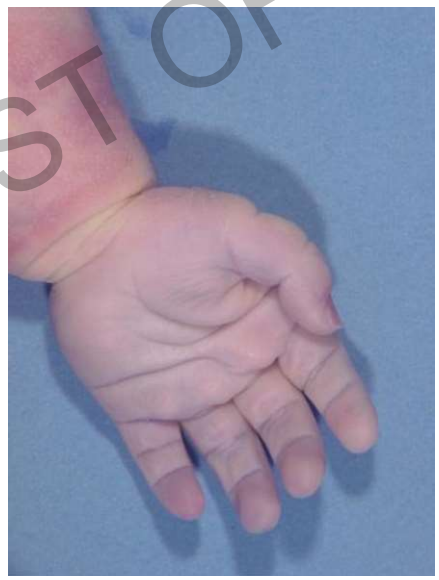




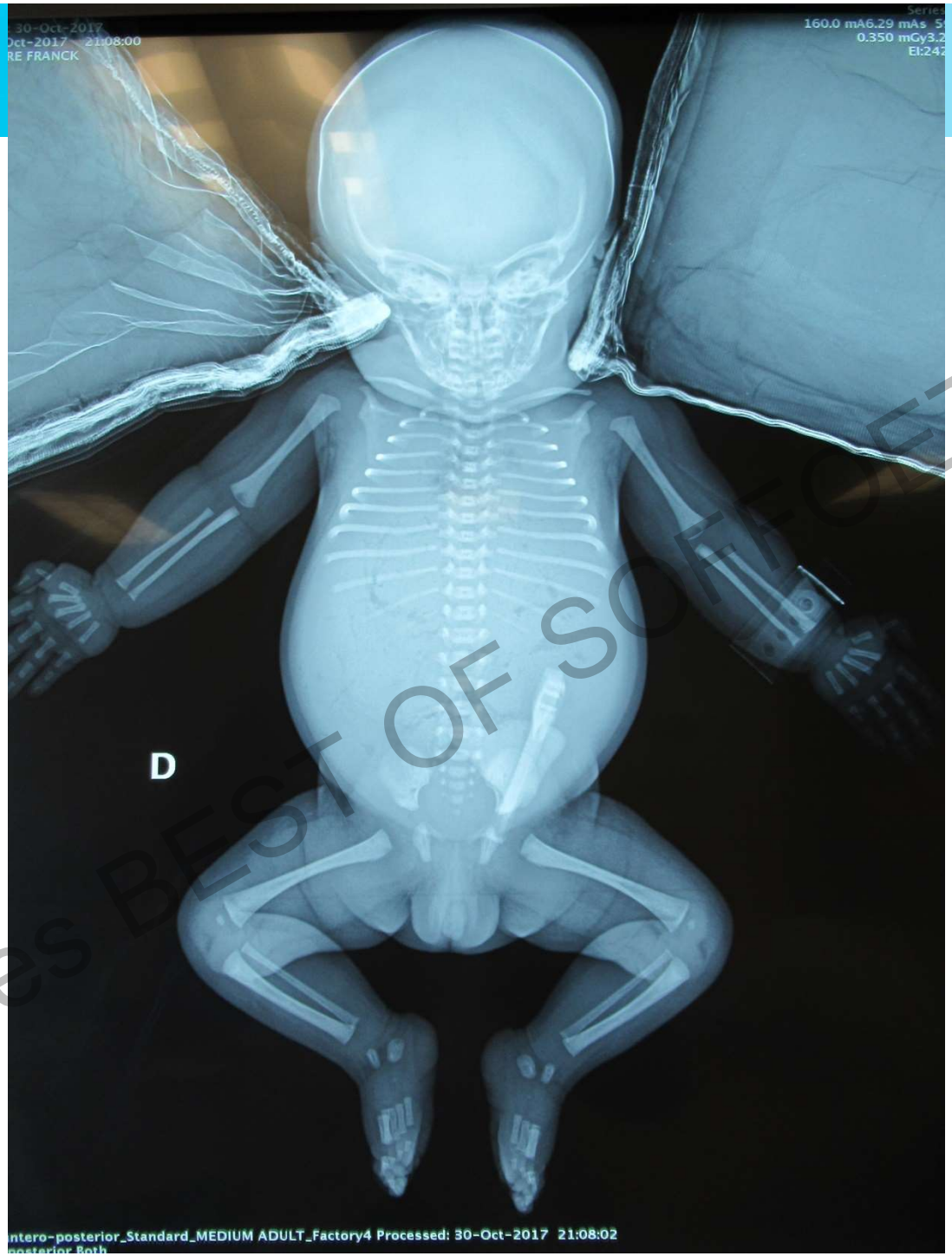




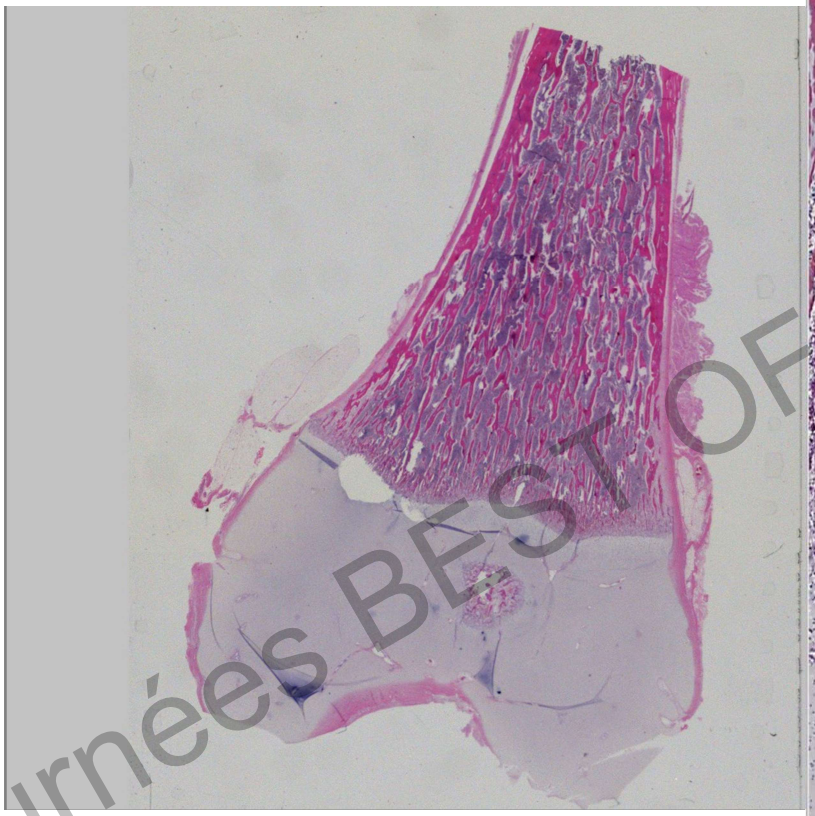


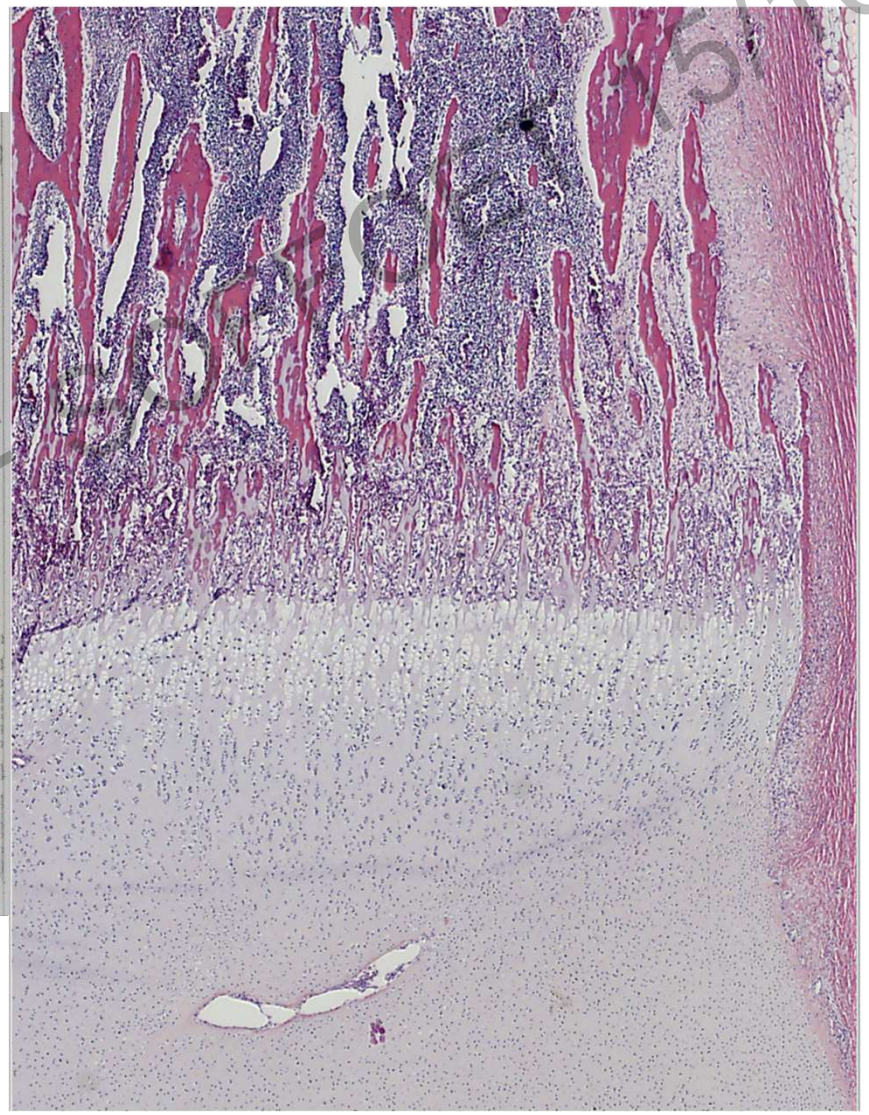
Right hand



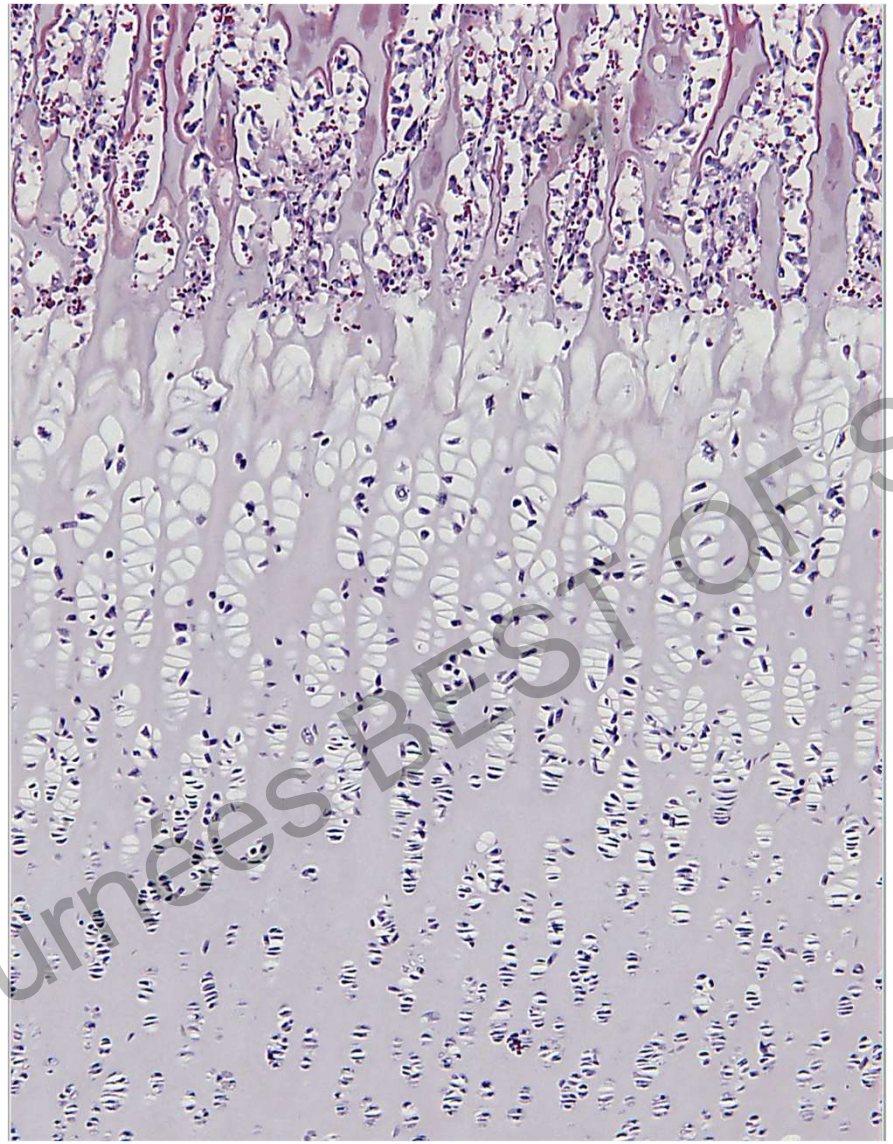
Post mortem Xray:
thin bones
advanced bone age
Thin ribs
Narrow and tall vertebrae

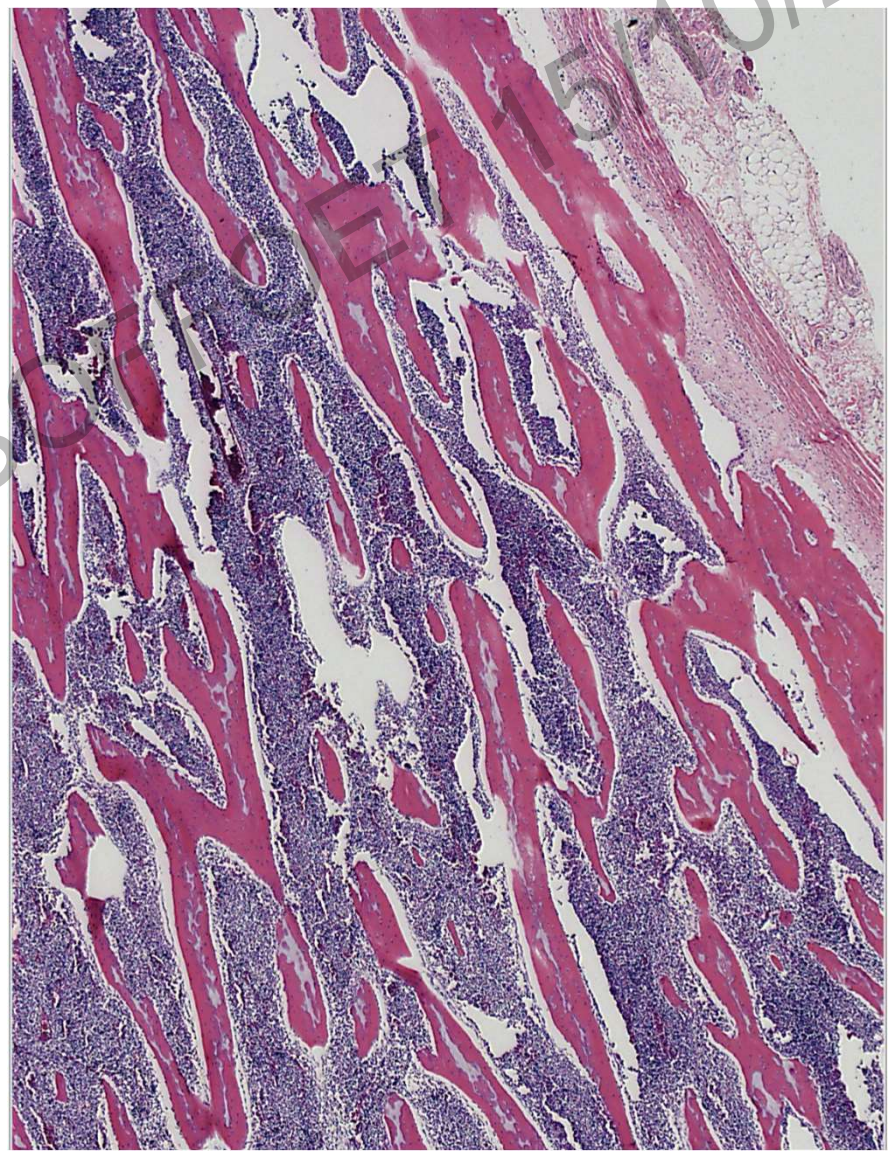
PHYSEAL GROWTH PLATE IS REGULAR



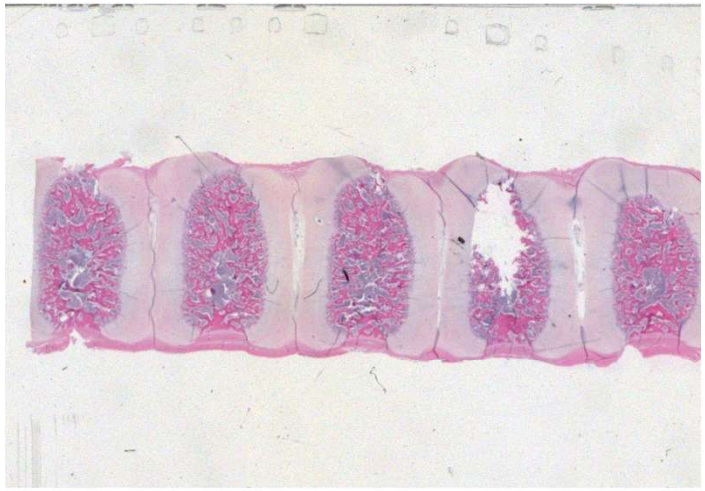


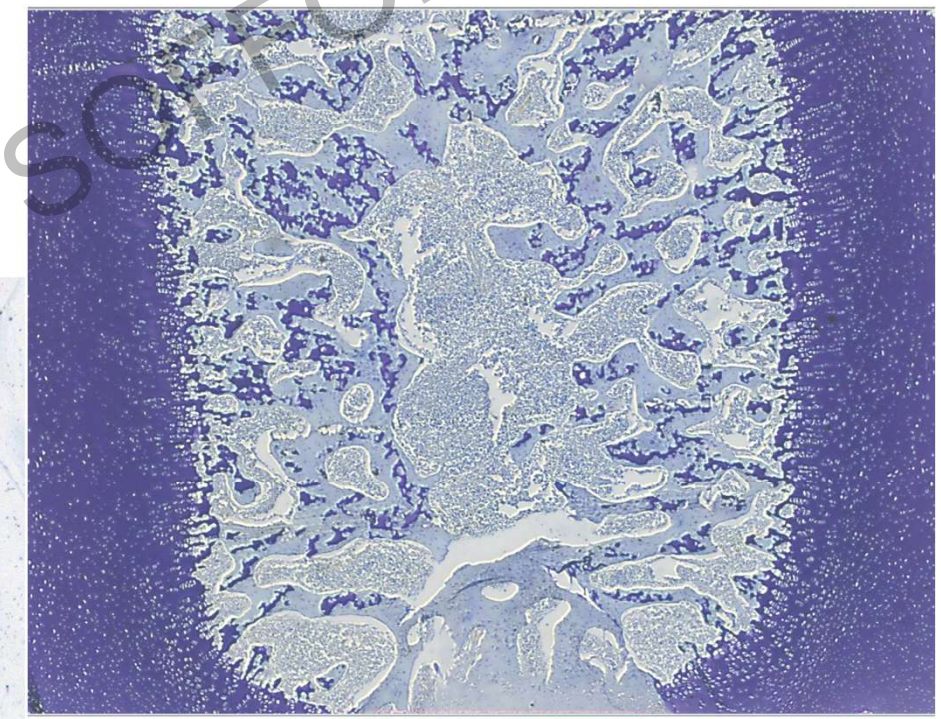
Hypoplastic resting cartilage

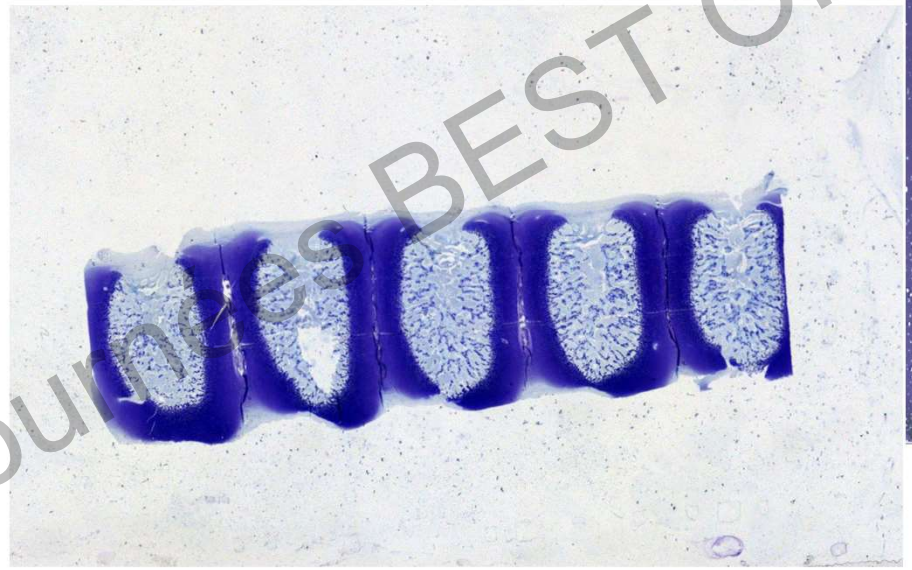




VERTEBRAL BODIES







In summary: Postmortem findings

- Normal weight
- Biometry : consistent with 28 -29 WG (term 34WG): 5 to 6 weeks growth retardation
- Macrocephaly : head circumference > 95 percentile
- Short limbs, short neck and thorax, enlarged abdomen
- Craniofacial abnormalities
- Organs were normal
- Slender bones, no angulations, no fractures

- **Any diagnosis?**

- Genetic investigations (post mortem)
  - No mutations *COL1A1 and COL1A2* (osteogenesis imperfecta) *ALPL* (hypophosphatasia) and *SOX9 (campomelic dysplasia)*
  - Lysosomal storage diseases were ruled out (NGS panel)

- Referred to Necker Hospital *(Pr Valérie Cormier-Daire)*

  - Sequencing of panel of genes responsible for skeletal dysplasias

  - **2 heterozygous compound mutations of *CUL7*** gene (one in each parent) *(Dr Sophie Rondeaux)*

  Protein encoded by this gene is a component of an E3 ubiquitin protein ligase complex

- **Diagnosis of 3M syndrome (Miller, Mc Kusick and Malvaux)**

Le séquençage à haut débit des gènes impliqués dans les Maladies Osseuses constitutionnelles a mis en évidence deux variants probablement pathogènes :

Gène	*CUL7*	*CUL7*
chromosomique	Chr6(GRCh37):g.43020448dup	Chr6(GRCh37):g.43017168G>C
cDNA, protéine	NM_014780.4:c.79dup, p.(Arg27Profs*7)	NM_014780.4:c.1802C>G, p.(Ser601*)
Statut	hétérozygote (460X)	hétérozygote (255X)
Mode d'hérédité de la maladie associée	autosomique récessif	autosomique récessif
Confirmation Sanger	oui	oui

Profondeur moyenne : 417 X
Couverture : 99,4 % des bases du panel sont couvertes à plus de 30X
Exons non/mal couverts (profondeur < 30X) : *ADAMTS17: exon 2 ; ANKRD11: exons 9,13 ; B3GALT6: exon 1 ; B3GAT3: exon 5 ; COL2A1: exon 3 ; COL9A1: exon 13 (ENST00000357250) ; GPX4: exon 1 ; PDE4D: exon 1 ; SLC10A7: exon 6 (ENST00000507030) ; STAT5B: exon 7*

CONCLUSION

Présence de deux variants probablement pathogènes dans le gène *CUL7* à l'état hétérozygote composite : c.79dup (p.(Arg27Profs*7)) (hérité de son père) et c.1802C>G (p.(Ser601*)) (hérité de sa mère). Ces variants entraîneraient l'apparition d'un codon stop prématuré. Ils ne sont pas répertoriés dans les bases de données de polymorphismes ou de mutations (dbSNP, gnomAD, ClinVar, HGMD-Pro). Les mutations de ce gène sont associées au syndrome 3M, ce qui est compatible avec le phénotype du foetus.

3 M Syndrome

- Rare skeletal dysplasia, first described in 1972
- Autosomal recessive
  - *CUL7* Gene (77,5%), *OBSL1* gene (16,3%) *CCDC8* gene (5%)
- Prenatal and postnatal Growth retardation (Dwarfism)
- Variable severity , sometimes up to -6 SD to -9 SD
- Low birth weight (not our case)

3 M Syndrome

- Characteristic craniofacial abnormalities: « Gloomy face »
  - Dolichocephaly, frontal bossing
  - Triangular-shaped face, mid face hypoplasia
  - Upturned nose, anteverted nares
  - Small mouth, large ears

- Sex ratio: 1
- No mental retardation
- Infertility and hypospadias reported
- Joint hyperlaxity ; scoliosis and lordosis; surgery can be necessary
- Adult size : 130 cm
- No efficiency of GH therapy

- New pregnancy 4 years later

- Despite a recurrence risk 25 %
- The couple refused prenatal genetic testing
- US close follow up is necessary until term (variability of size)
- Healthy baby

CONCLUSION

- Antenatal US and radiological features suggest skeletal dysplasias
- Autopsy findings confirm prenatal data and sometimes make the diagnosis (but genetic investigations remain necessary)
- In case of a rare disease, review in a reference center (Necker Hospital) => guide further genetic investigations
- NGS targeted gene panels improves diagnosis rate
- **Optimal genetic counselling**

Claude Monet
Cathédrale de Rouen

Thank you for your attention!