XXXVIIth IPPA Advanced Course 2015
Fontainebleau, France

COMMON and UNCOMMON SKELETAL DYSPLASIAS and DYSOSTOSES

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COMMON and UNCOMMON SKELETAL DISORDERS

viewed from a differential diagnostic point of view
after specific appearances

PART 1

- ✓ FRACTURED BONES
- ✓ SLENDER BONES
- ✓ ANGULATED BONES

PART 2

- ➢ STIPPLED BONES
- ➢ ABSENT BONES
- ➢ DYSOSTOSES

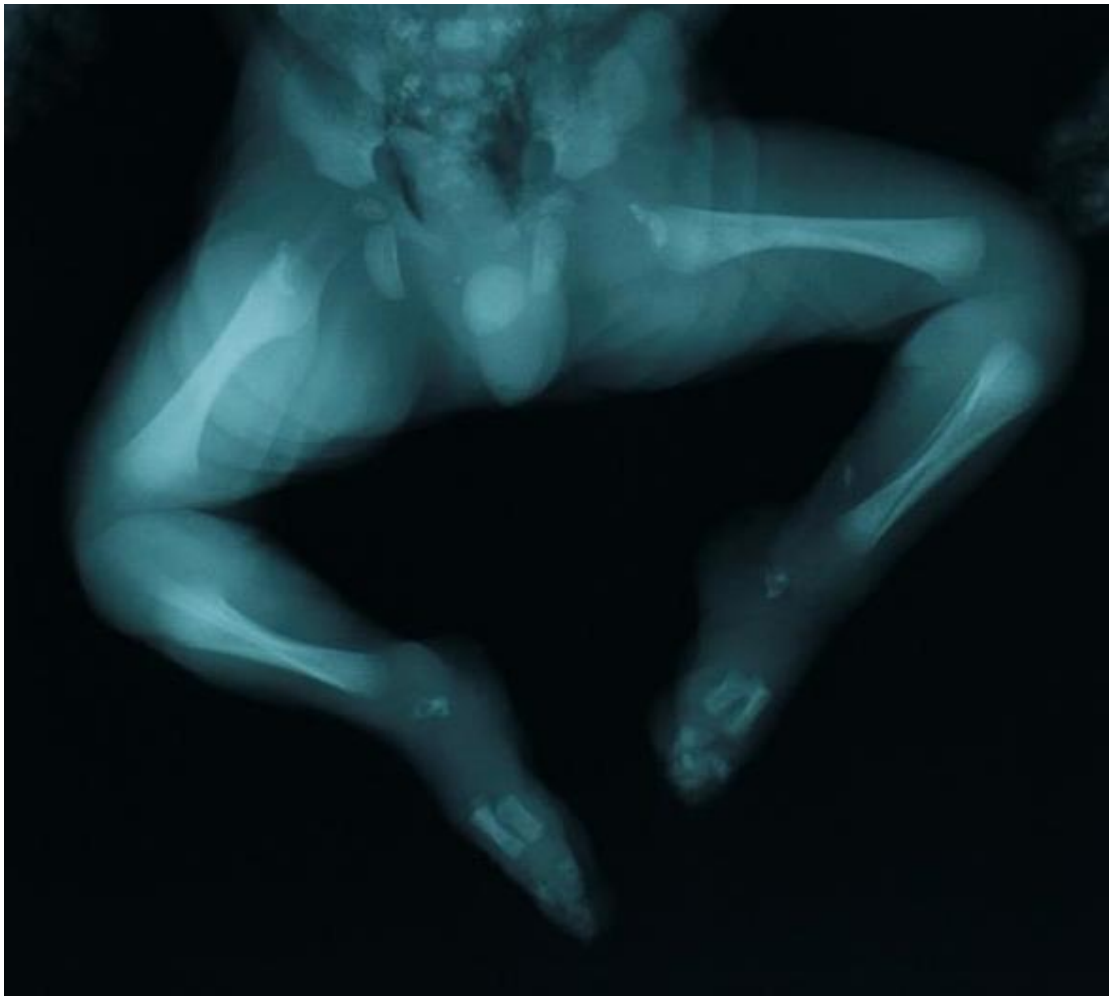
STIPPLED BONES (epiphyses)

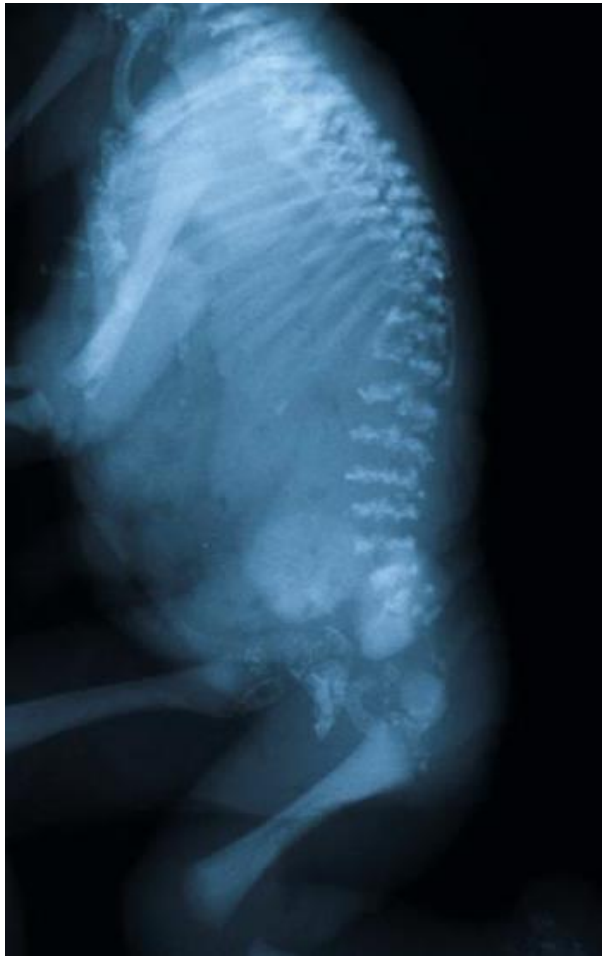
- Chondrodysplasia Punctata (CDP)
  - Rhizomelic CDP, AR
  - CDP Conradi – Hünermann type, X-liked dominant
  - CDP Brachytelephalangic type, X-liked recessive
- Greenberg/HEM dysplasia
- Zellweger syndrome
- Binder phenotype (maxillofacial dysostosis)

TOP due to short limbs or other abnormalities rather than stippling (but may be seen on late USS).

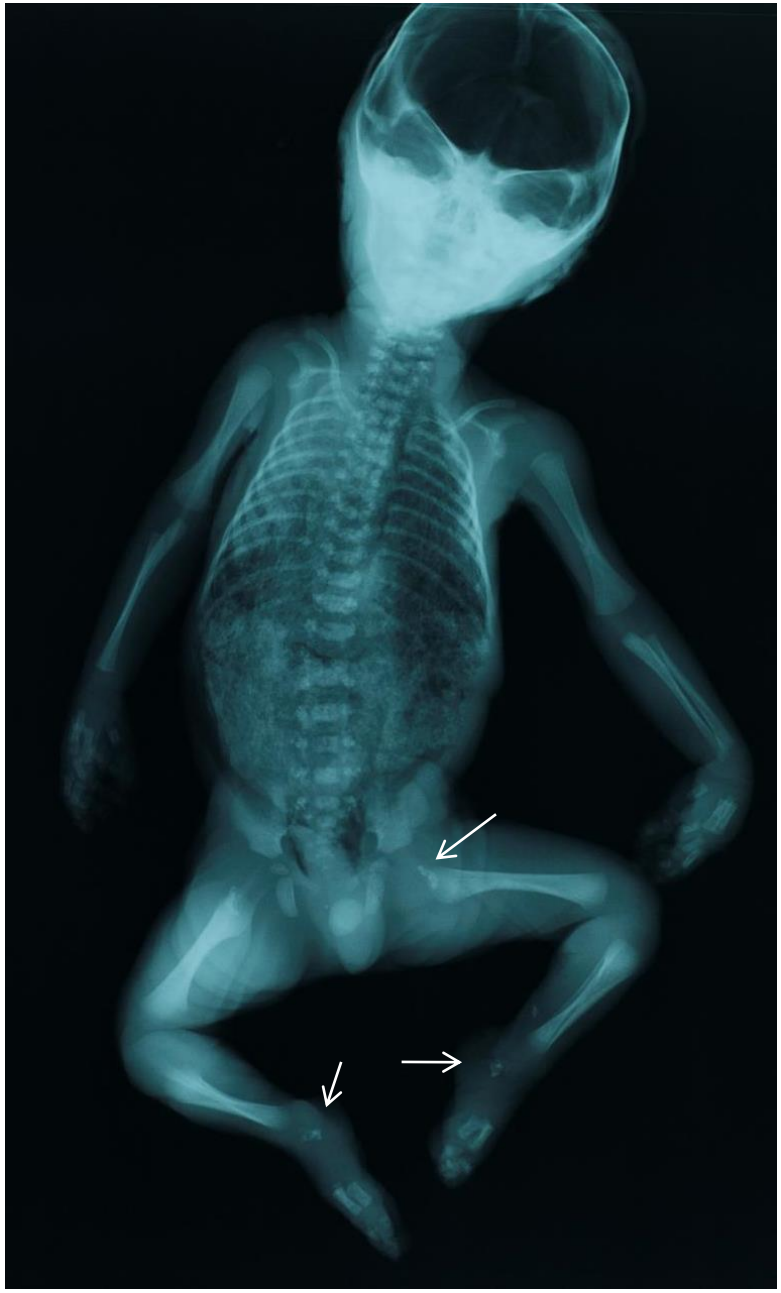
Stippling may be seen in:

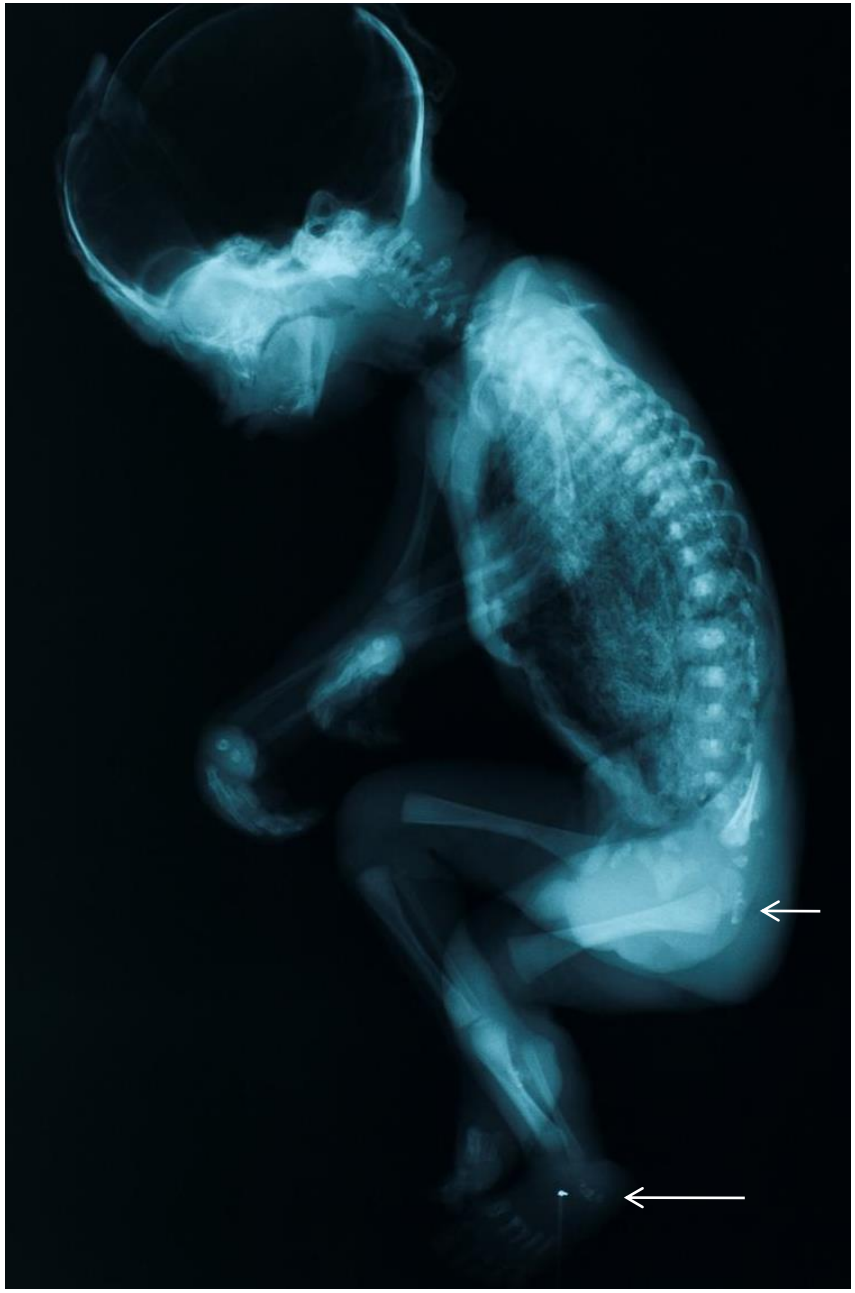
- Smith-Lemli-Opitz syndrome
- Chromosomal abnormalities (tris18; tris 21)
- Metabolic disorders (lysosomal storage)
- Drug-induced embryopathies (warfarin; hydantoin; alcohol; phenacetin)



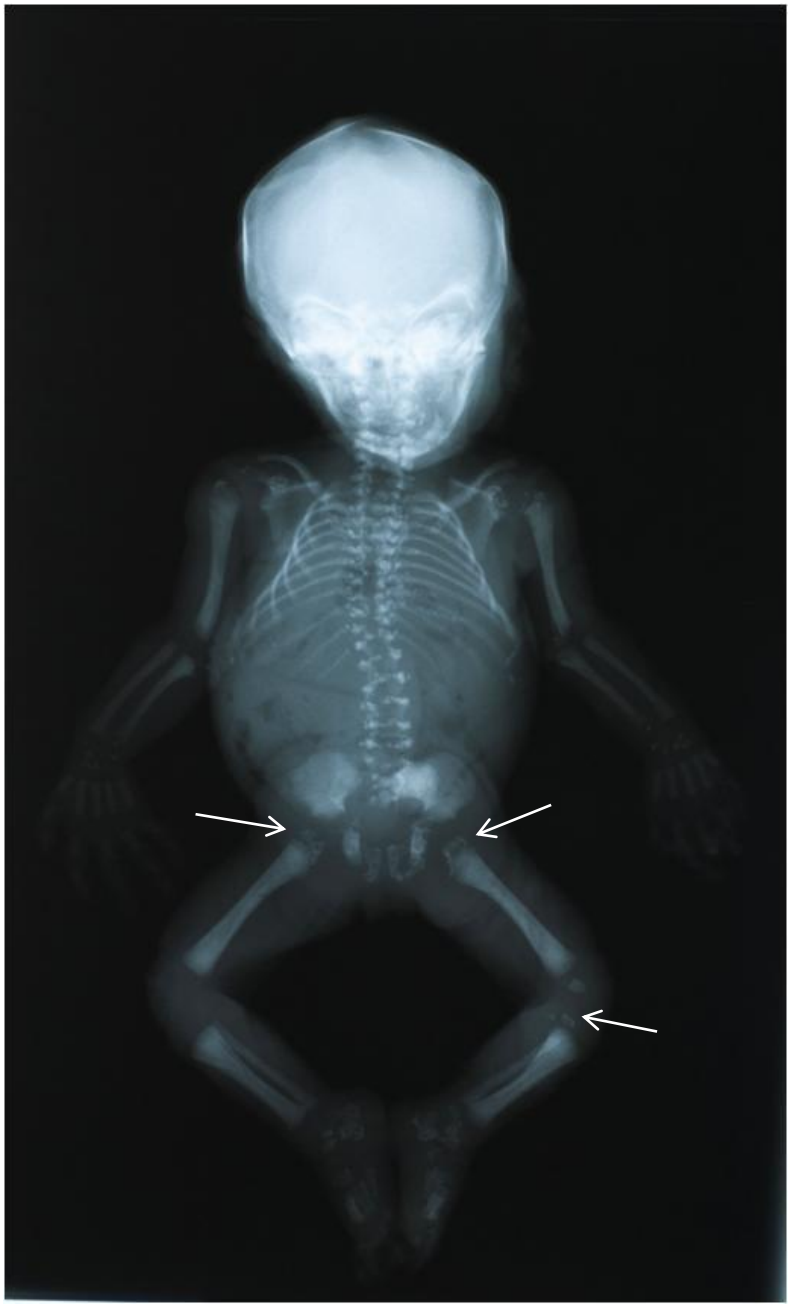


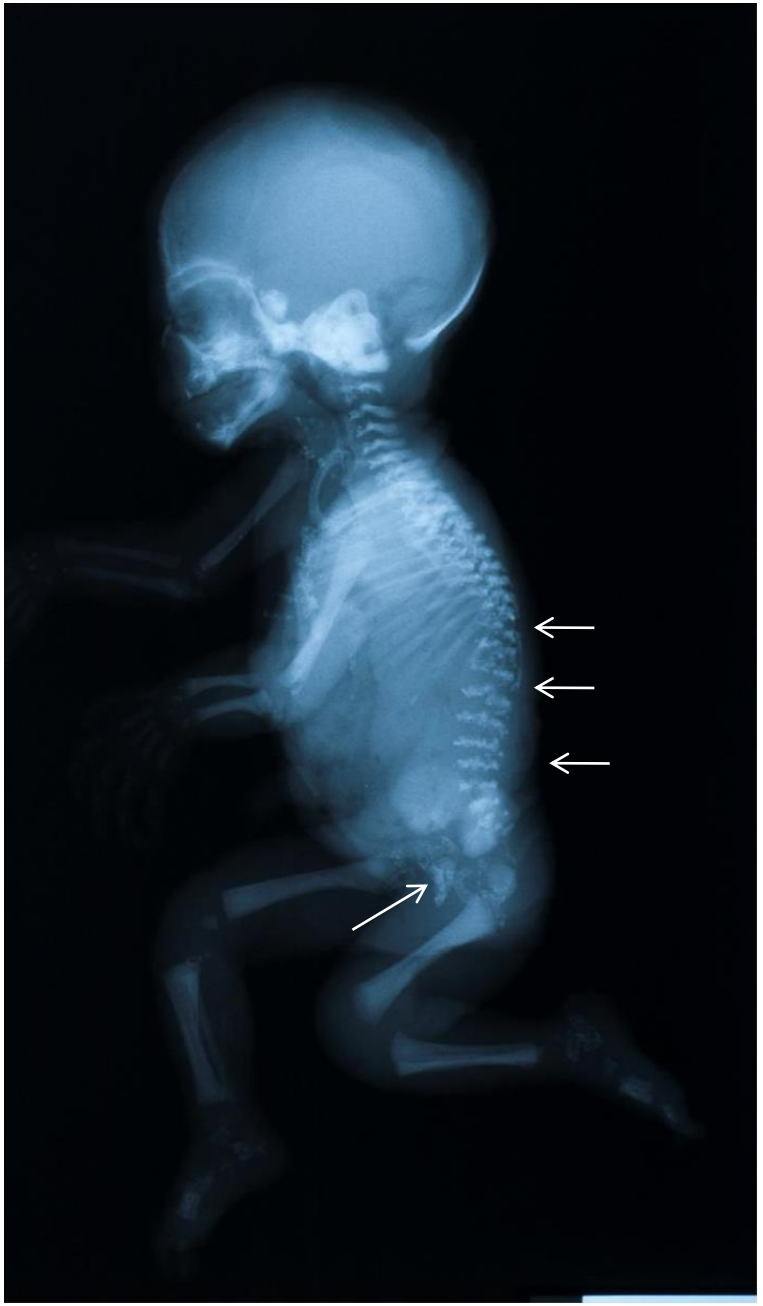
Chondrodysplasia Punctata



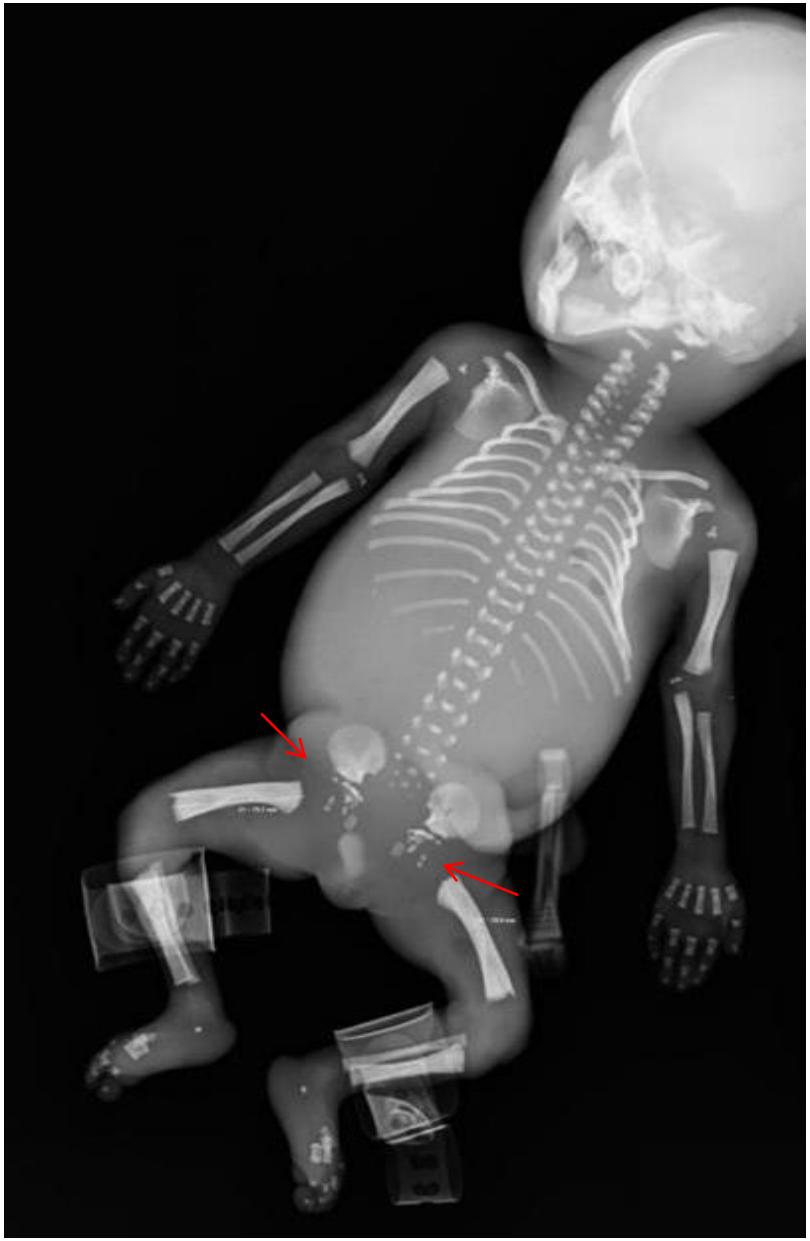


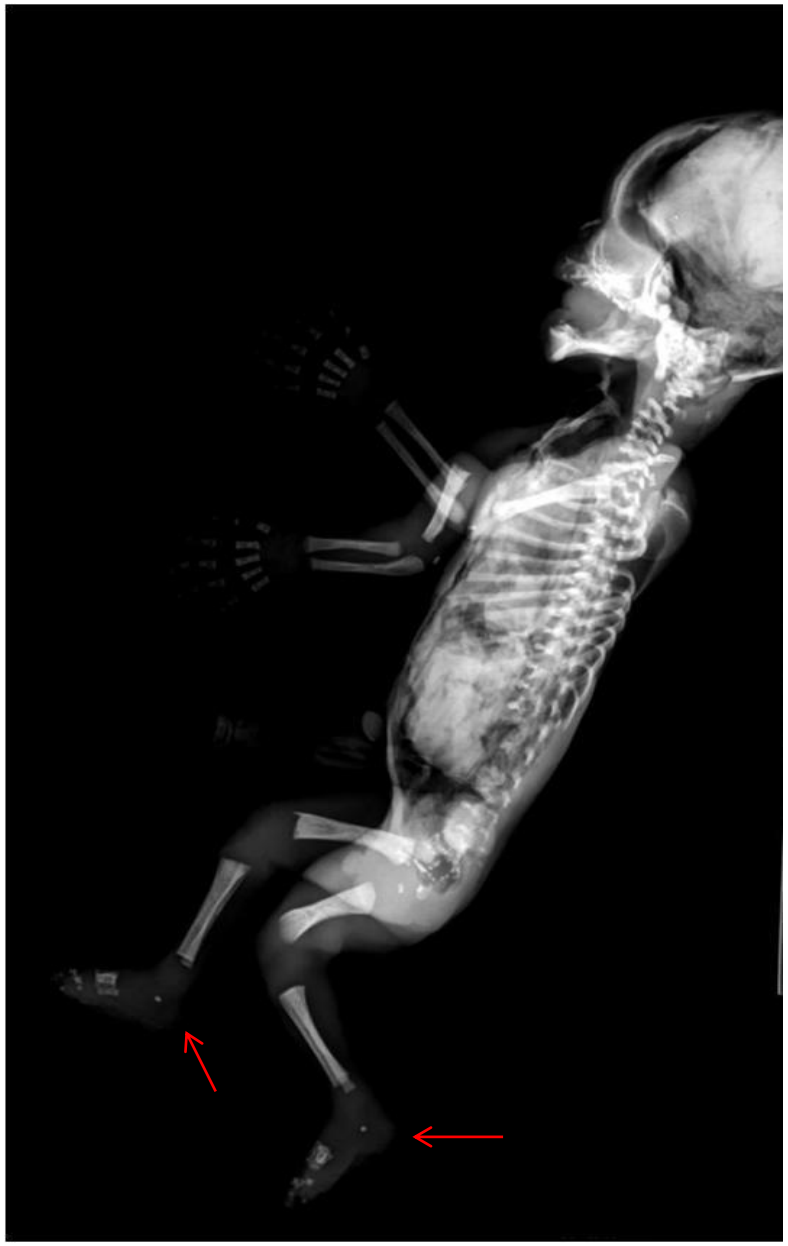
stippling





stippling





Epiphyseal stippling

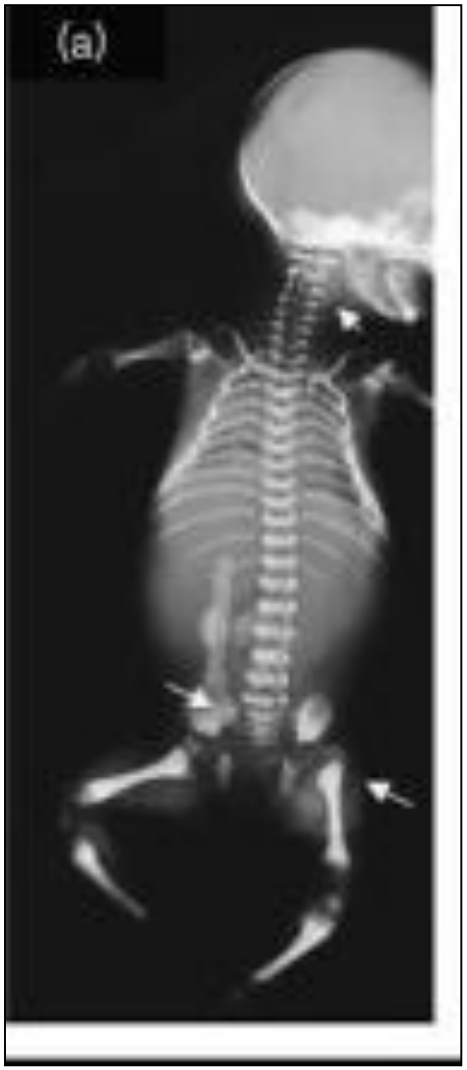
STIPPLED BONES

Chondrodysplasia Punctata Rhizomelic AR

Deficiency of multiple or isolated peroxisomal enzymes

3 genotypes with a similar phenotype

High mortality rate in infancy



X-ray
Symmetric rhizomelic shortening
Flared metaphyses
Coronal clefting of vertebrae on lateral view
No stippling on the spine

Image from
Chondrodysplasia punctata: a clinical diagnostic and radiological review.
Irving, Melita; Chitty, Lyn; Mansour, Sahar; Hall, Christine

Clinical Dysmorphology. 17(4):229-241, October 2008.
DOI: 10.1097/MCD.0b013e3282fdcc70

STIPPLED BONES

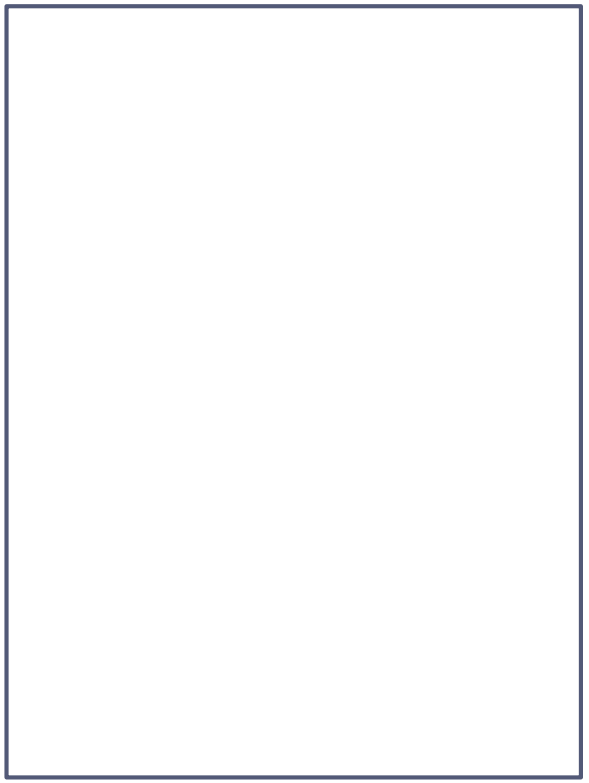
Chondrodysplasia Punctata
Conradi - Hünermann X-linked dominant

Exclusively **female** patients (incompatible with life in males)

Prognosis is good.
Ichthyosiform erythroderma

25% of CDP patients are the C-H type.

X-ray
Asymmetric rhizomelic shortening
Stippling in many epiphyseal areas



CDP – CH type

Rhizomelic/lethal type	Conradi-Hunermann type
Inheritance: Autosomal recessive	Inheritance: X-linked dominant
Symmetric rhizomelic limb shortening	Asymmetric and occasional limb shortening
Stippling in spine absent/coronal clefts present	Spine: stippling present at endplates and bodies, later leads to kyphoscoliosis
Stippling noted in large joints, sparing hands and feet Laryngeal and tracheal cartilage stippling also present	Hands and feet also involved in addition to large joints. No extracartilaginous stippling
Mental retardation present and death in infancy	Compatible with normal intelligence and normal life span

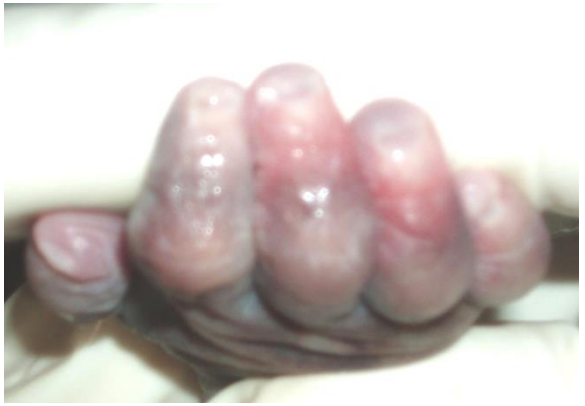
Differences between Rhizomelic and Conradi-Hunermann type Chondrodysplasia punctata

World J Radiol.2014 October 28; 6(10): 808-825.
Published online 2014 October 28. doi: 10.4329/wjr.v6.i10.808.

STIPPLED BONES

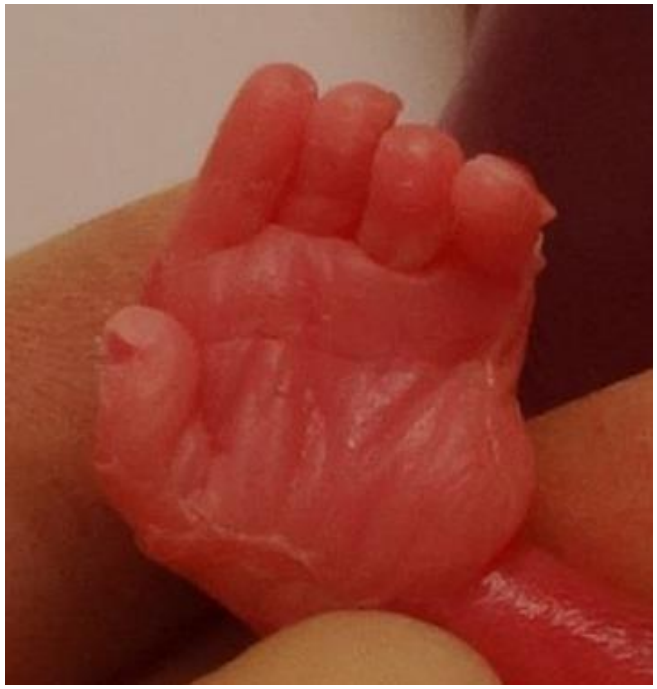
Chondrodysplasia Punctata Brachytelephalangic X-linked recessive

mutations in the arylsulfatase E gene



Exclusively **male** patients

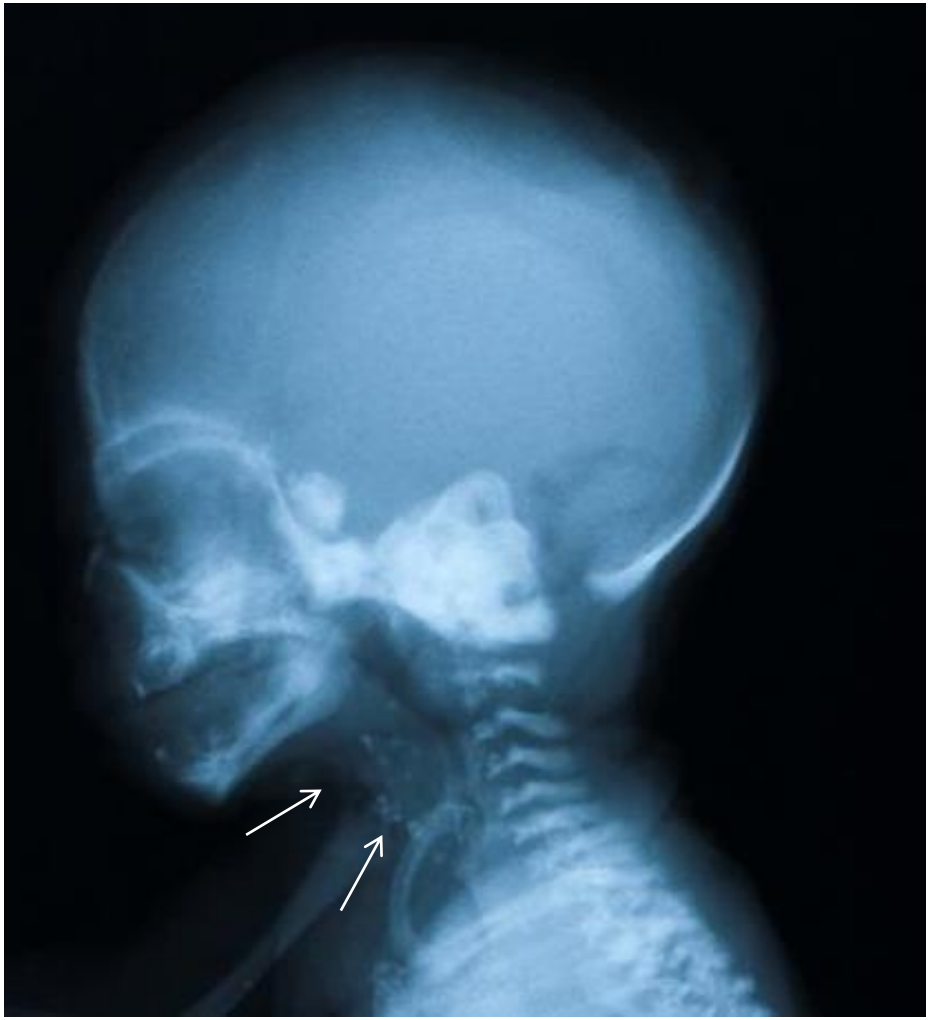
Polyhydramnios described
Spinal cord compression and respiratory problems in some severe cases



22/40w

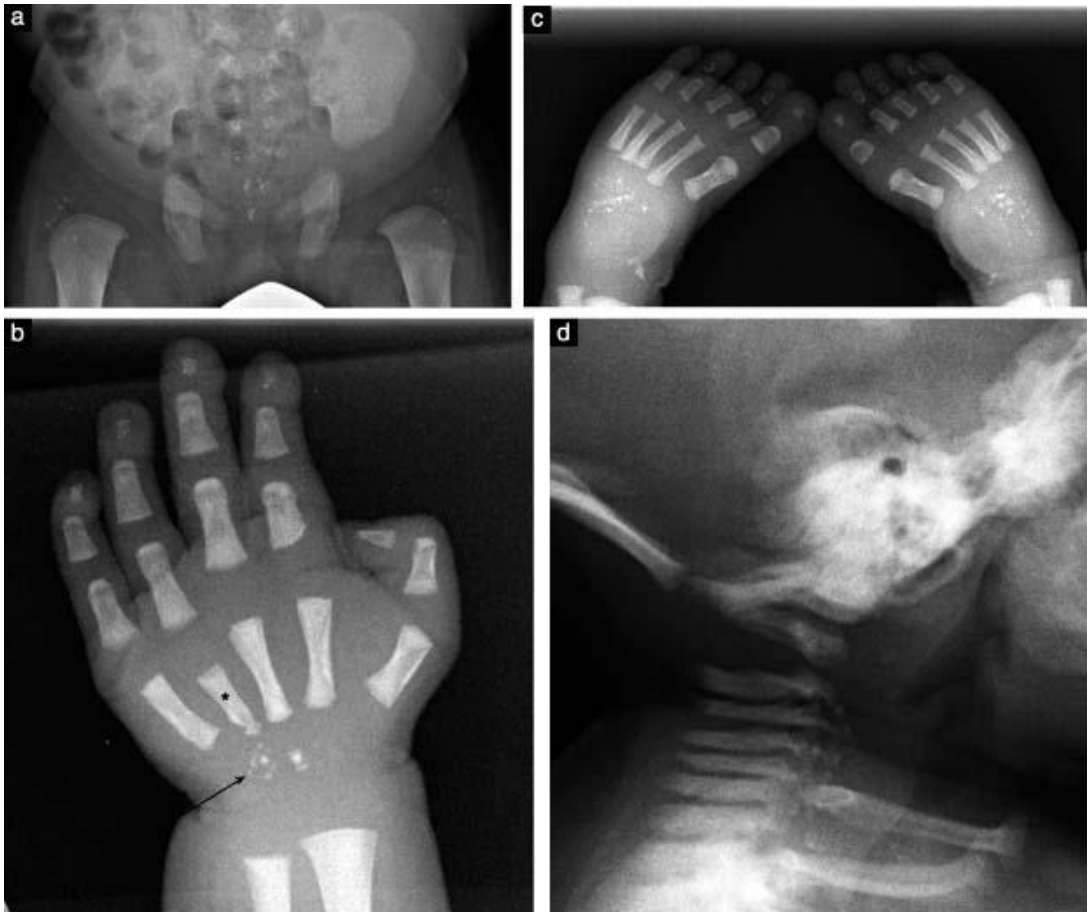
X-ray
Stippling in multiple epiphyses
+
Paravertebral and laryngotracheal regions

Stippling not seen at 14/40w and 22/40w in fetuses with proven CDP-XR.



laryngotracheal stippling

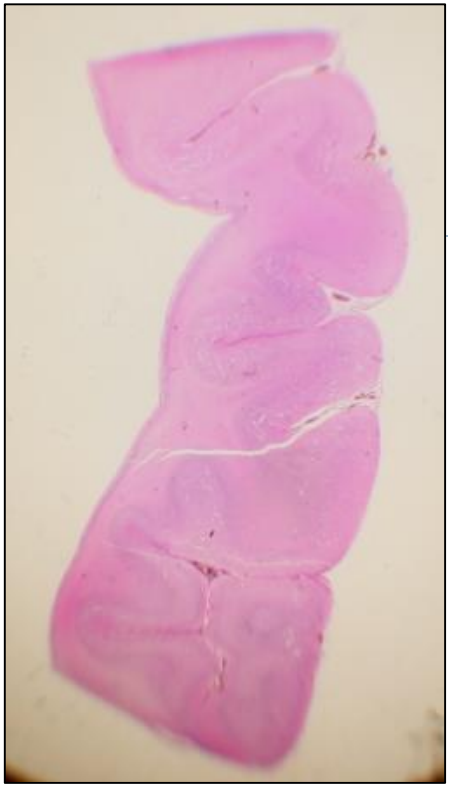
Prenatal diagnosis of brachytelephalangic chondrodysplasia punctata: case report



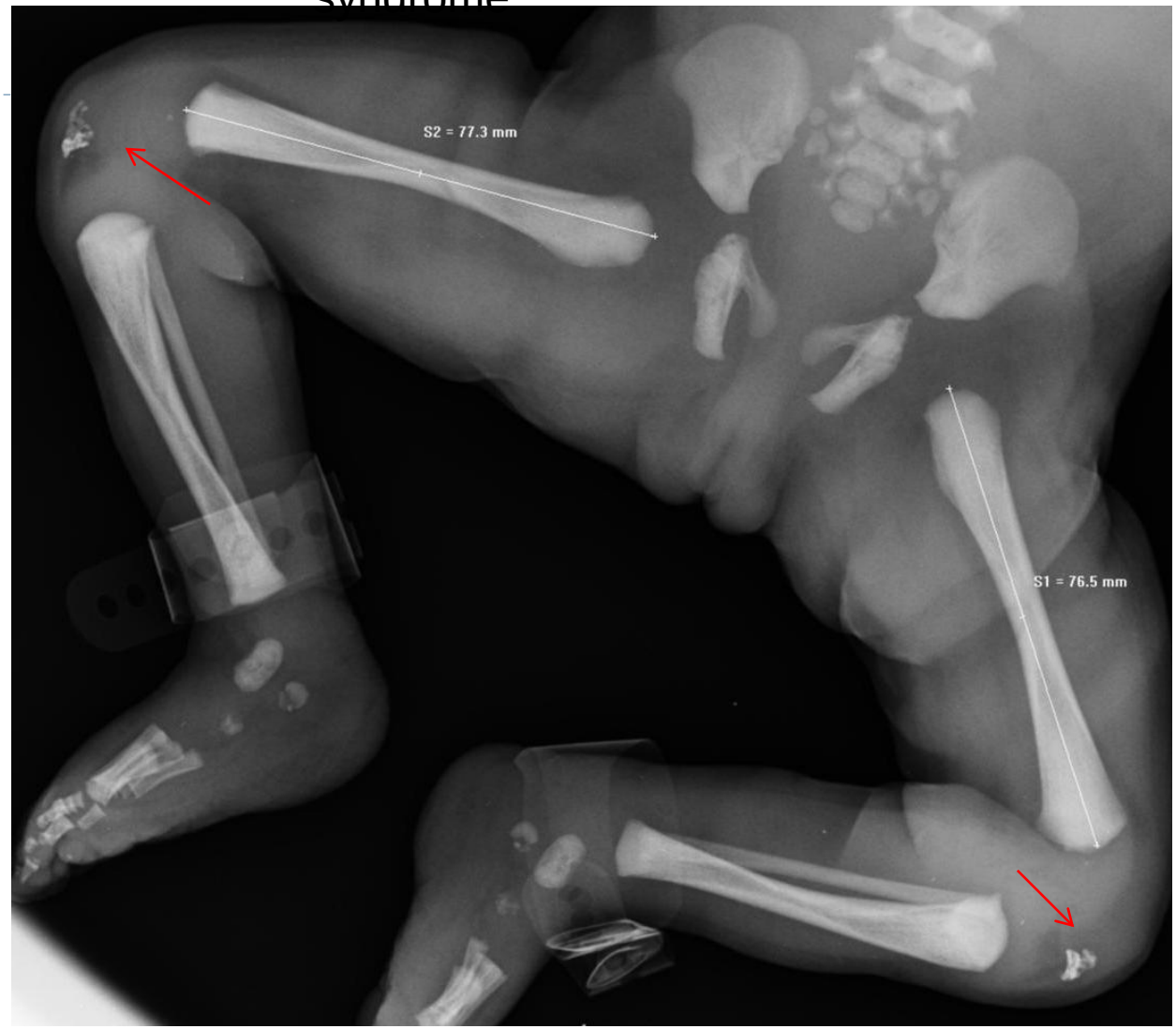
hypoplastic 4th metacarpal

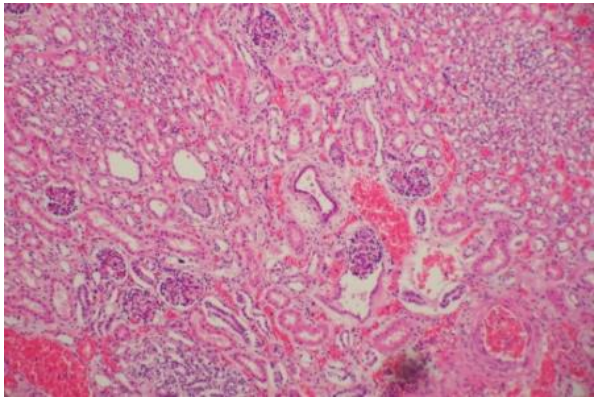
40/40w

Ultrasound in Obstetrics and Gynecology
Volume 34, Issue 6, pages 724-726, 23 OCT 2009 DOI: 10.1002/uog.7452
http://onlinelibrary.wiley.com/doi/10.1002/uog.7452/full#fig2

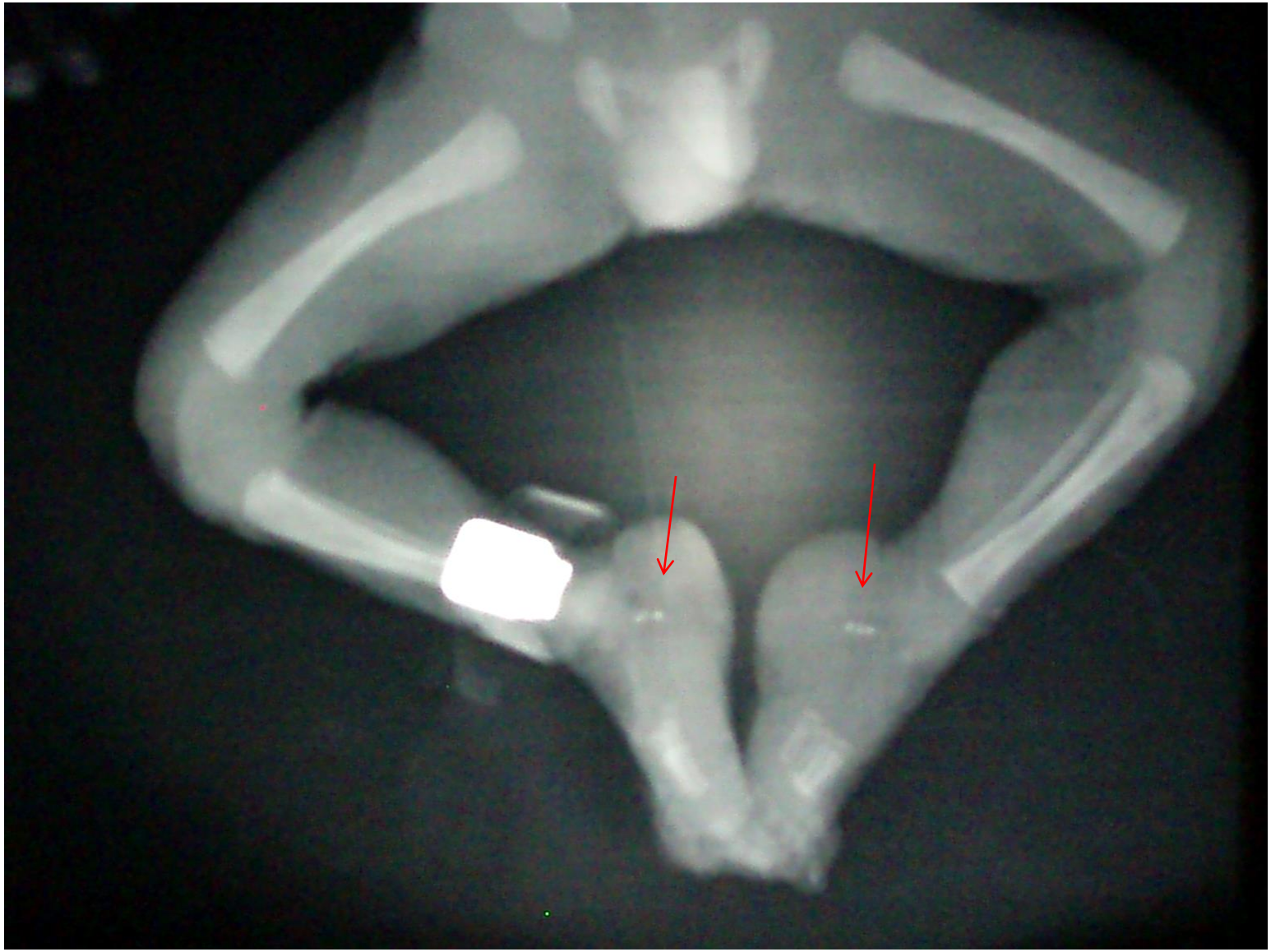


Stippling in Zellweger syndrome



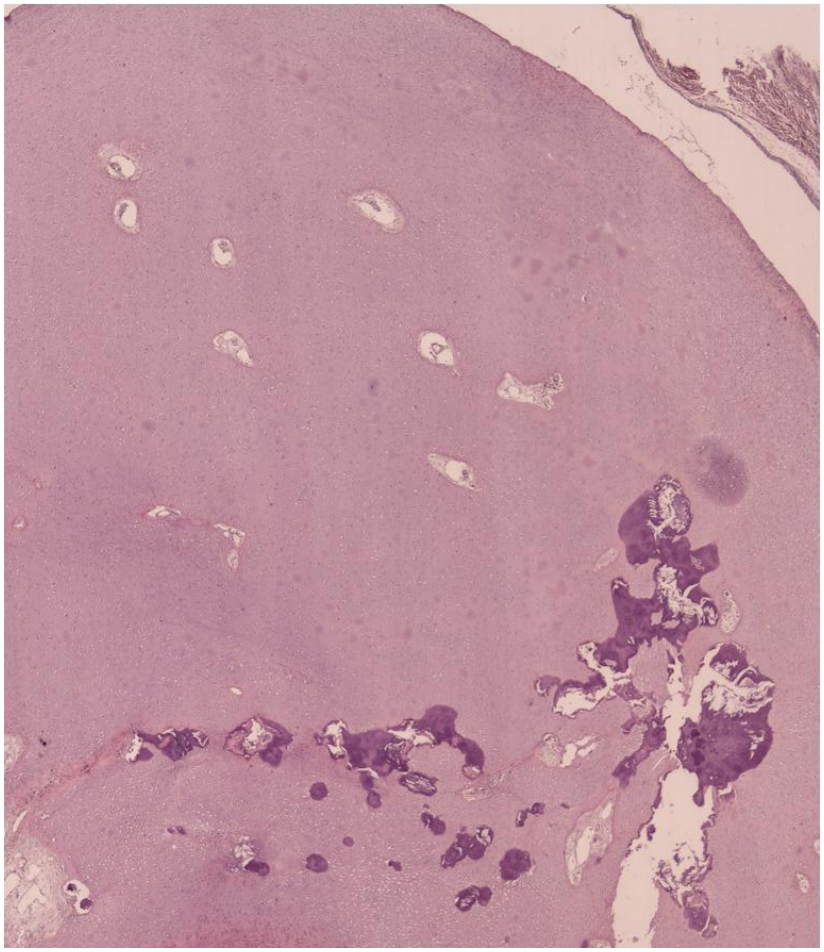


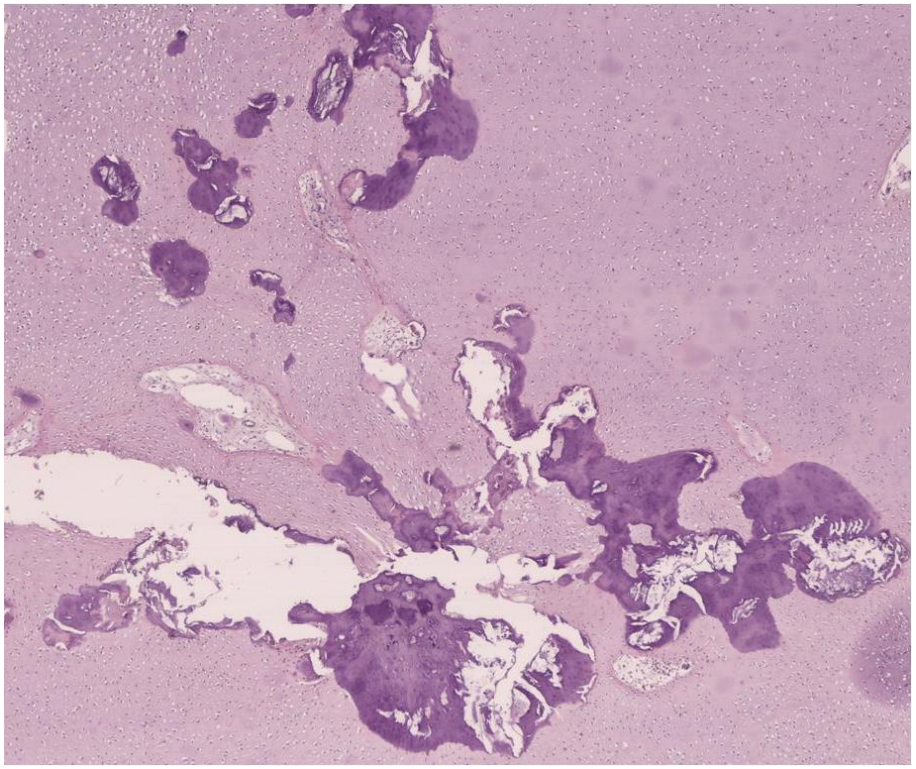
Abnormal patella calcification



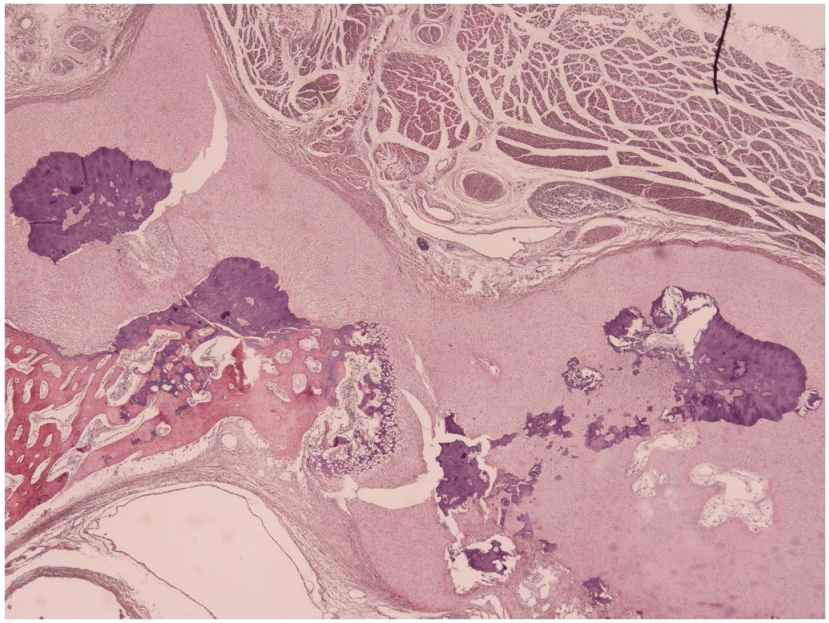
Stippled tarsal bones in maternal

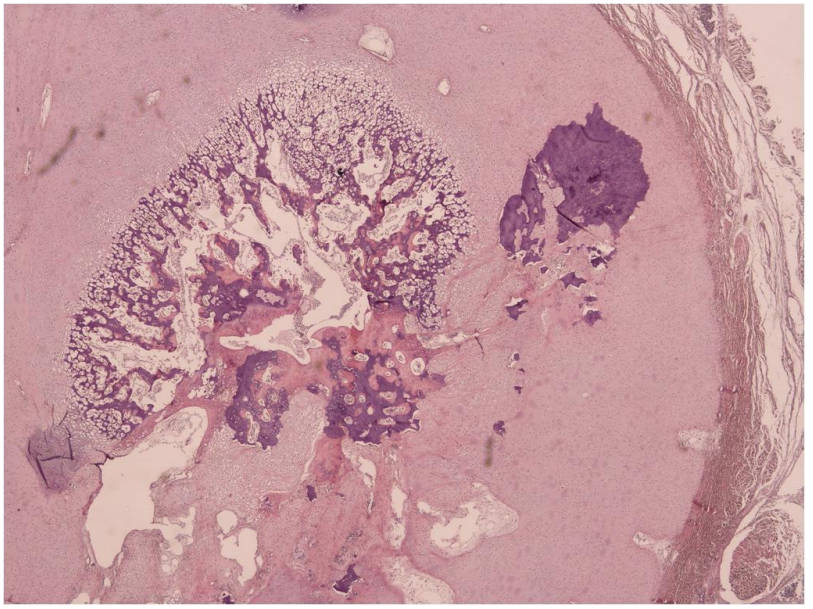
CDP Histology

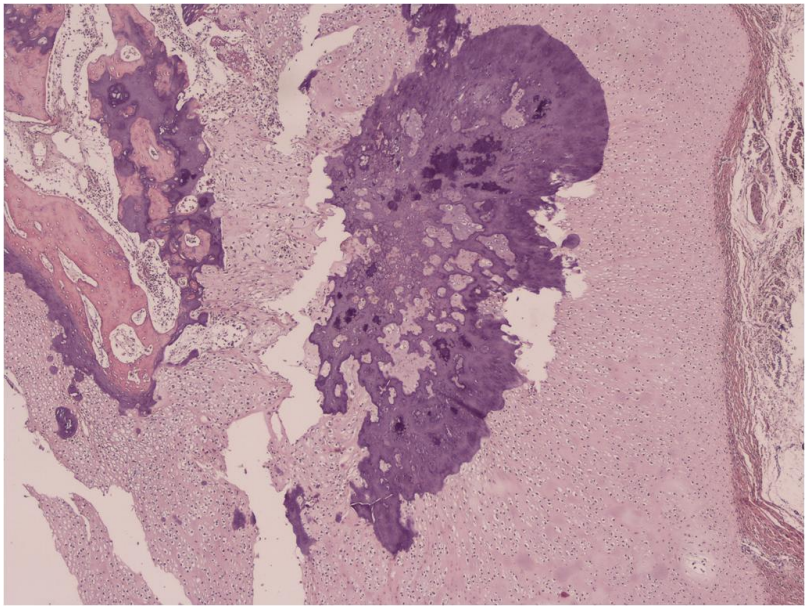


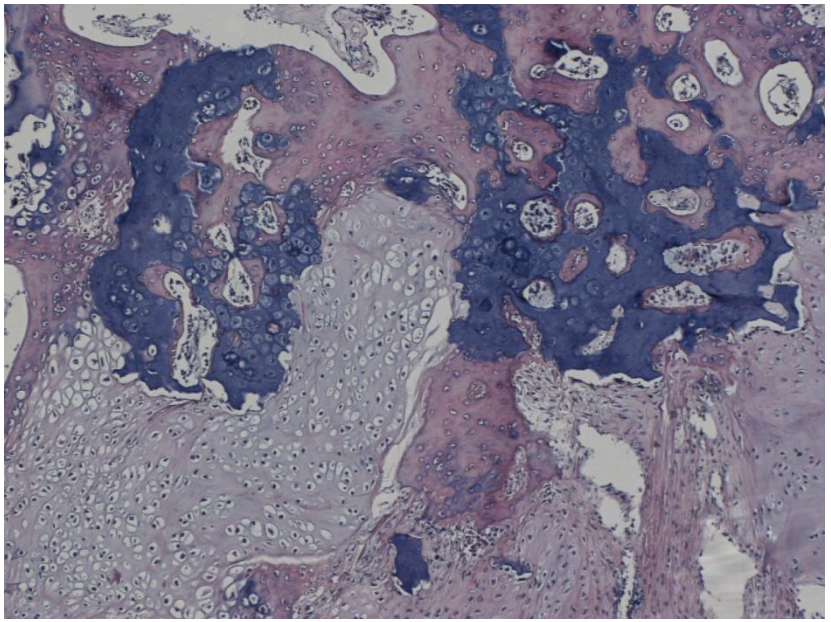


Stippling: abnormal calcification in the resting cartilage of the femoral head

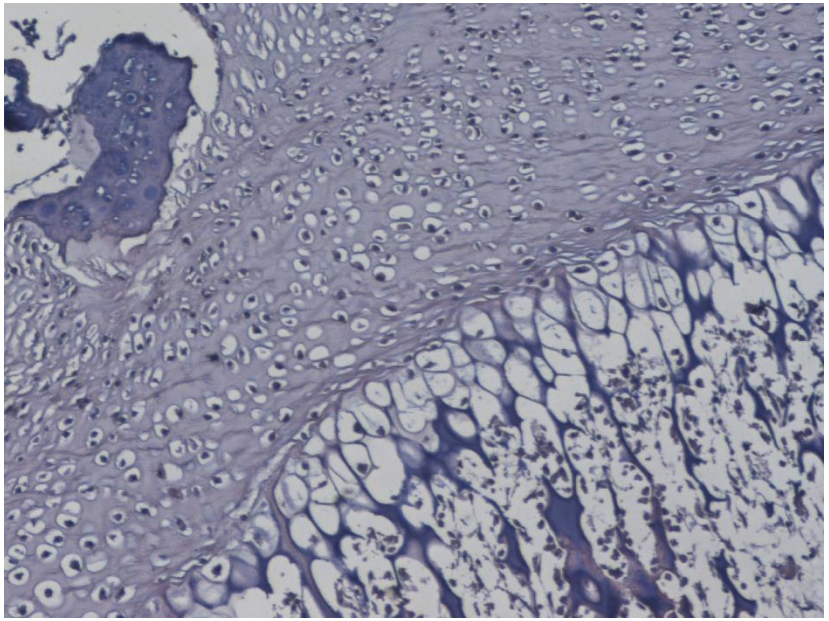


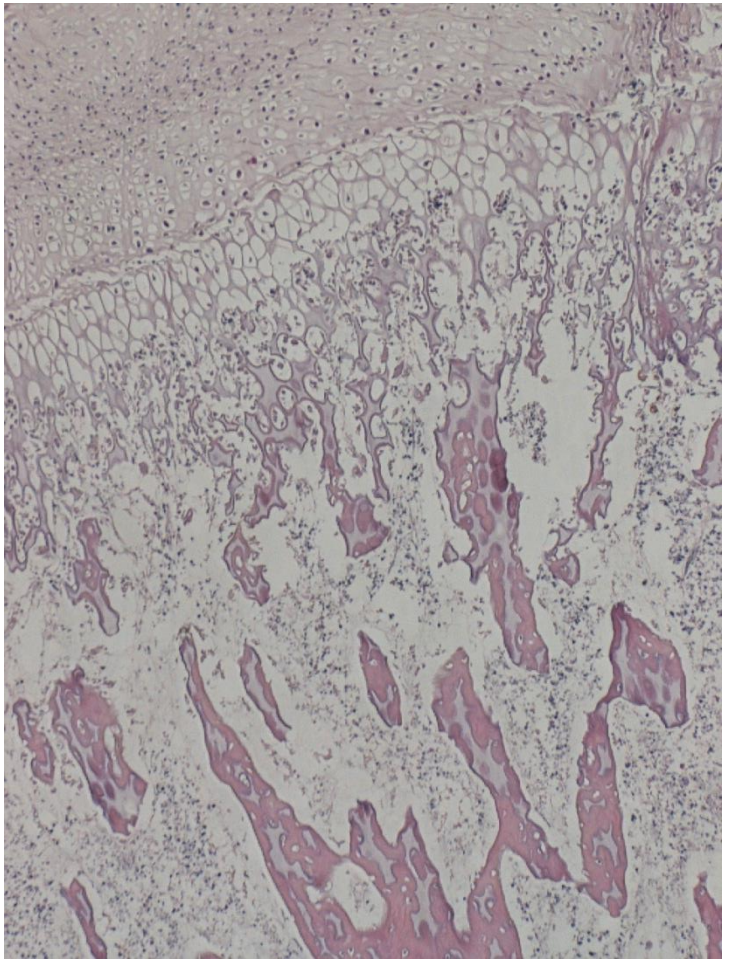






Abnormal ossification and stippling of the vertebrae





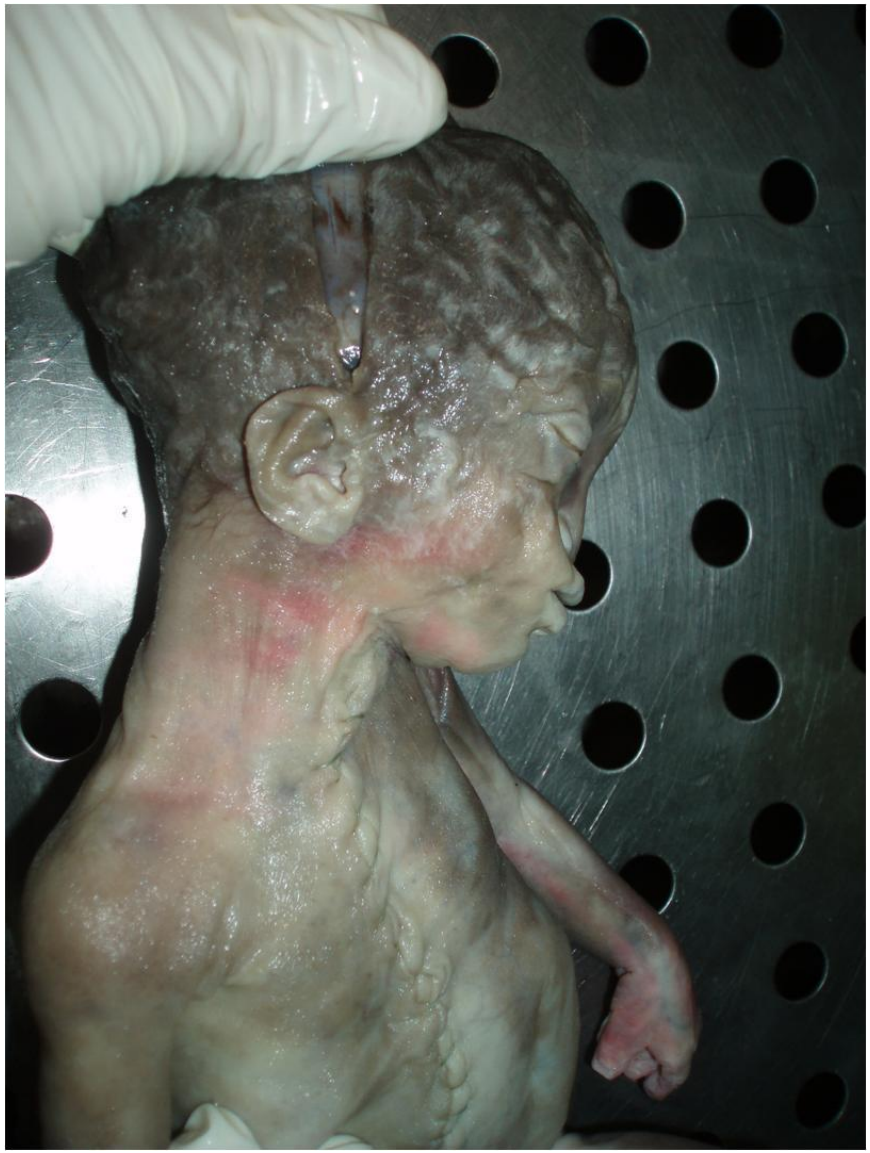
Femur: severely retarded physeal growth plate

Binder Phenotype in Chondrodysplasia Punctata

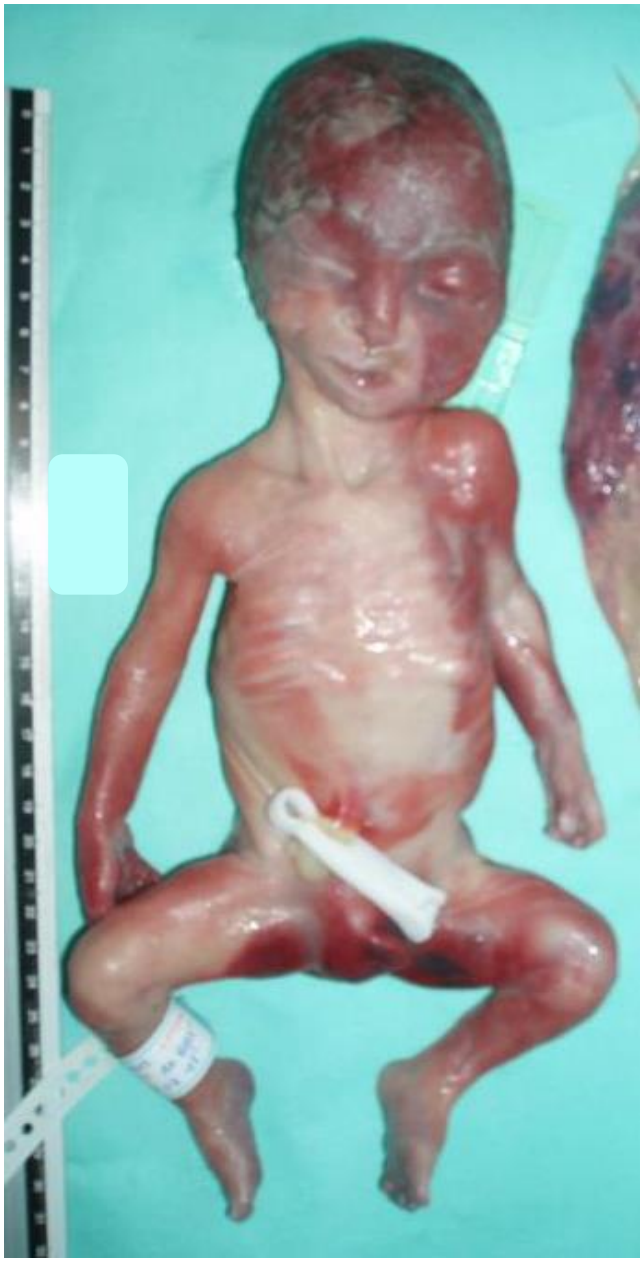
Maxillonasal dysplasia/dysostosis

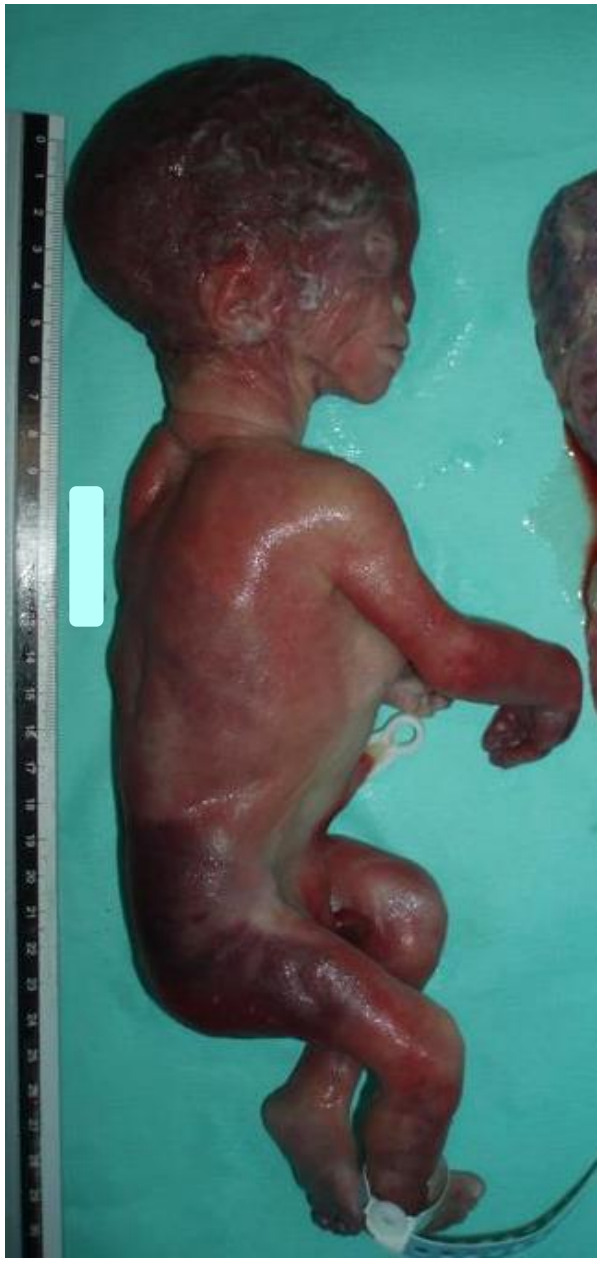
a flat profile without nasal eminence, contrasting with nasal bones of normal length

- midface hypoplasia
- absence of anterior nasal spine
- flat profile with convex upper lip
- flat or depressed nasal bridge
- obtuse or flat fronto-nasal angle
- short columella with normal philtrum
- acute naso-labial angle with peri-alar flatness

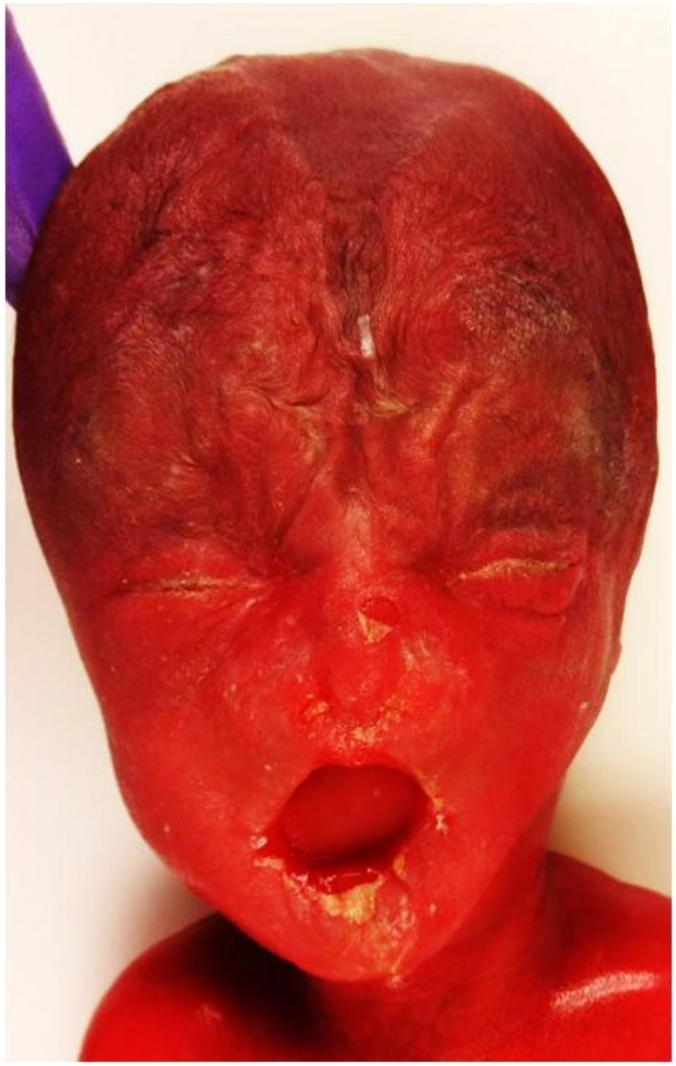


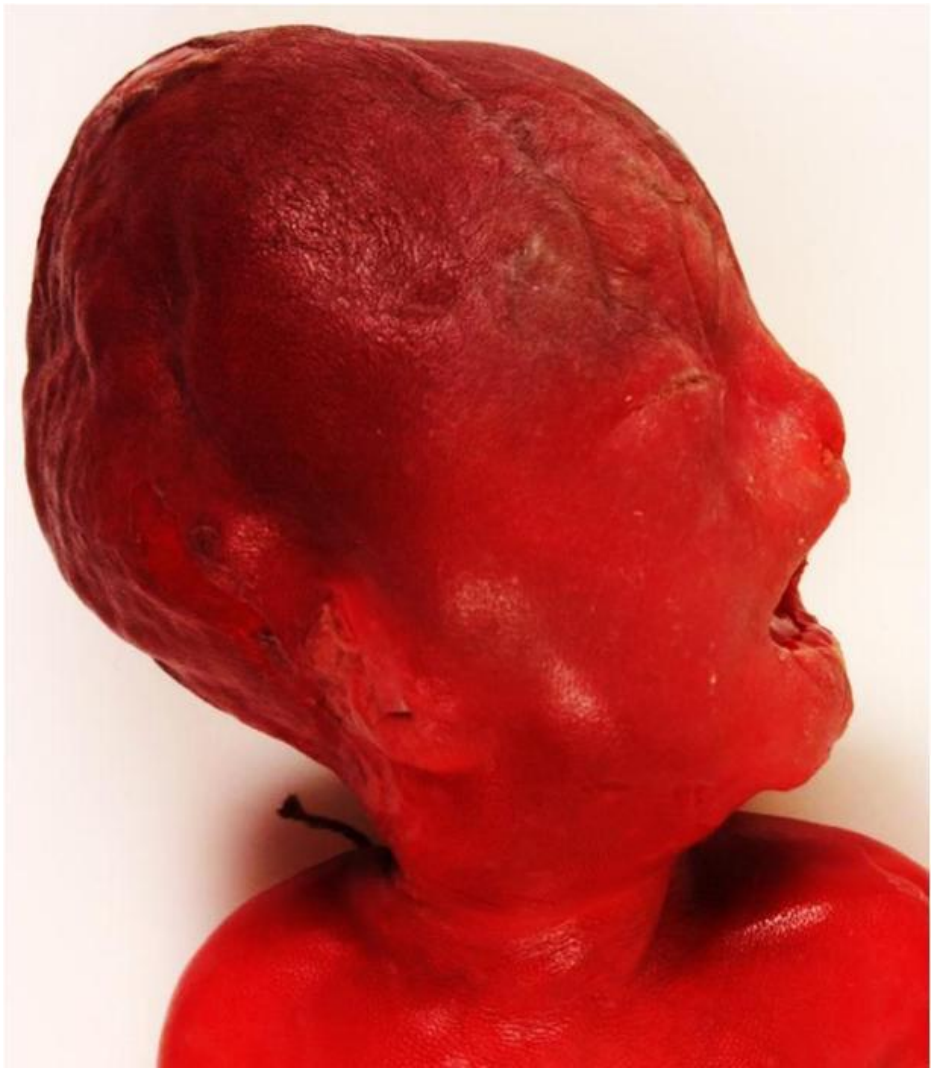
- Binder phenotype is associated with CDP of various types, more so with the brachytelephalangic type.



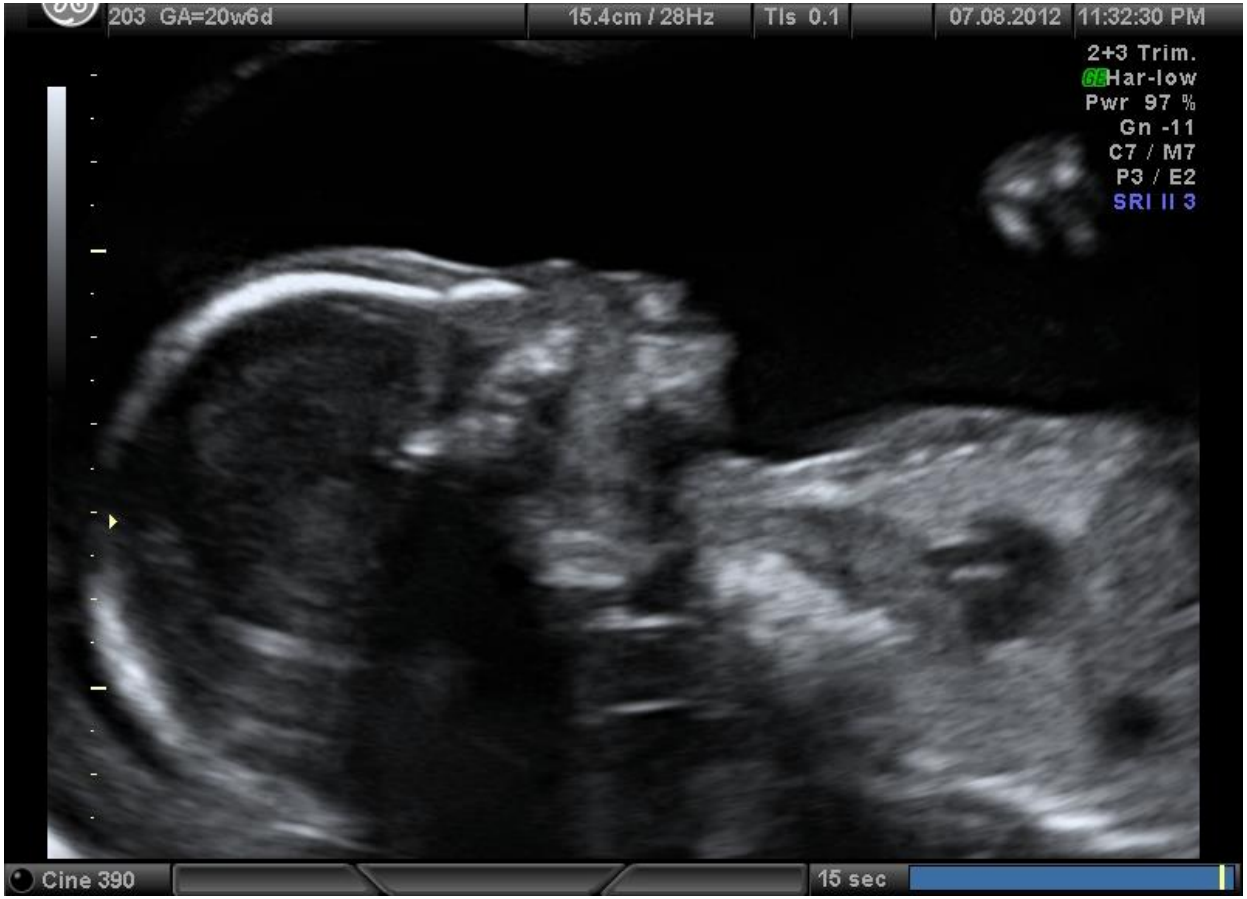


Binder phenotype

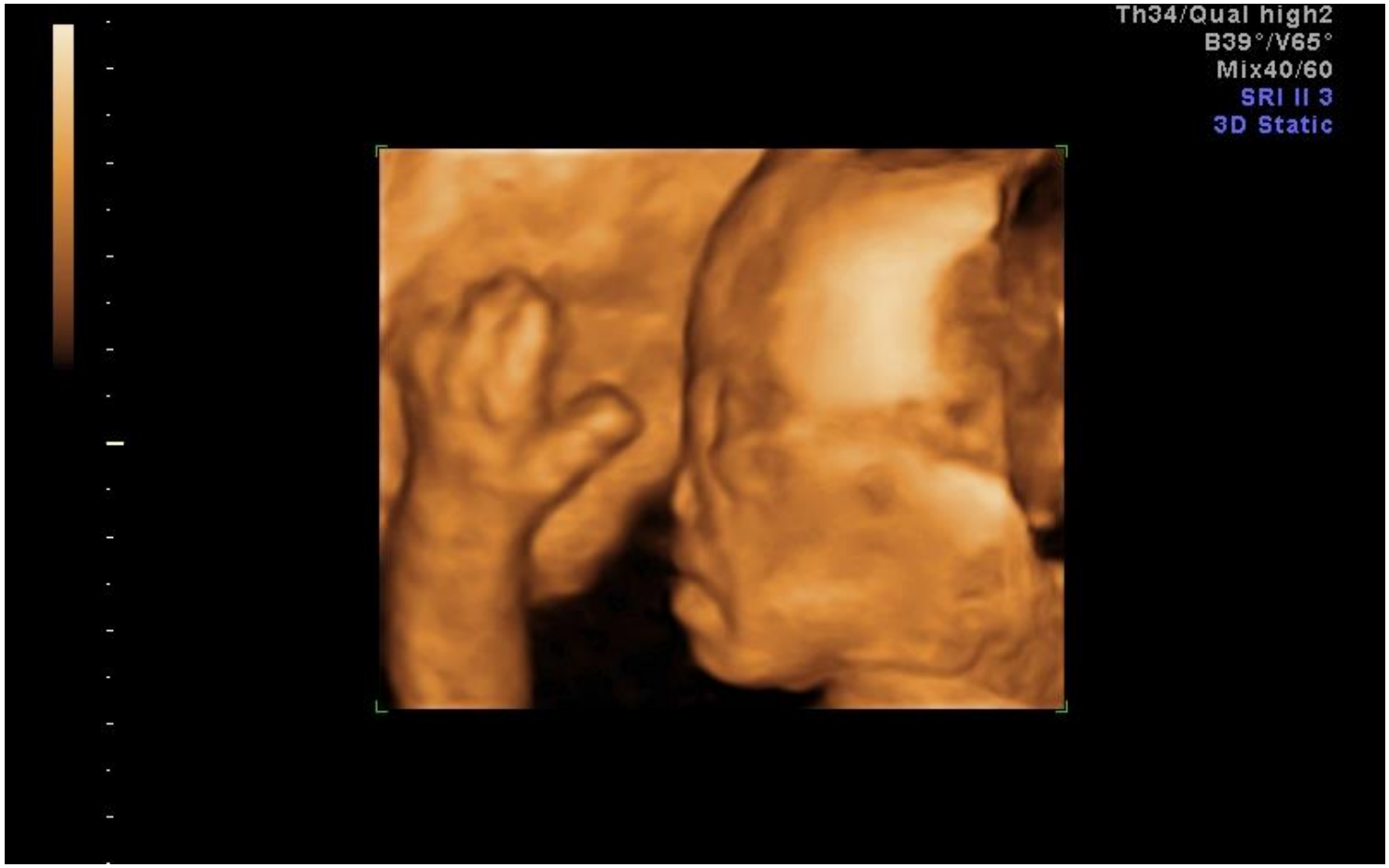




Binder phenotype



Binder phenotype on USS



Binder phenotype on 3-D USS

STIPPLED BONES

HEM / Greenberg Dysplasia

HEM: Hydrops **- E**ctopic calcification - **M**oth-eaten dysplasia

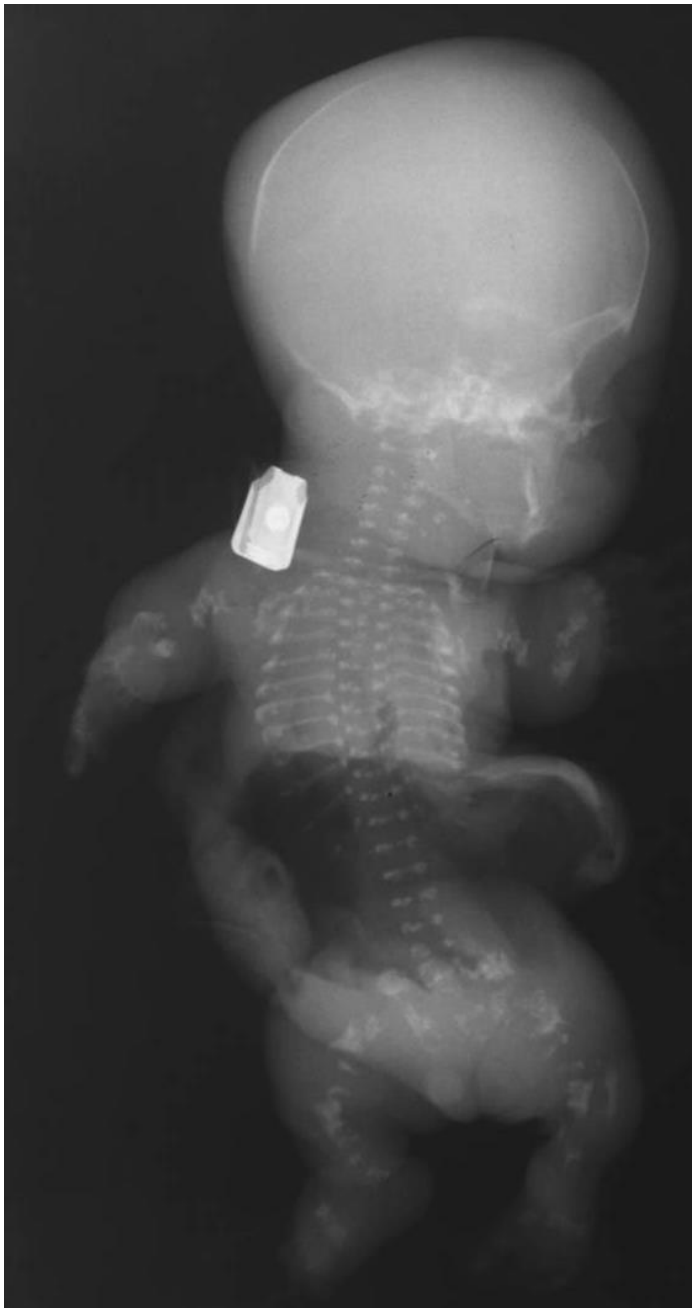
AR mutations in *LBR* gene encoding lamin B receptor

Lethal *in utero*

Gross:
Fetal hydrops
Severe micromelia
(can be confused with Achondrogenesis)

Patient fibroblasts show increased levels of cholesta-8,14-dien-3-beta-ol, suggesting
a defect of sterol metabolism. (Summary by Konstantinidou et al. *Prenatal Diag. 28: 309-312, 2008)*

Konstantinidou, A., Karadimas, C., Waterham, H. R., Superti-Furga, et al. ***Pathologic, radiographic and molecular findings in three fetuses diagnosed with HEM/Greenberg skeletal dysplasia.*** *Prenatal Diag. 28: 309-312, 2008.*



Greenberg Dysplasia

X-ray

Severe shortening of all long bones with a moth-eaten radiographic appearance

Platyspondyly

D/d from Achondrogenesis

Greenberg Dysplasia

Histology: Disorganization of chondroosseous calcification and ectopic ossification centers

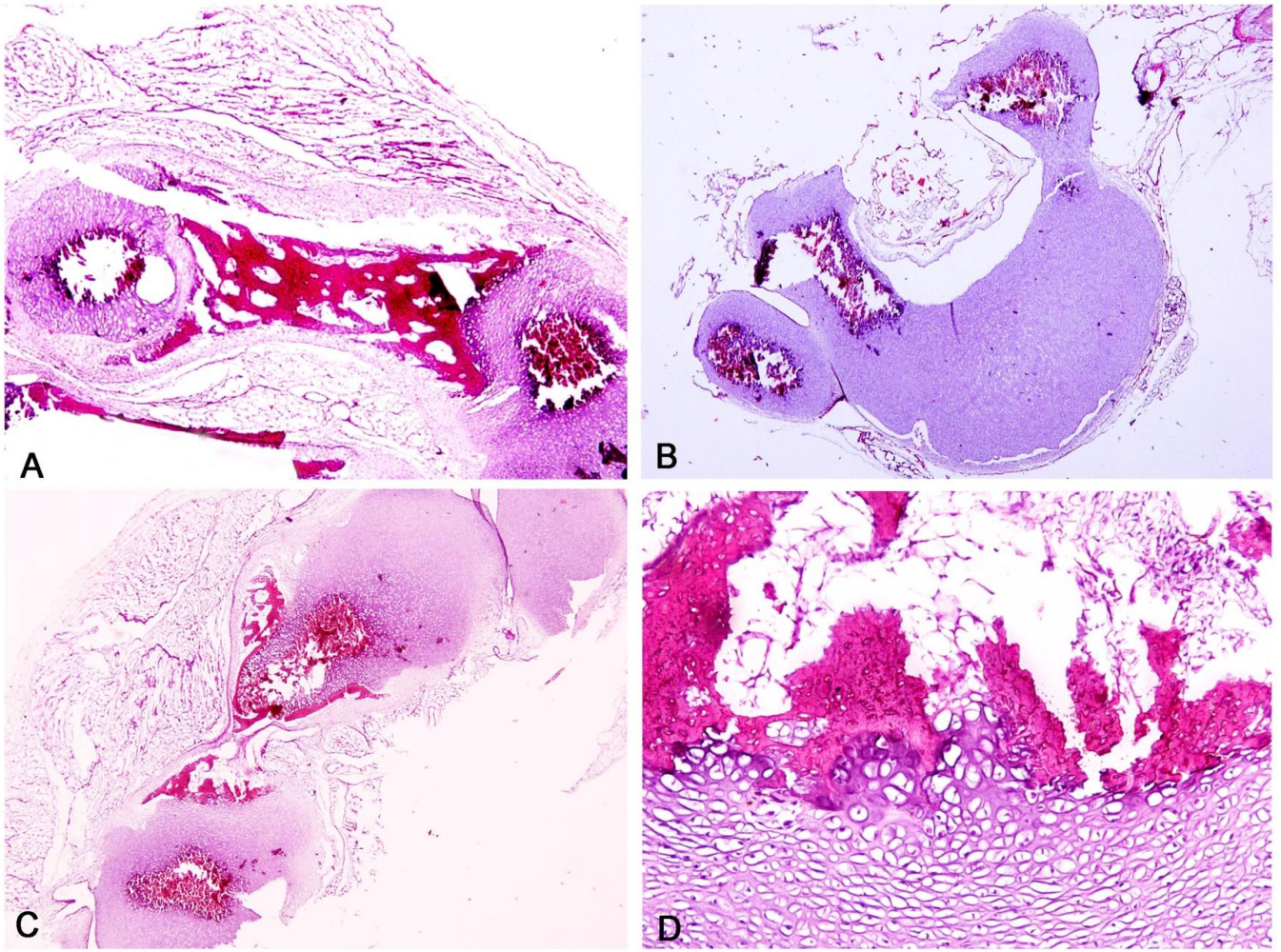


Image from:

Konstantinidou, A., Karadimas, C., Waterham, H. R., Superti-Furga, et al. ***Pathologic, radiographic and molecular findings in three fetuses diagnosed with HEM/Greenberg skeletal dysplasia.*** *Prenatal Diag. 28: 309-312, 2008.*

ABSENT BONES

Limb hypoplasia - reduction defects

- Terminal transverse LRD
- Cornelia de Lange syndrome
- Split hand – foot malformation group
- Roberts syndrome
- Tetra-amelia syndrome

Other :

- Filamin B disorders
- Grebe dysplasia
- Femoral hypoplasia group
- Radial aplasia disorders
- Ulnar, Fibular ,Tibial aplasia disorders

.....

The list is not exhaustive …

ABSENT BONES

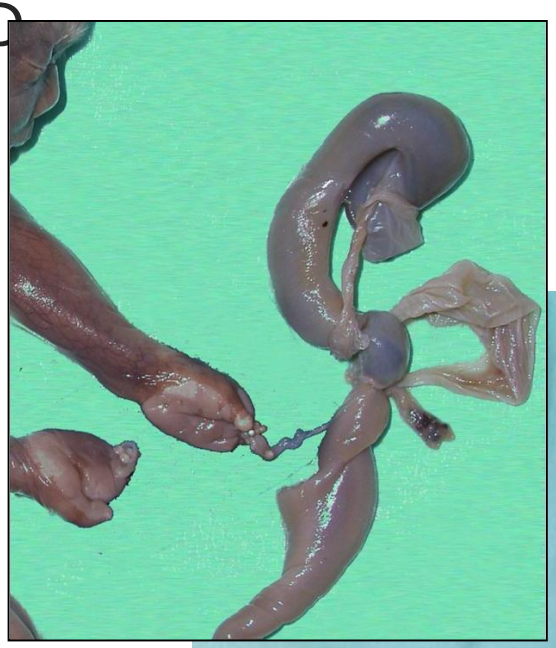
Limb Reduction defects (LRD)

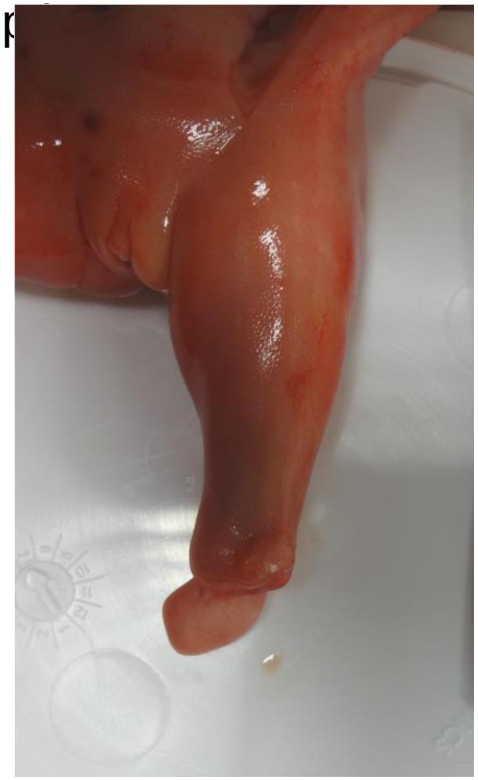
Terminal Transverse LRD

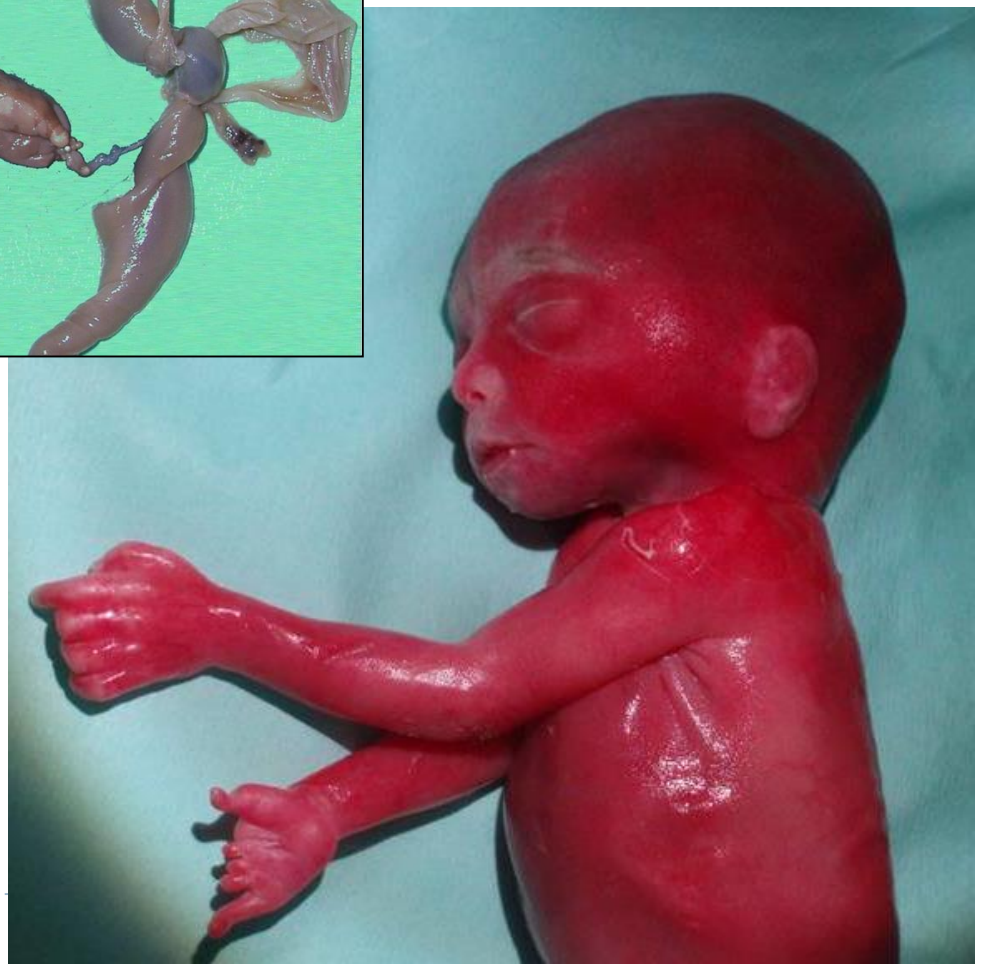
Usually sporadic

Secondary etiology
- Amniotic bands
- Vascular

disrup







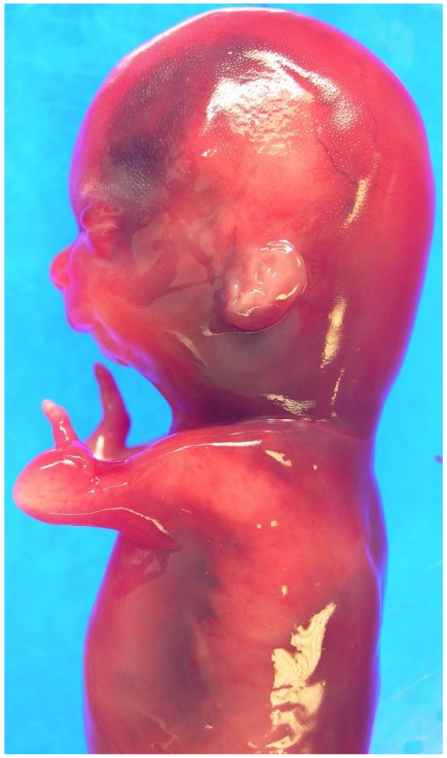
When there is a constricted stump ("nubbin"), the defect is considered

Limb Reduction defects (LRD)

de Lange syndrome AD

Cornelia de Lange syndrome
Brachmann - de Lange syndrome

"Cohesinopathy"
Mutations in *NIPBL* gene, encoding protein delangin, involved in the chromosome cohesion apparatus
more often than core cohesion subunits SMC1A and SMC3.

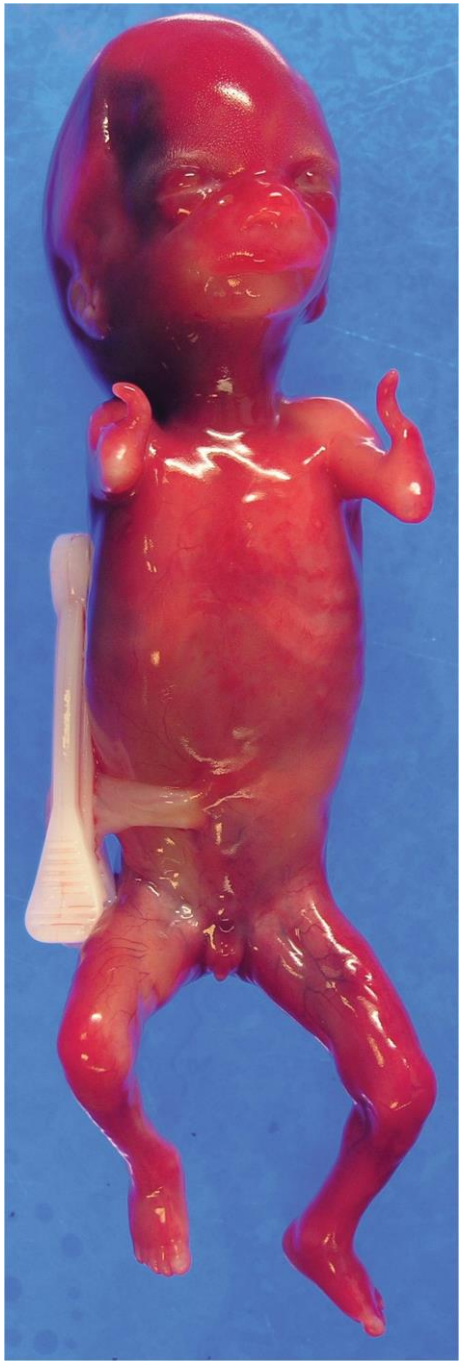


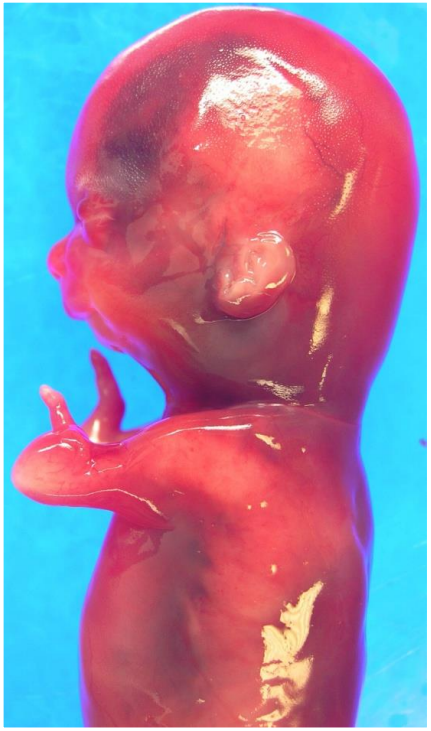
intellectual disability

Limb defect:

"*Chicken wing*" short arms with a single digit (monodactyly) representing the hand bilaterally
Pterygium formation on the inner part of the elbows

Typical facial features:
long philtrum, retrognathia, hypertelorism, synophrys, eylashes may be visible.





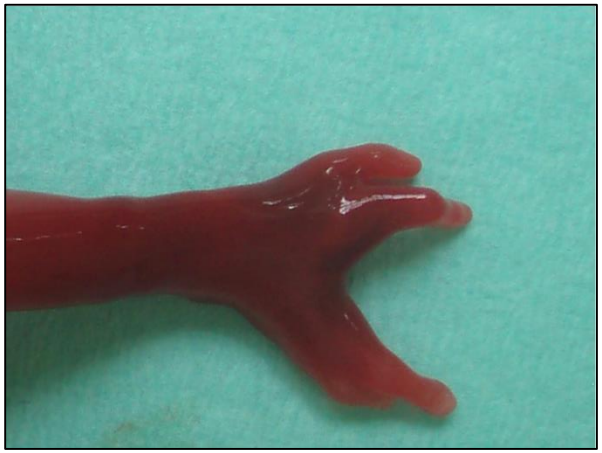
Cornelia de Lange syndrome

Image from:
Skeletal Dysplasias. In: The Pediatric and Perinatal Autopsy Manual edited by Marta C. Cohen, Irene Scheimberg. Cambridge University Press 2014

Split hand – foot malformation group (SHF)

Split hand – foot malformation isolated (SHFM 1-5)

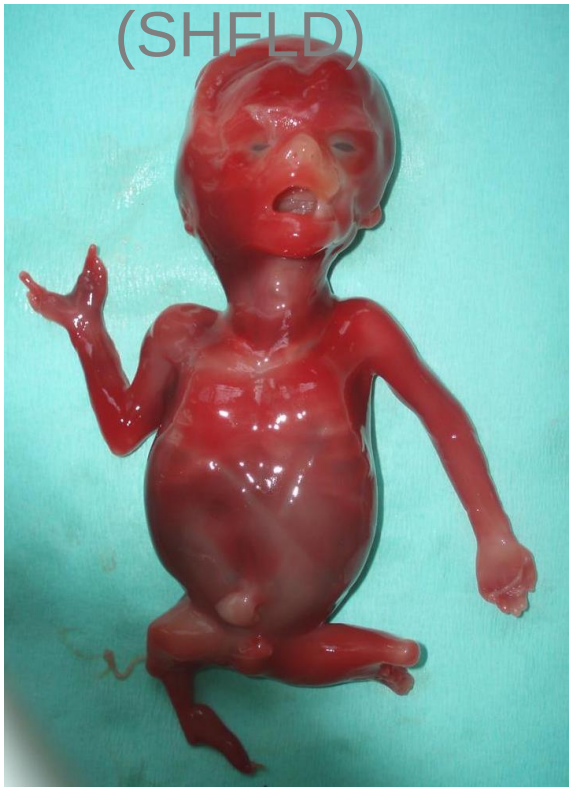
Split hand – foot malformation with long bone deficiency (SHFLD 1-3) AD

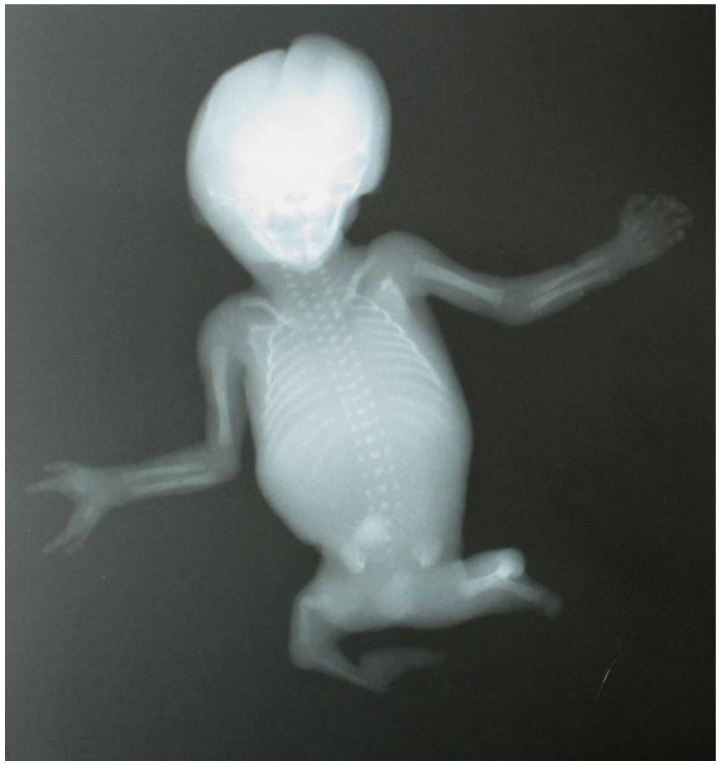


cleft hand

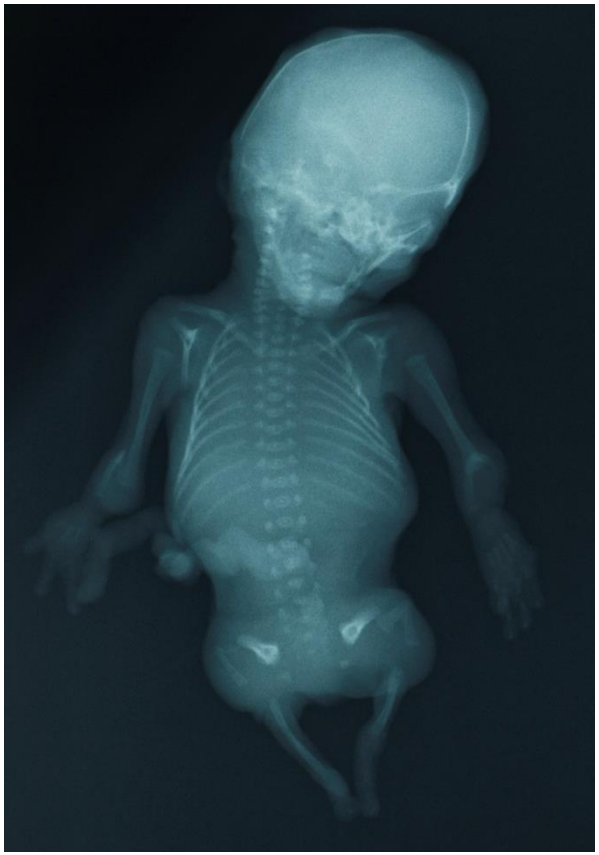
"lobster claw" shaped

Split hand – foot malformation with long bone deficiency (SHFLD)





Split right hand, bifid left femur, transverse left limb defect, and hypoplasia of other long bones



Split right hand, hypoplastic angulated femurs, bilateral tibial and radial hypoplasia, fibular and ulnar aplasia, and hypoplasia of long bones in feet

The full-blown syndrome: bilateral aplasia of the tibias and split-hand/split-foot deformity

Various combinations may occur.

Long bone deficiency: usually **tibial** hypoplasia / aplasia

- Distal hypoplasia or bifurcation of the femurs, hypo- or aplasia of the ulnas, and hypoplastic toes may be included; fibular hypoplasia/aplasia has also been reported.

Phocomelias

(Greek *phoka* = seal, *melos* = limb; *phocomelia* = seal limb)

Roberts syndrome (RS) AR

Roberts Phocomelia

Autosomal Recessive "Cohesinopathy"

mutations in *ESCO2* gene, encoding a protein required for the establishment of sister chromatid cohesion during S phase

In 50% of cases the chromosomes present the typical RS effect with centromere puffing and sister chromatid separation in areas of constitutive heterochromatin.

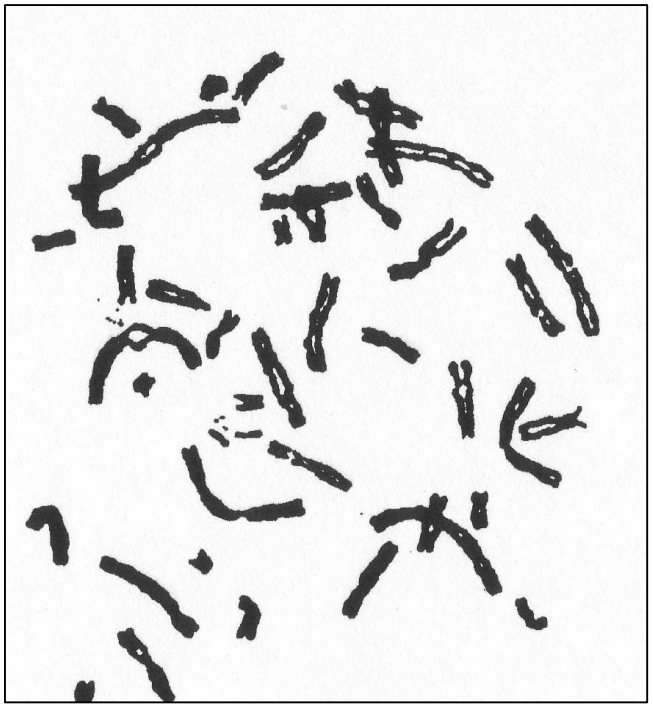
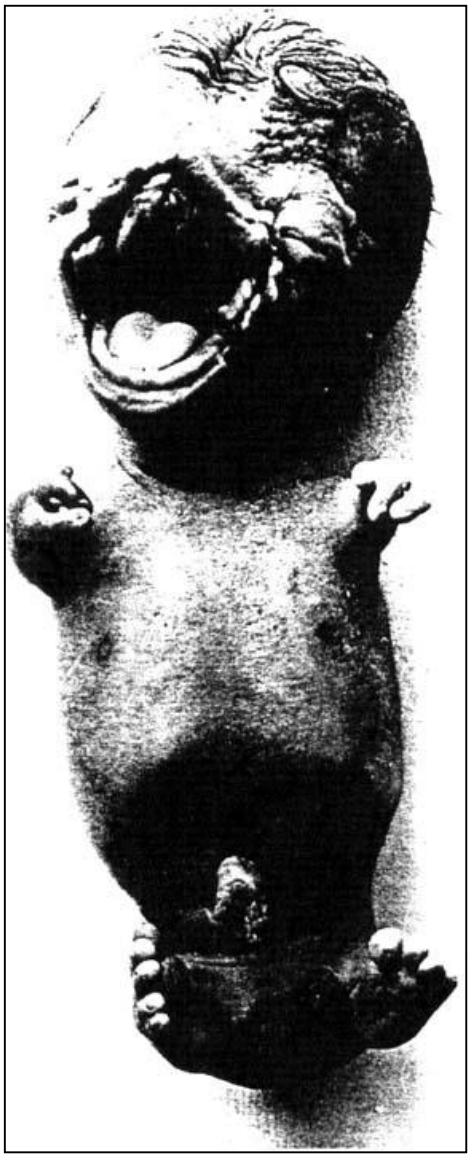


Image from:
Pavlopoulos PM, Konstantinidou AE, et al.
Clin Genet 1998;54:512-16

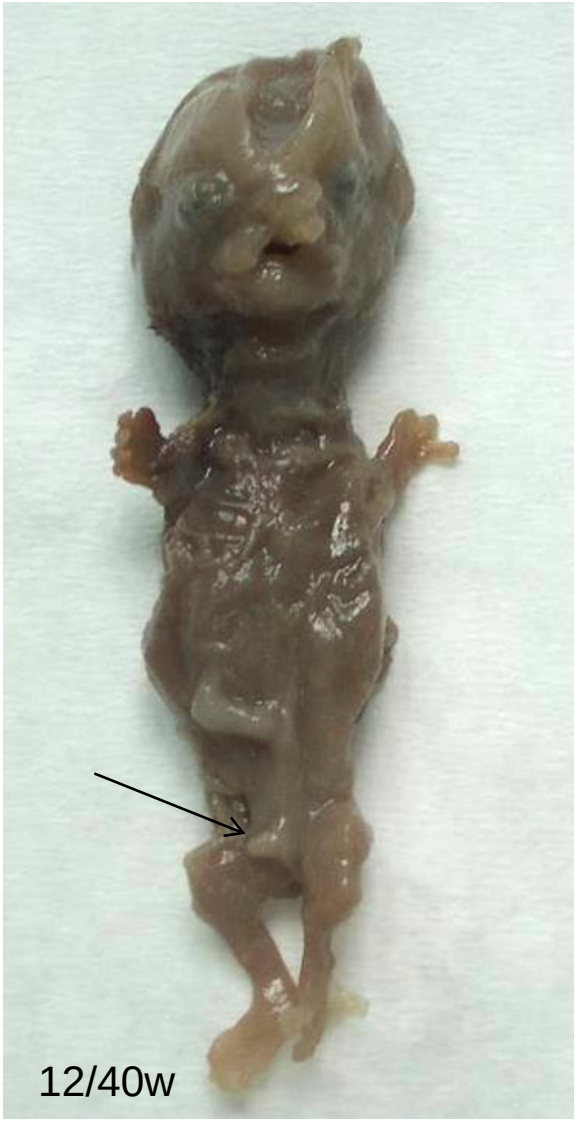
Roberts syndrome (RS) AR



Alternatively the syndrome is called
"Long bone deficiencies associated with cleft lip-palate"
or
"Pseudothalidomide syndrome".

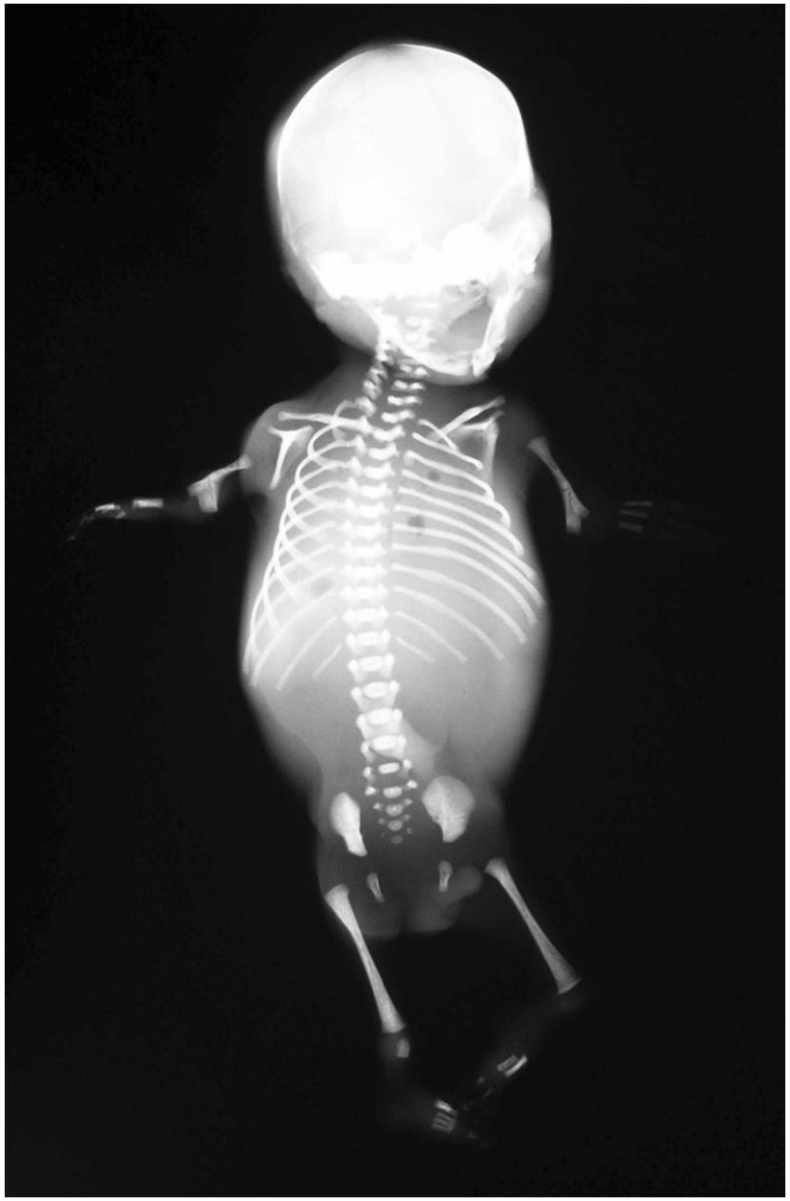
- Facial clefting
- Symmetrical limb defects resulting in tetraphocomelia in most cases

- hypertelorism,
- facial hemangioma
- clitoral or penile enlargement



A severely affected fetus with RS exhibiting tetraphocomelia and meningocele herniating through a large craniofacial bony defect.

Image from:
Pavlopoulos PM, Konstantinidou AE, et al. Clin Genet 1998;54:512-16



Milder form of RS

Flaring of the distal humerus bilaterally

Absent thumbs

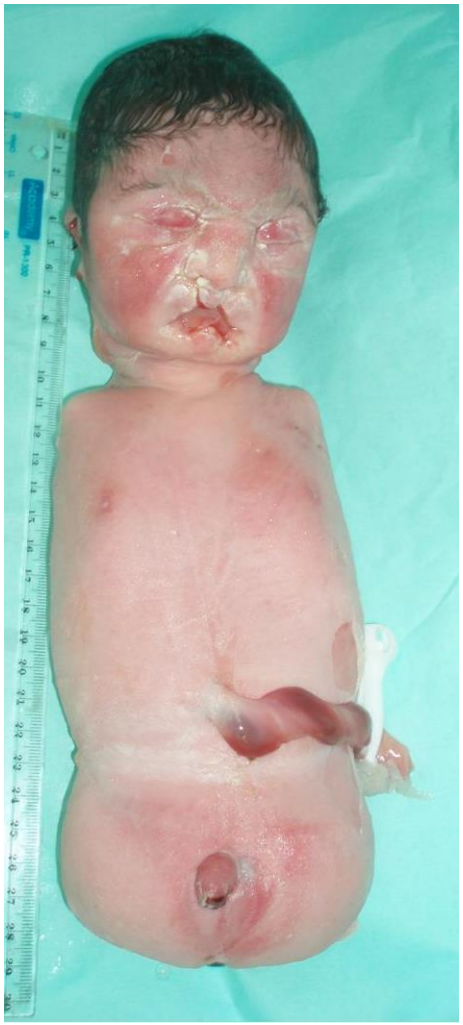
Poorly developed or absent mesomelic bones bilaterally

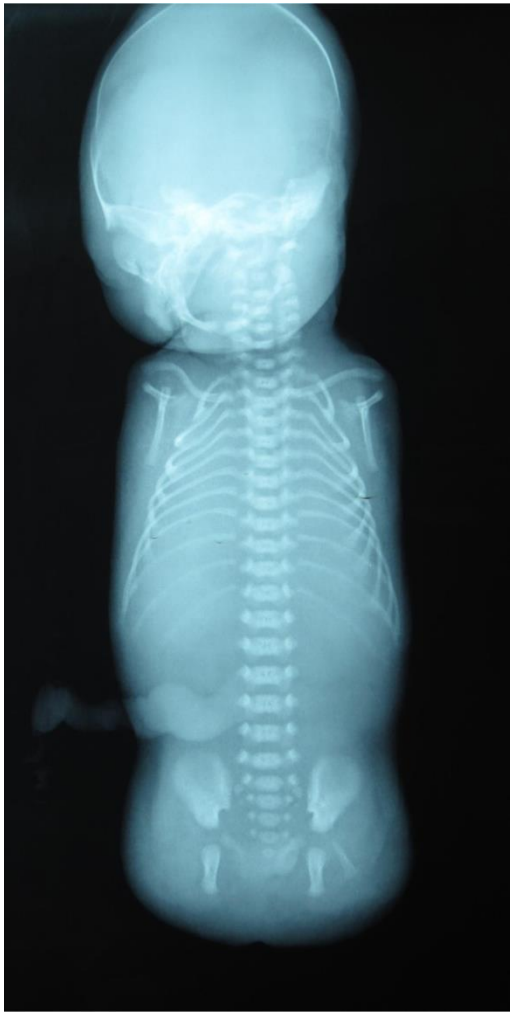
Image from:
Skeletal Dysplasias. In: The Pediatric and Perinatal Autopsy Manual edited by Marta C. Cohen, Irene Scheimberg. Cambridge University Press 2014

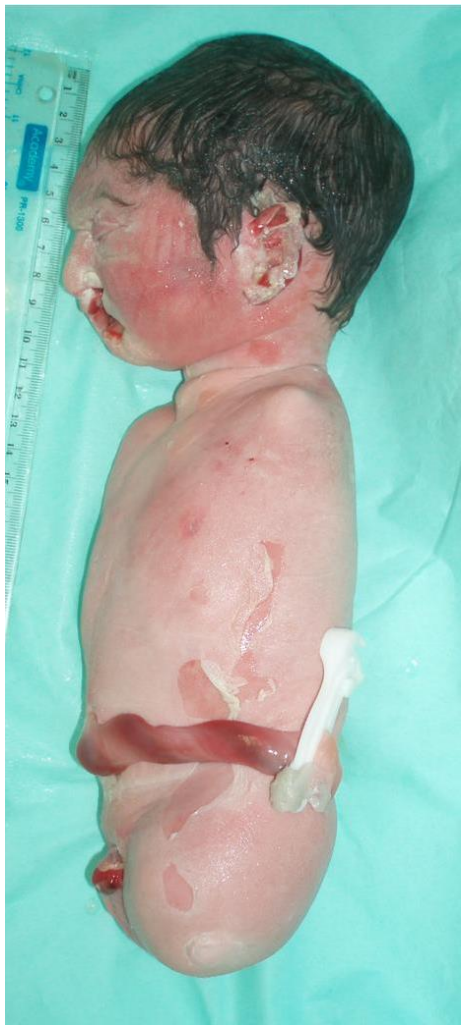
Tetra-amelia syndrome AR

WNT3 gene mutations

Absence of all 4 limbs *(Greek: tetra = four)*







- Craniofacial, urogenital, cardiopulmonary, CNS, and skeletal malformations.
  The lungs are severely hypoplastic or aplastic.

ABSENT BONES

Longitudinal bone reduction defects

Atelosteogenesis (AO) type 1 and 3
Spondylo-humero-femoral hypoplasia

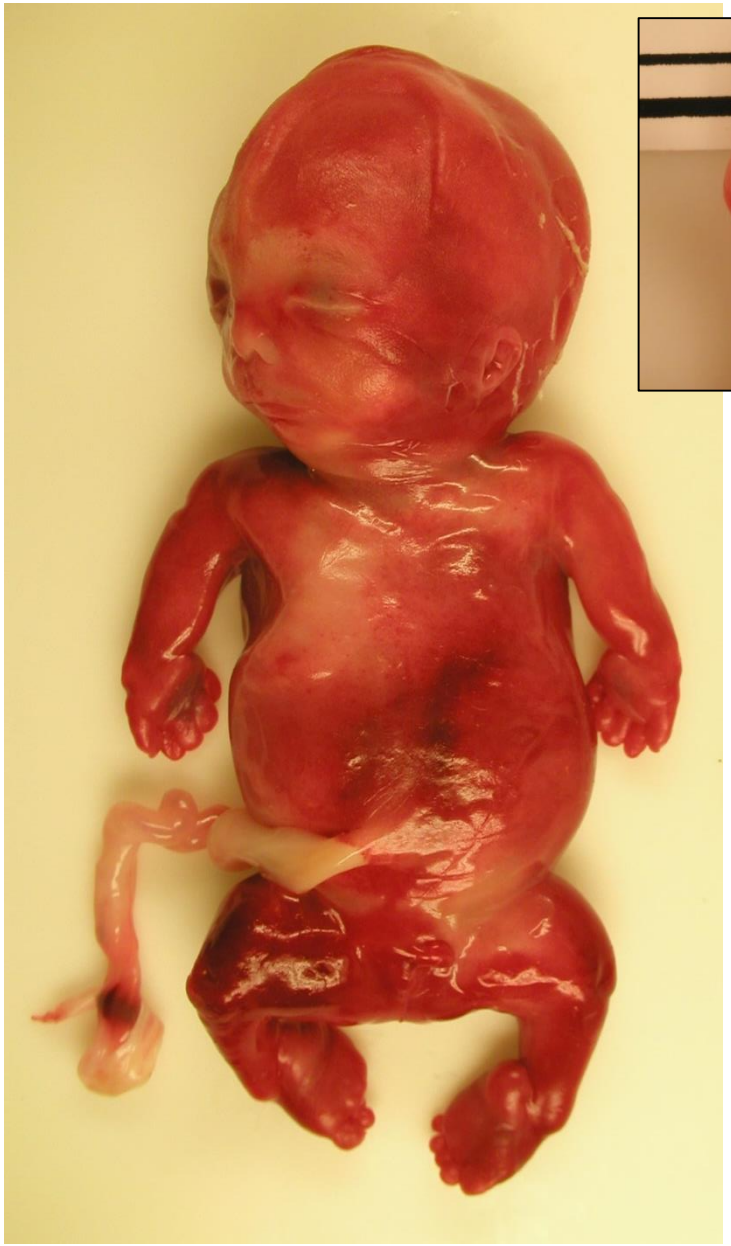
Boomerang Dysplasia
very rare

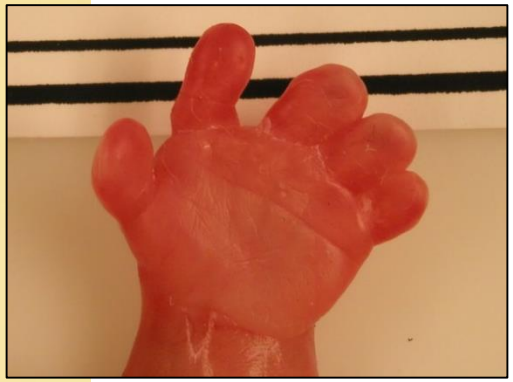
Allelic disorders
Continuous pathological spectrum

Filaminopathies

Mutations in *FLMNB* gene
Filamin B cytoskeletal protein

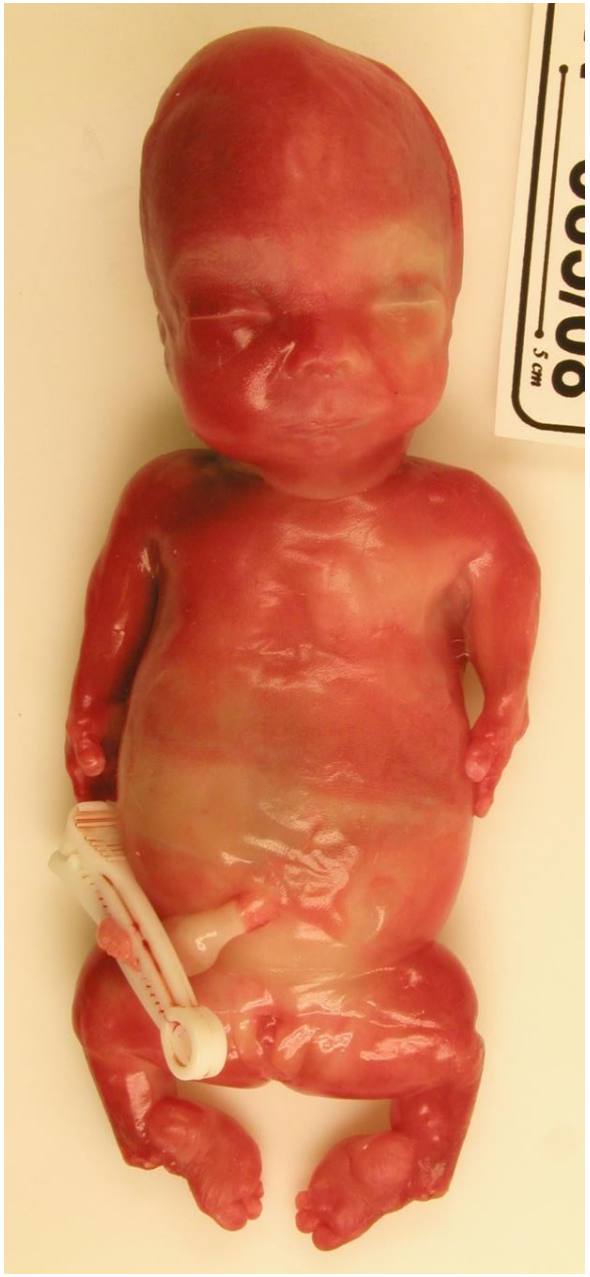
Severity
Boomerang >AO1> AO3> Larsen syndrome



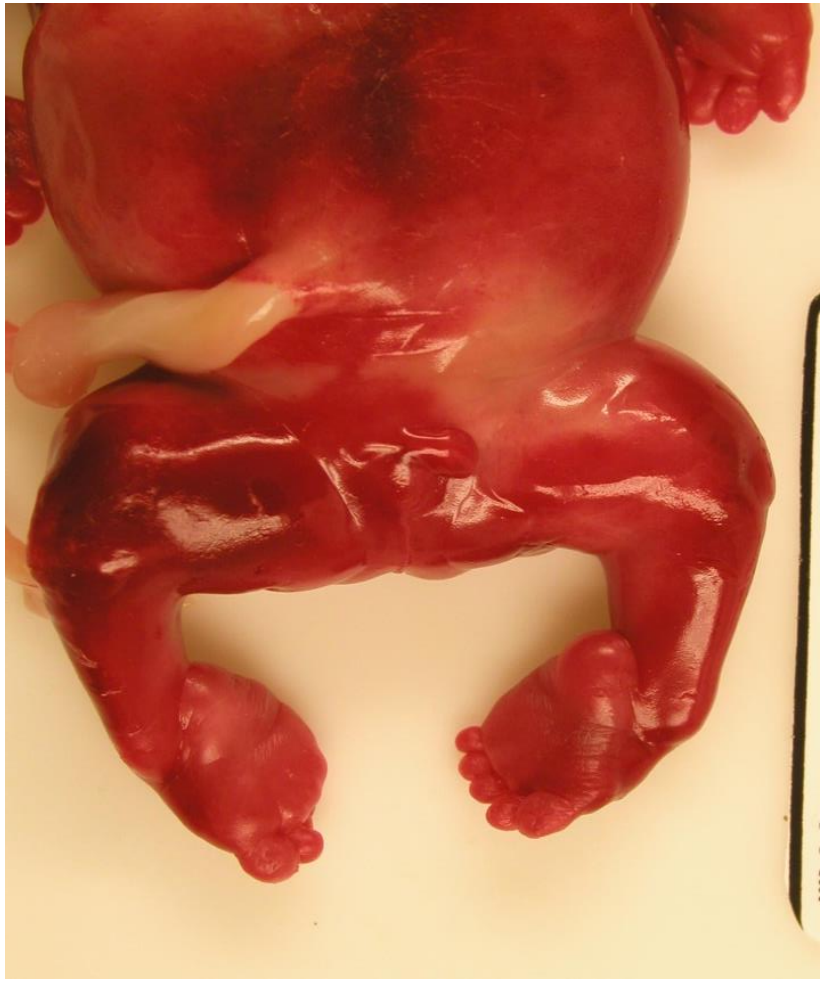


AO1:
brachydactyly

Severe micromelia
Bowed limbs
Thoracic hypoplasia
Severe talipes (frog-like position)
Micrognathia +/ – Cleft palate
(Hydrops – polyhydramnios)



AO1

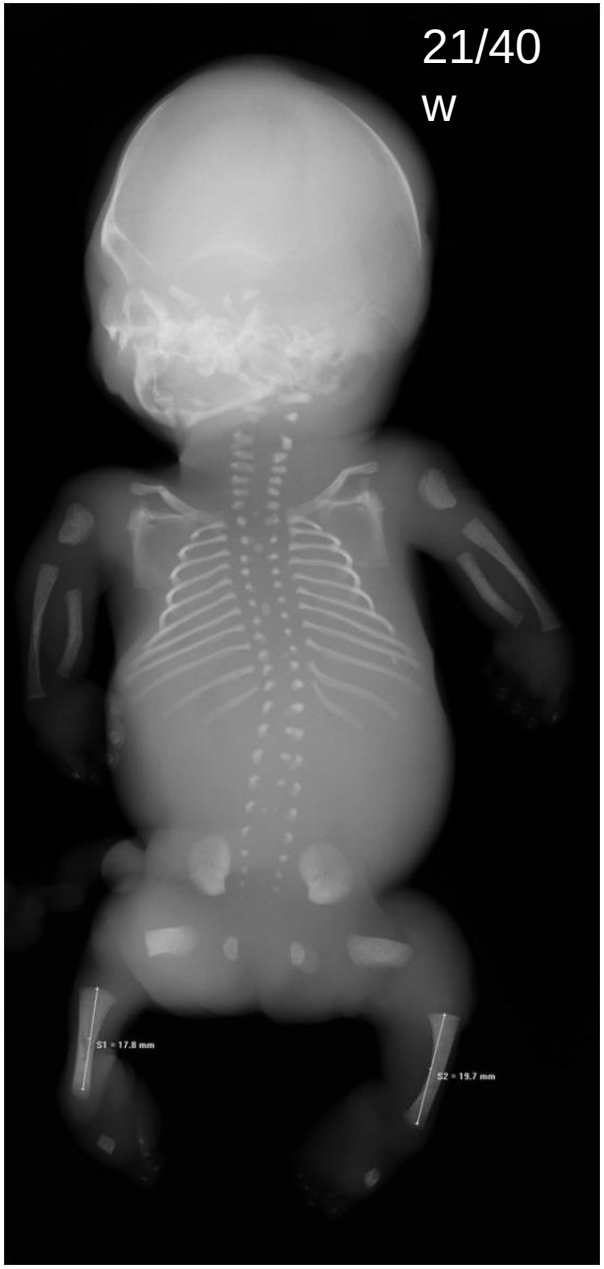


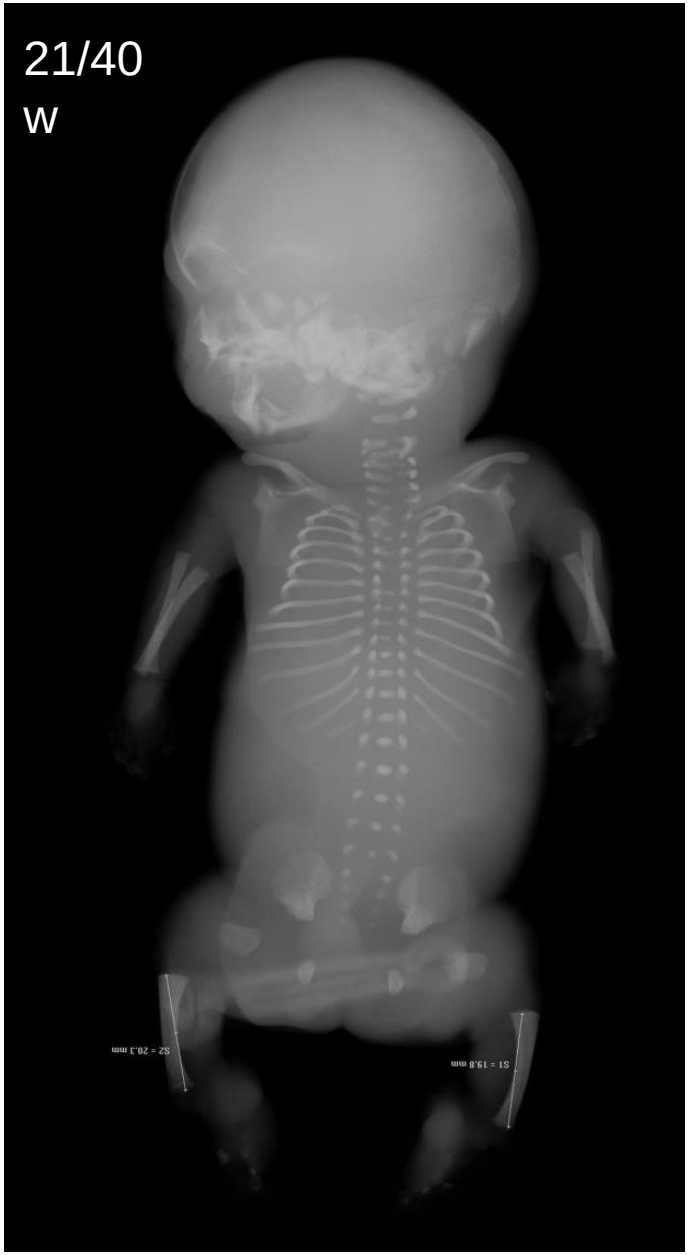
AO/Boomerang

X-ray

- Abnormal spinal ossification
- Hypoplastic/absent humeri
- Hypoplastic/absent femurs
- Absent fibulae
- Absent bones in hands and feet

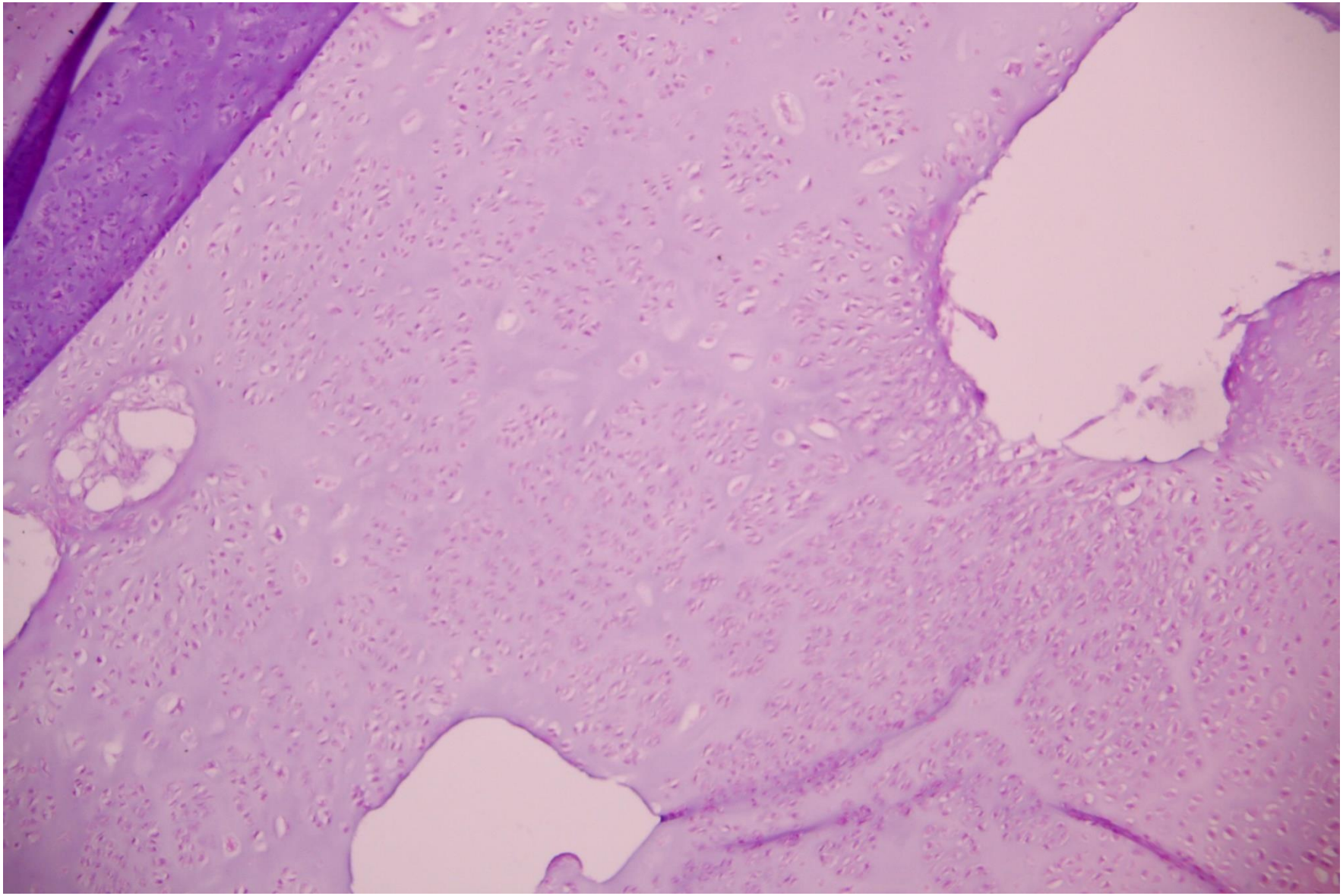
Note:
Distal tapering
(also seen in AO2)
Bizarre shapes, e.g. block shaped



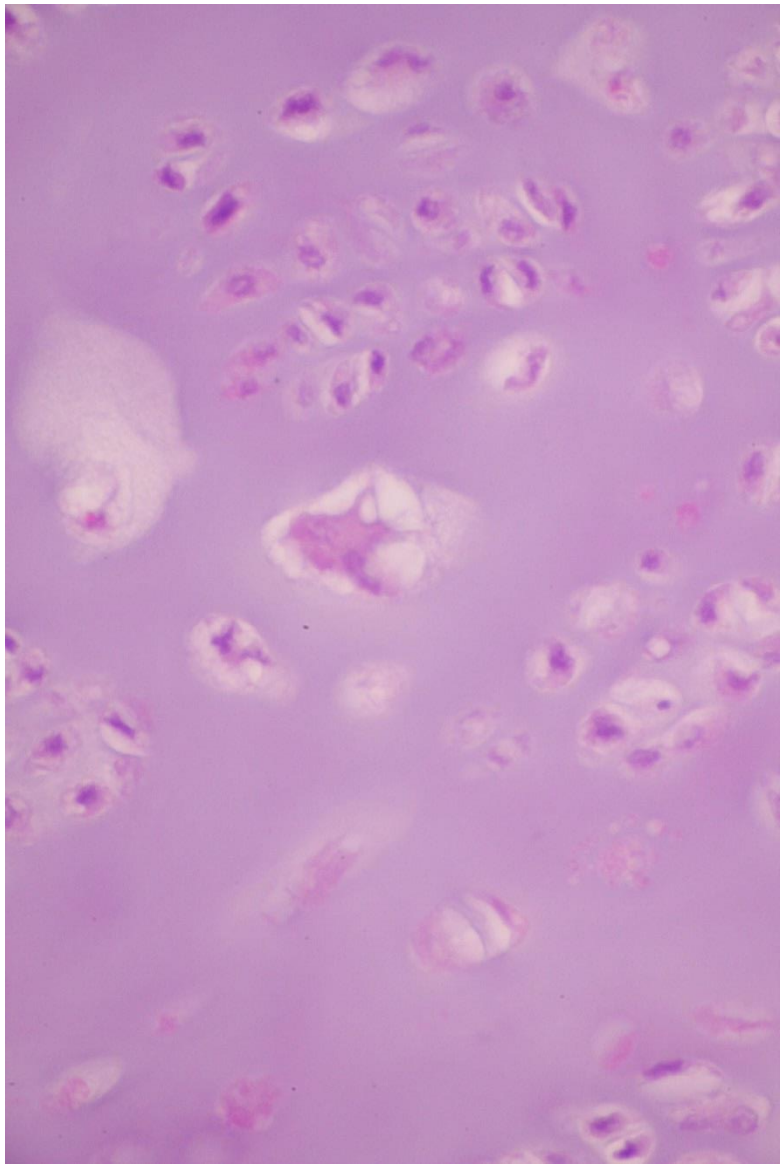


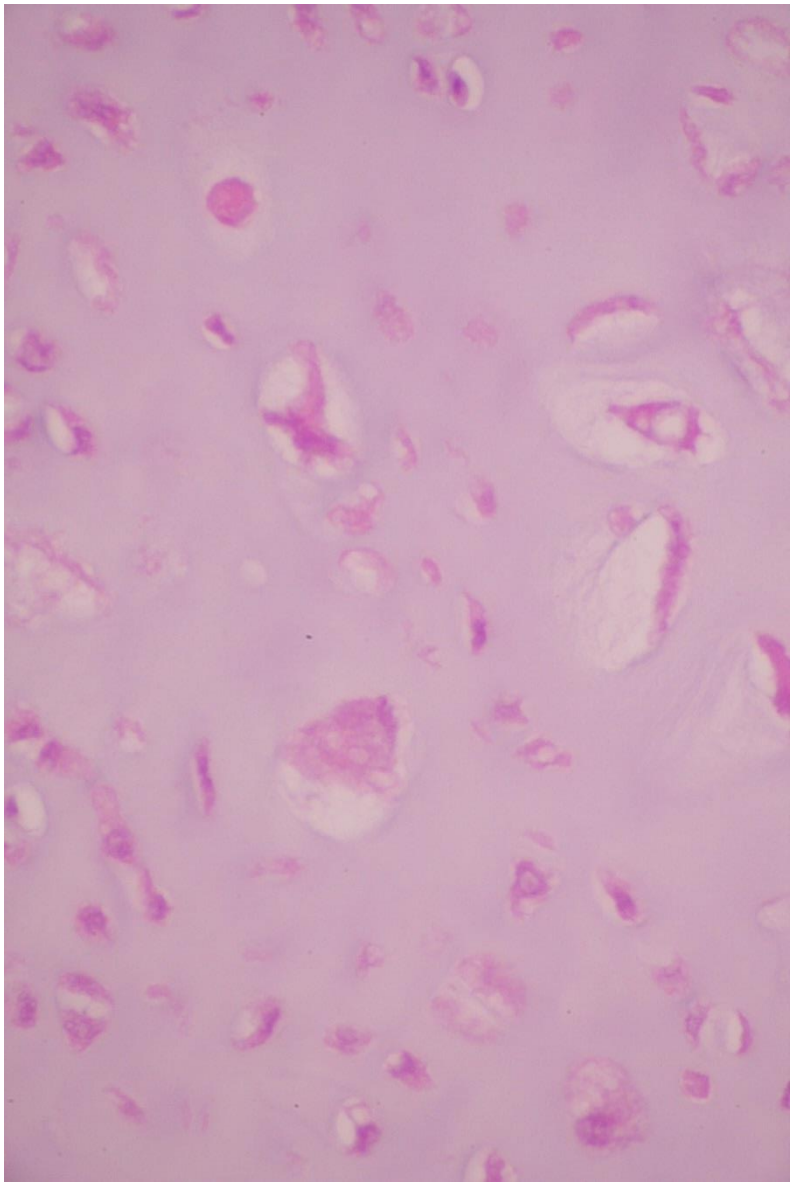
- *Absent bones*: humerus, femur, carpal, metacarpal, metatarsal, proximal and middle phalanges

Histology

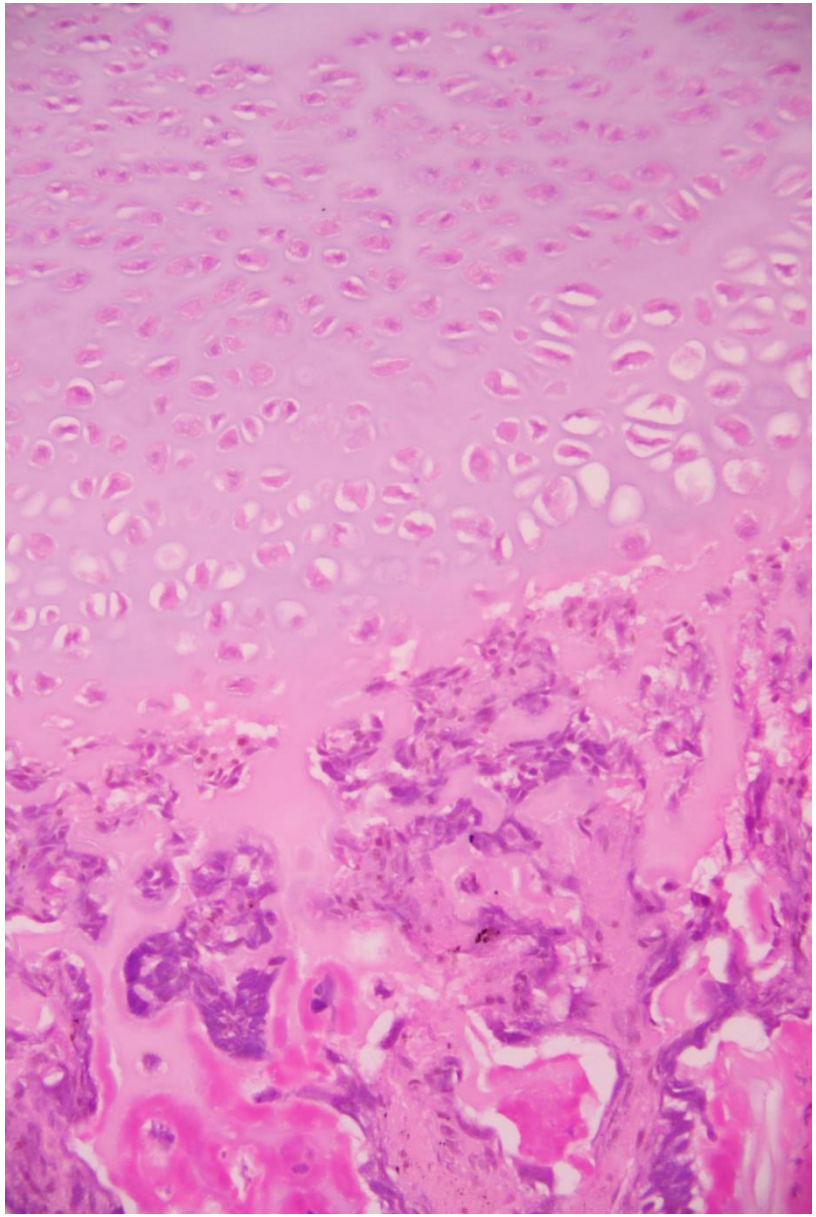


Hypocellular areas interspersed with normal cellularity





AO1 and Boomerang: “Giant” multinucleated chondrocytes



Severely retarded, focally disorganised physeal growth plate

ABSENT BONES

Longitudinal bone reduction defects

Grebe dysplasia AR

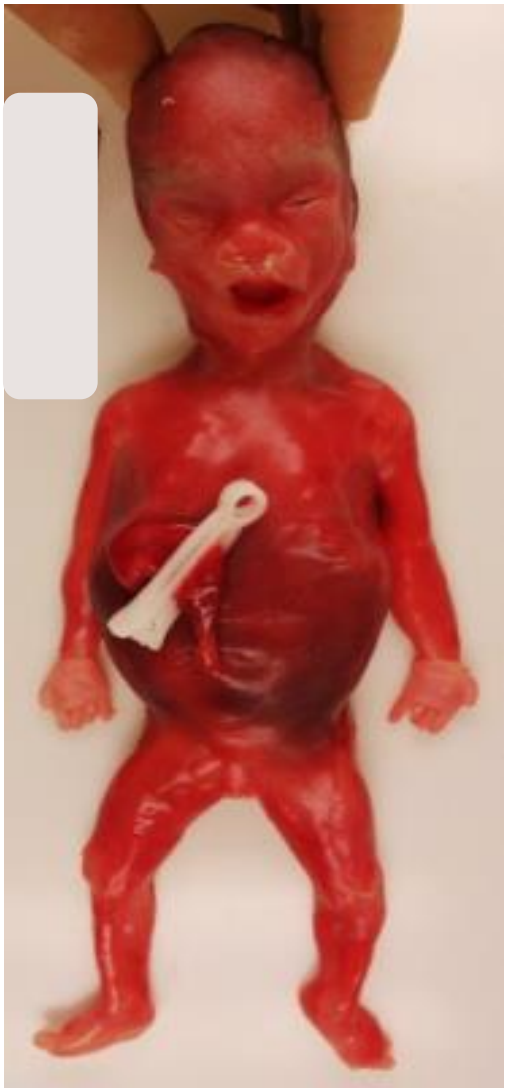
(du Pan Brachydactyly – Fibular aplasia)

GDMP1 (GDF5) mutations

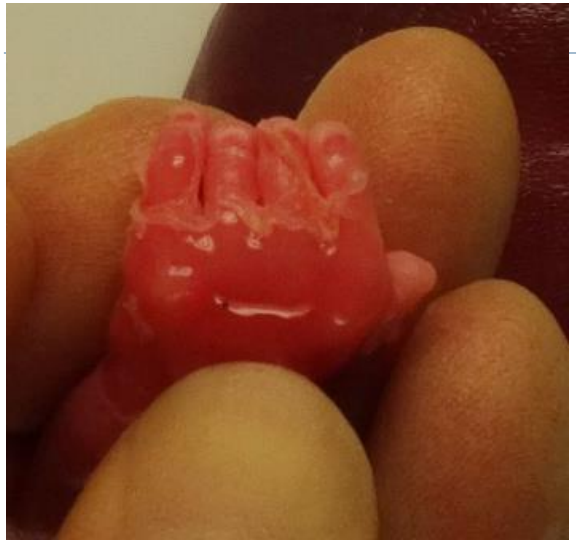
TOP at 22/40 weeks

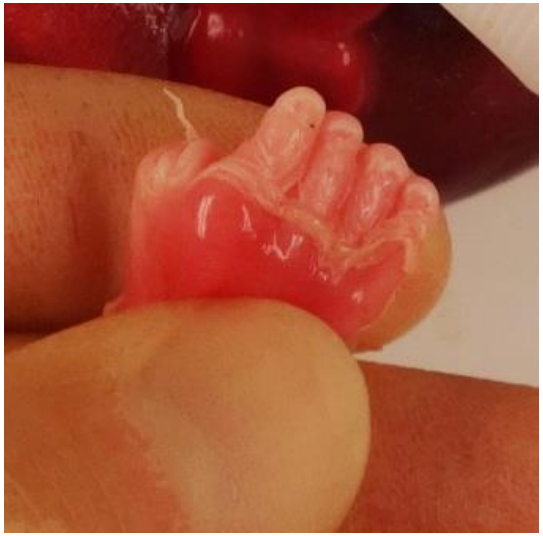
On USS:

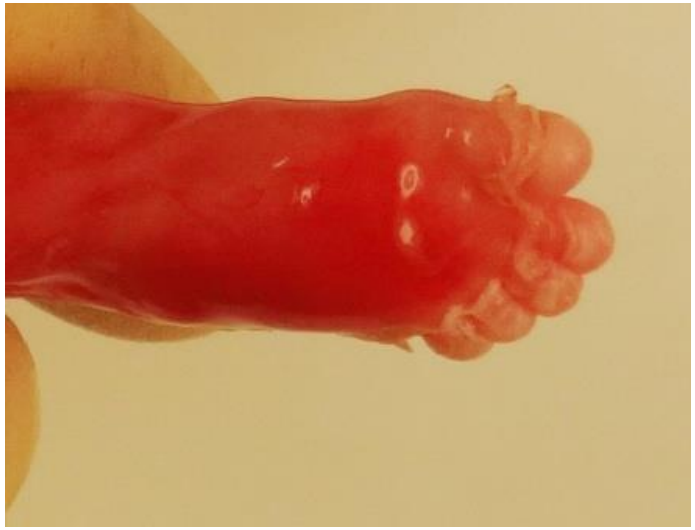
Bilateral talipes. Both fibulas missing.
Short long bones (under 5th c.)



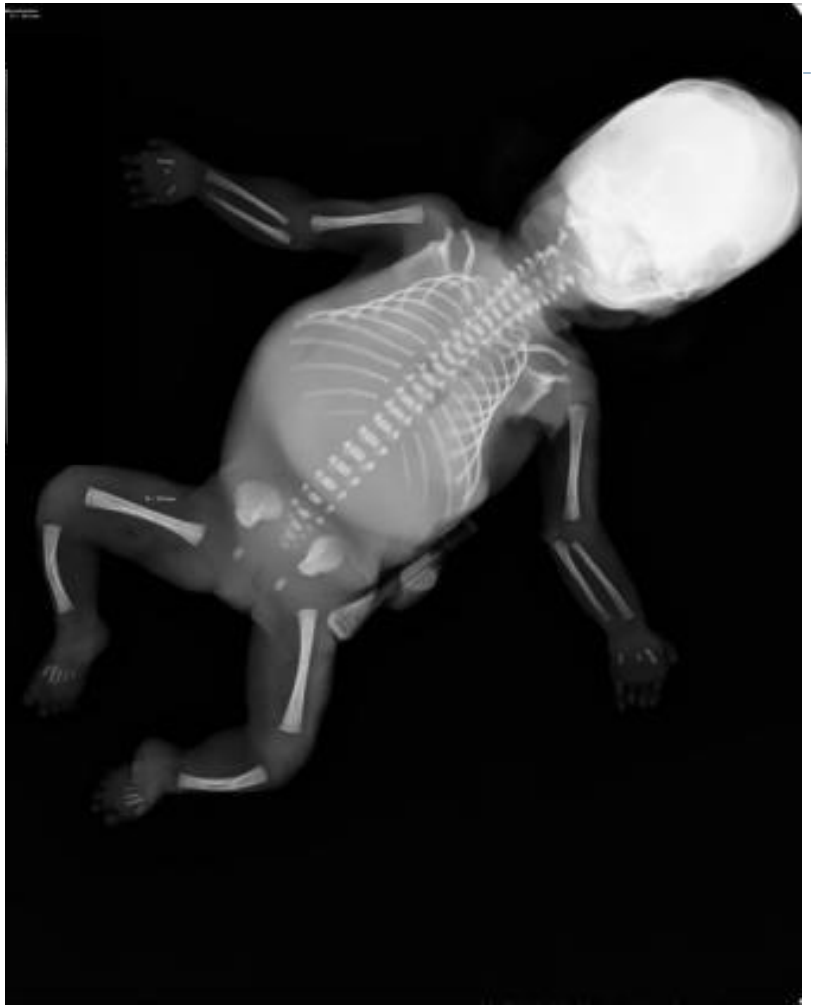
brachydactyly



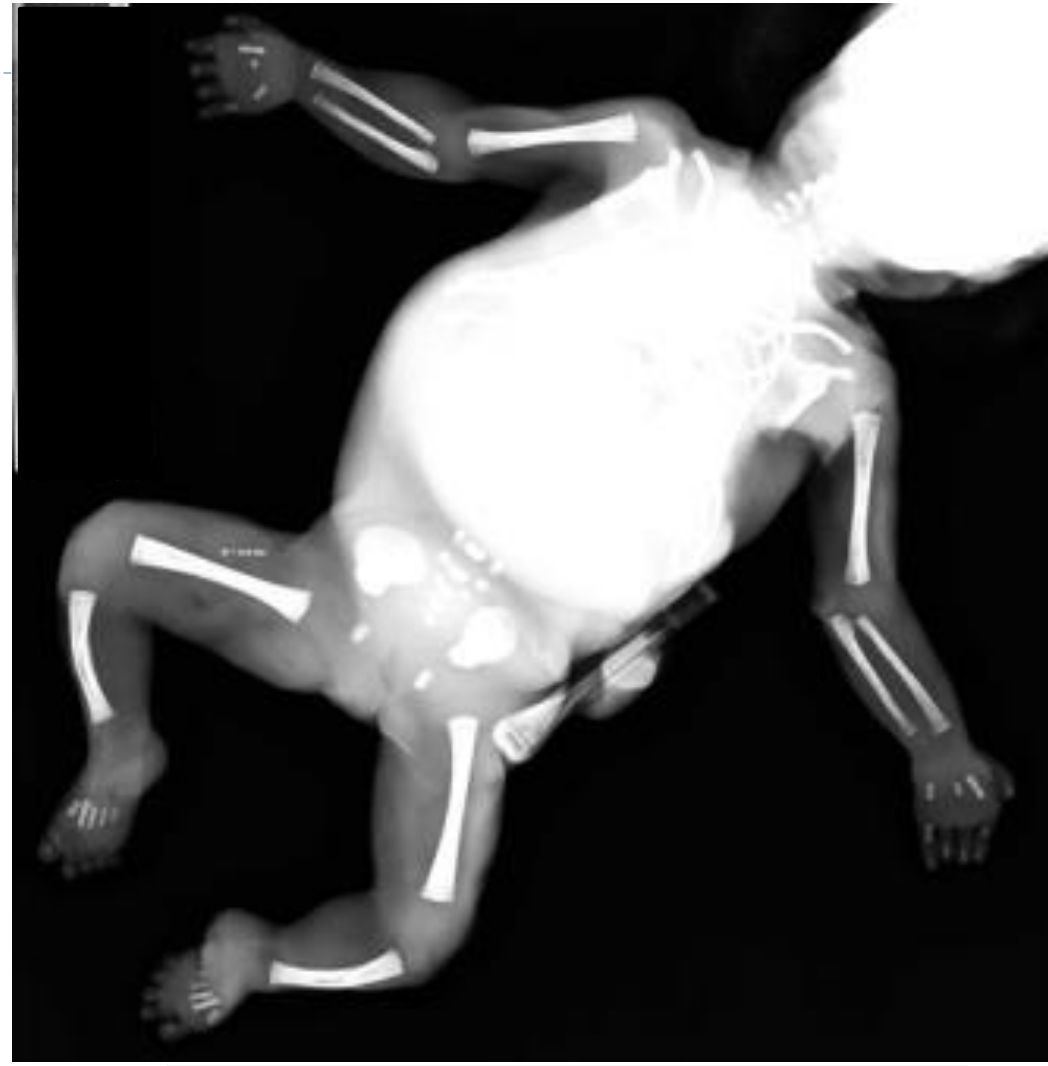




Grebe dysplasia – X-ray



Missing fibula
Short, slightly bent tibia



Irregular and missing metacarpal bones

Grebe dysplasia
(du Pan Brachydactyly – Fibular aplasia): Acro-mesomelic dysplasia

ABSENT BONES

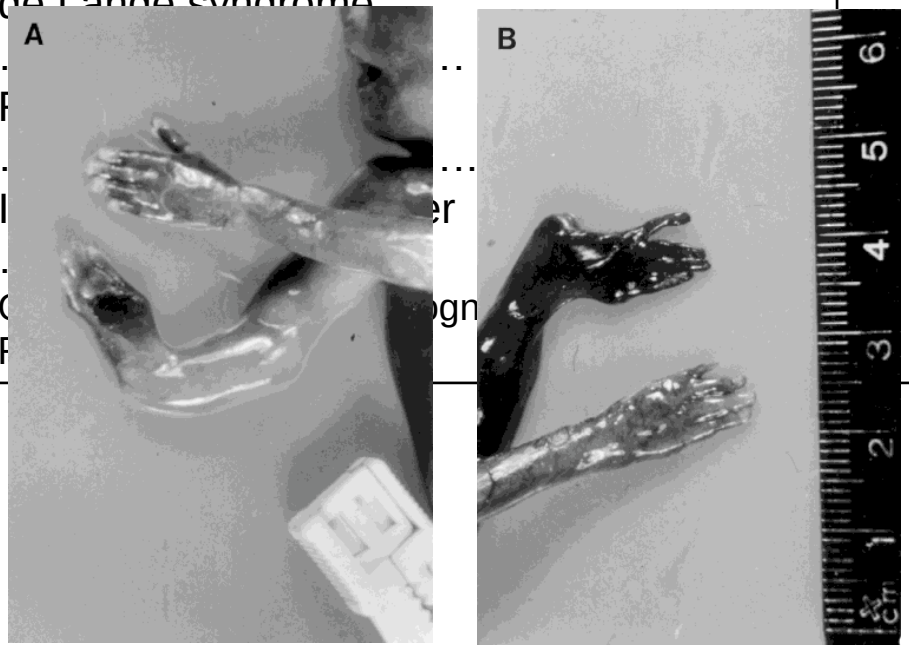
Longitudinal bone reduction defects

- Femoral hypoplasia group (presented under “angulated bones”)
- Tibial aplasia /hypoplasia: sporadic or AR (tibial hemimelia), also seen with the SHFLD group as AD
- Fibular aplasia /hypoplasia: relatively common, mostly sporadic, also seen in the “femoral hypoplasia group”
- Ulnar aplasia /hypoplasia: rare, associated with craniosynostosis syndromes

- Radial aplasia /hypoplasia disorders: radial ray anomaly, most common LRD

Radial aplasia / hypoplasia / Radial ray (Rr) disorders

VACTERL association …… Trisomy 18 and tris13 (occasionally) …….. Thrombocytopenia – Absent Radius (TAR) …... Fanconi anaemia groups …… Holt-Oram syndrome …… de Lange syndrome …	Recognisable constellation of defects Multiple defects mmmmmm Rr +genitourinary +cardiac +hydrocephalus Heart + Hand defects Upper limb LRD + typical facies Phocomelia + cleft lip palate Various defects	SP Chromo - AR AR AD AD AR



Radial ray field defect:
Radius: short to hypoplastic to absent
Thumb: hypoplastic to absent

Cox PM et al.
VACTERL With Hydrocephalus in Twins Due to Fanconi Anemia (FA): Mutation in the FAC Gene. Am J Med Genet 68:86–90 (1997)

DYSOSTOSES

A dysostosis affects one or a few skeletal elements while the other bones remain normal.

Dysostoses can be of predominantly **craniofacial**, **axial** or **acral** involvement.

These disorders can be asymmetric.

There is usually no dwarfism.

Chondro-osseous histology is often normal.

Axial Costovertebral Dysostoses

Spondylocostal dysostosis (SCD)

Spondylothoracic dysostosis (STD)

Former **Jarcho-Levin syndrome**:

A heterogeneous group of disorders characterized by multiple spinal malsegmentation.

The label “Jarcho-Levin syndrome” is to be avoided and spared only for SCD type 1.

Fusion of ribs is necessary for the diagnosis of both SCD and STD.

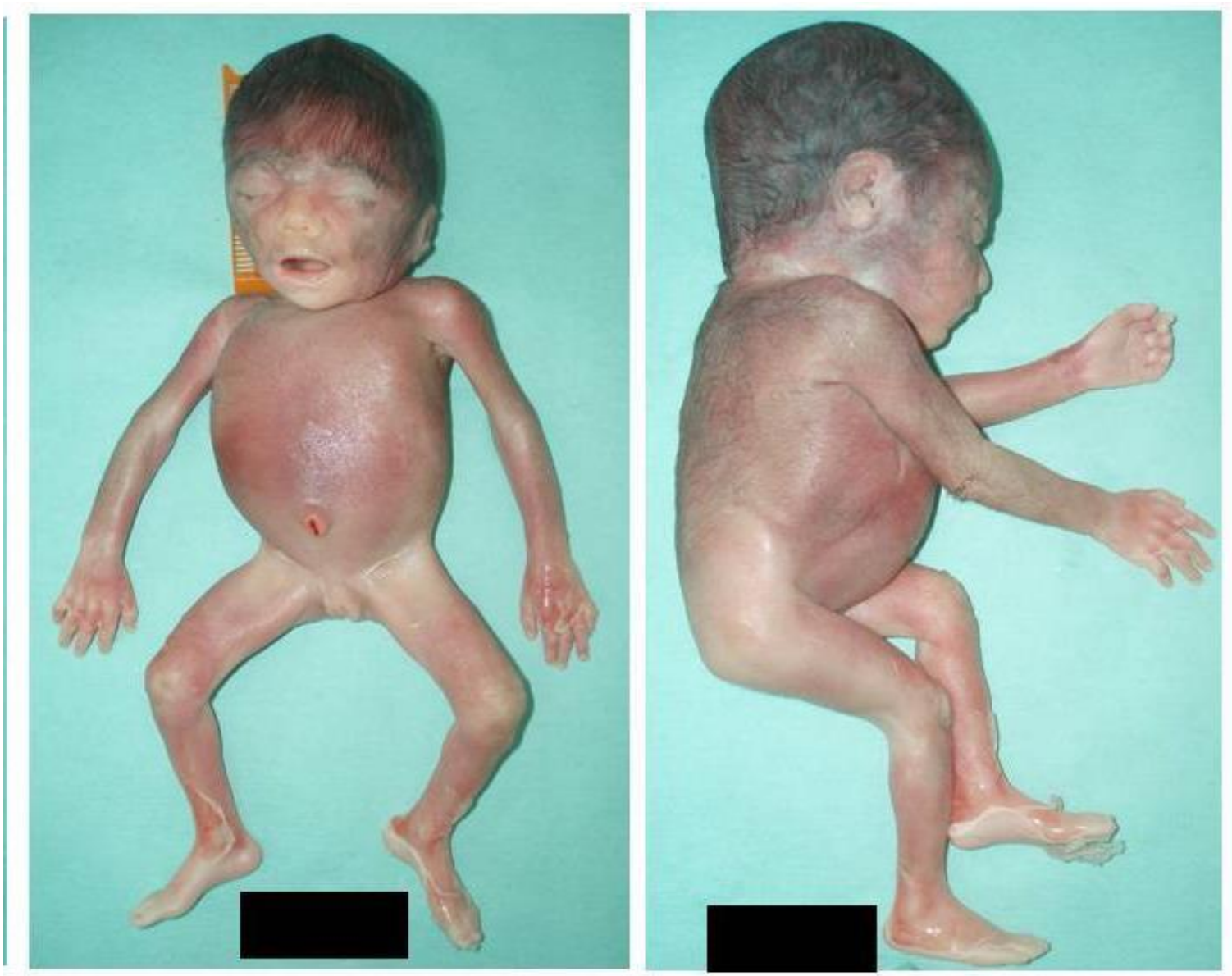
It has been suggested that mild thoracic asymmetry with mild scoliosis characterises Spondylocostal dysostosis, whereas a very short but overall symmetric thorax is a feature of Spondylothoracic dysostosis.

Spondylocostal dysostosis type 1 (true Jarcho-Levin syndrome)

The **Autosomal Recessive Spondylocostal dysostosis type 1** is linked to ***DLL3*** gene defects and is likely to present in the fetal and perinatal period.

Patients with the early lethal form of Spondylocostal Dysostosis die perinatally with respiratory complications; other forms of the syndrome allow survival to a later age.

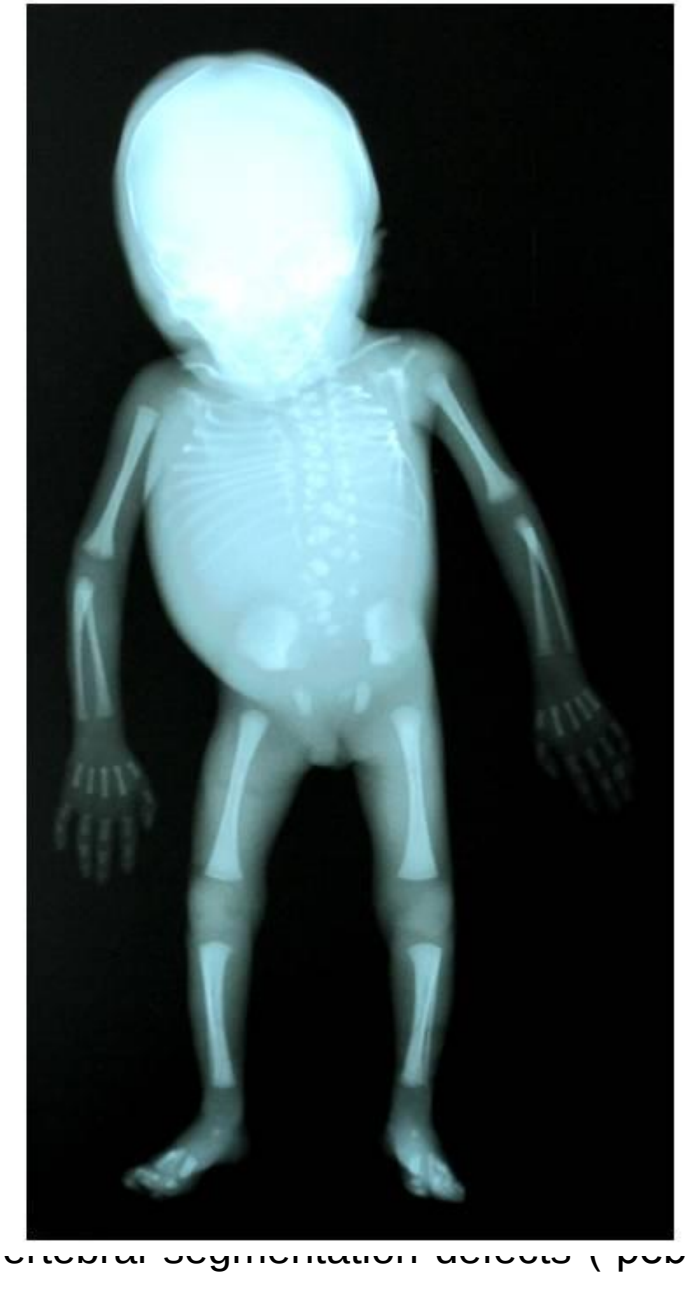
Major visceral malformations (neural tube defects such as spina bifida and meningomyelocele, hindbrain malformations, cardiovascular and urogenital malformations) have been associated with the former heterogeneous Jarcho-Levin syndrome. These appear to be more common in **sporadic** cases of spinal malsegmentation rather than familial cases.



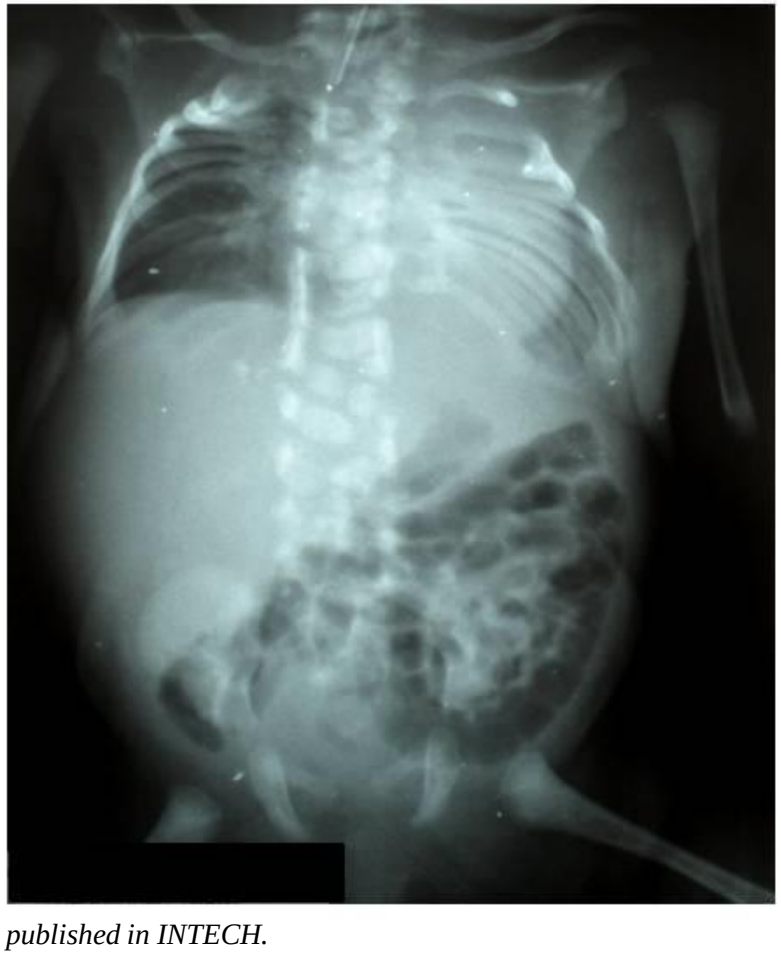
First published in INTECH.

- The baby with Spondylocostal dysostosis has a short neck with low frontal and occipital hairline, hirsutism, a short distended trunk in contrast to extremities of normal length. Mild scoliosis may be present

X-ray



SCD type 1



First published in INTECH.

Multiple vertebral segmentation defects ("pebble beach" appearance) accompanied by deformity o
ribs.

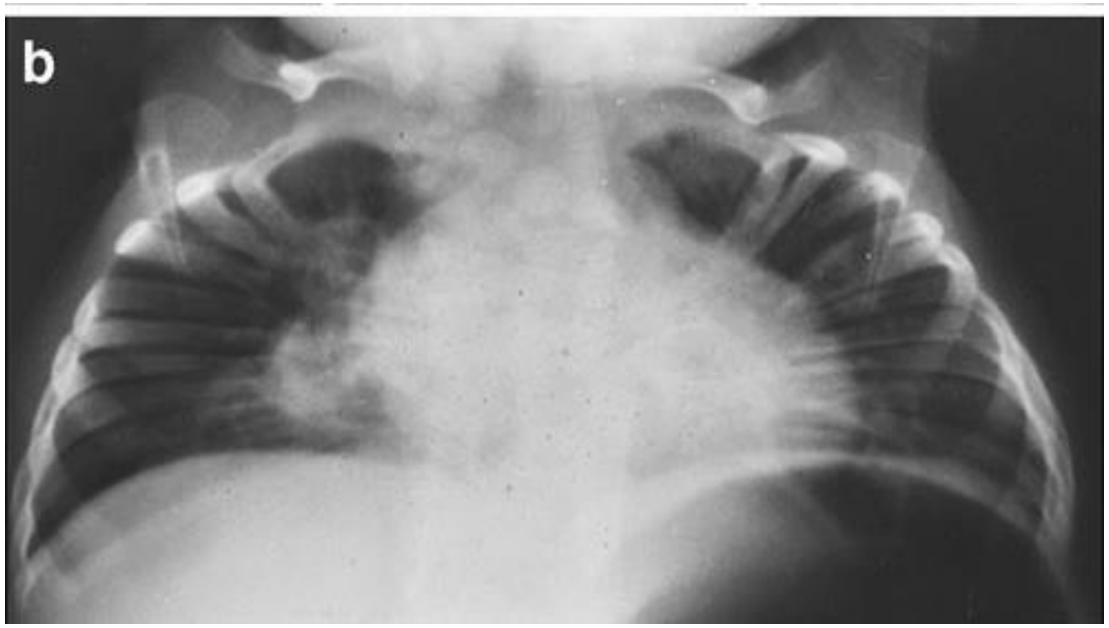
The ribs are focally fused, some may be missing, others overgrown. There is some left/righ
ymmetry.

Spondylothoracic dysostosis (STD)

(Lavy-Moseley syndrome)

Autosomal Recessive

MESP2 gene defects



Berdon W.E. et al.
Pediatr Radiol (2011) 41:384–388

Small symmetrical thorax

The thoracic spine is fused.

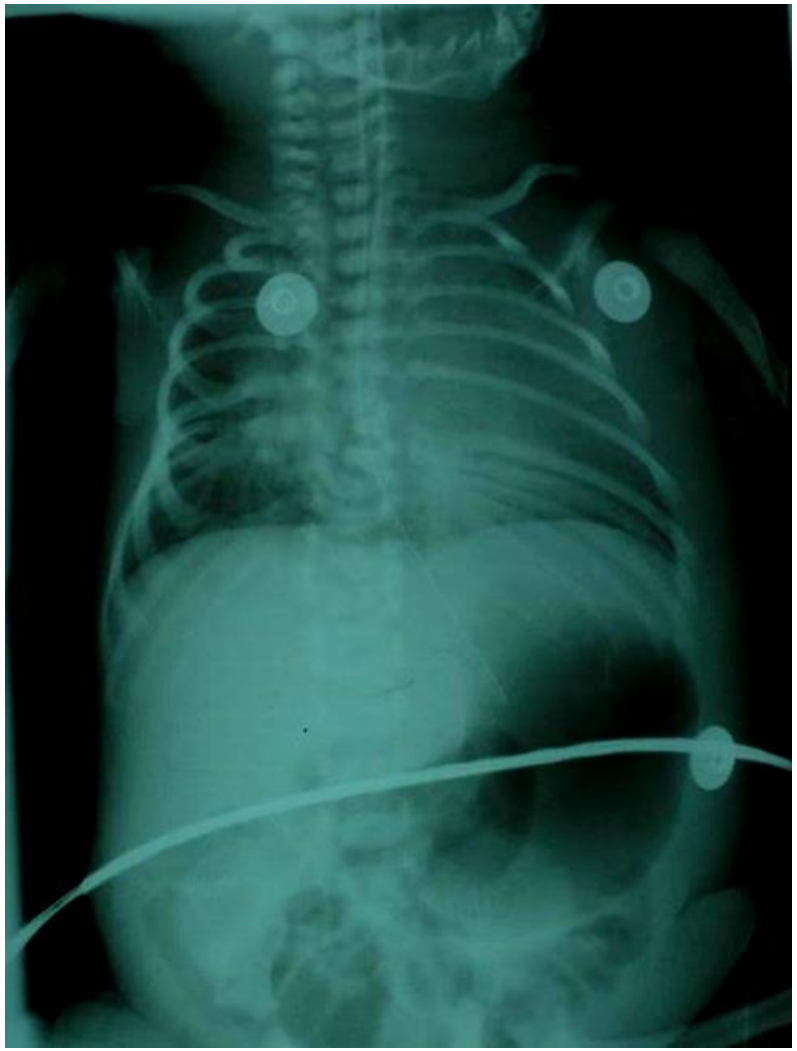
The ribs are fused posteriorly creating a fan-like or “crab” configuration.

Mild scoliosis may be present, but is uncommon.

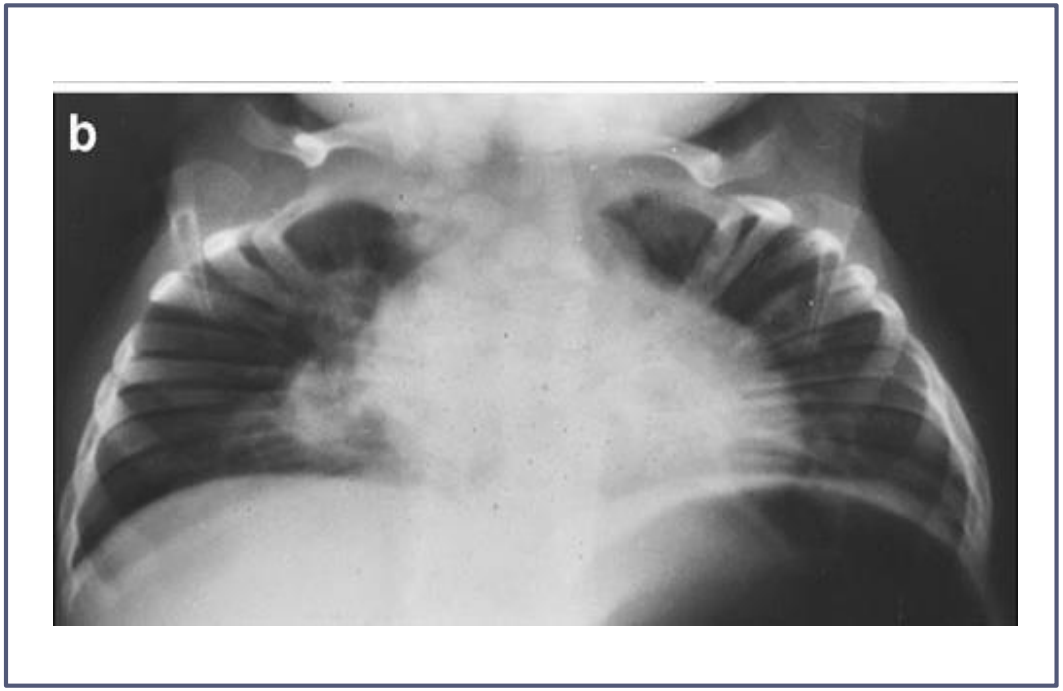
The entire cervical spine is fused with the occiput of the skull fused to C1.

- In **STD**: inguinal and umbilical hernia, urogenital abnormalities and imperforate anus are occasionally seen.

SCD / J-L



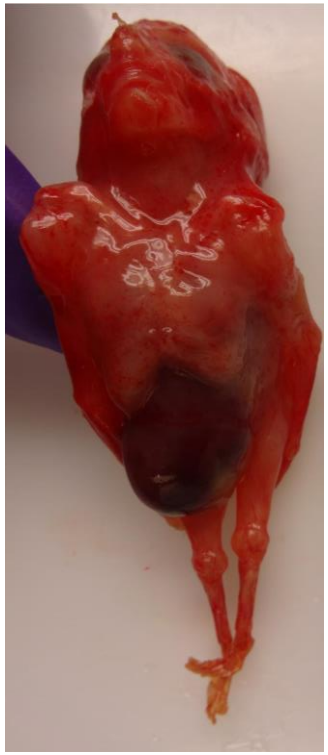
STD / L-M

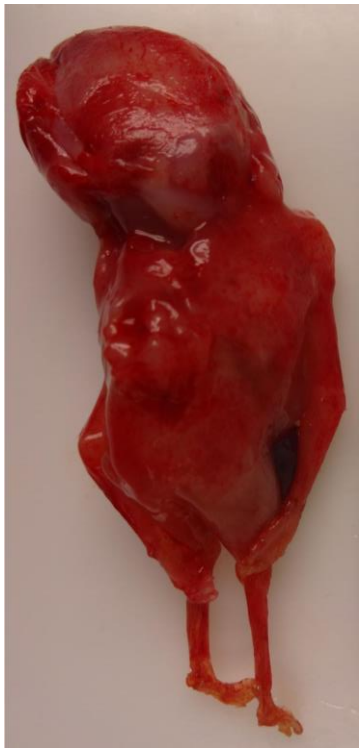


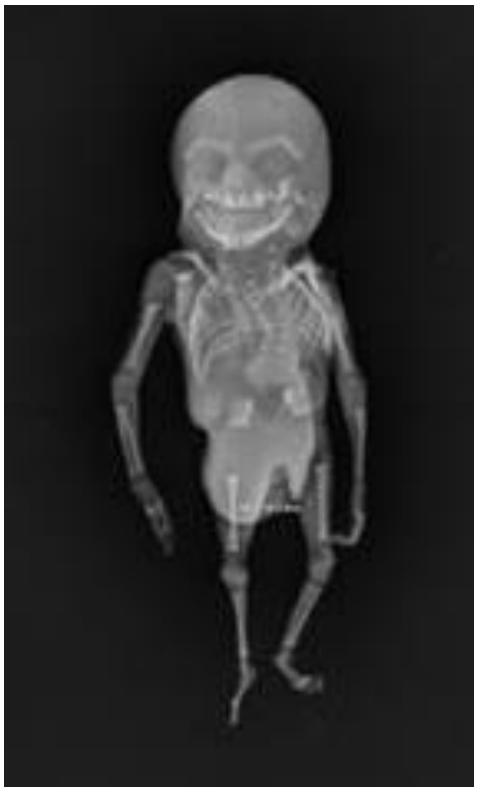
Berdon W.E. et al.
Clinical and radiological distinction between spondylothoracic dysostosis (Lavy-Moseley syndrome) and spondylocostal dysostosis (Jarcho-Levin syndrome)
Pediatr Radiol (2011) 41:384–388

Fusion of ribs is essential for both SCD and STD.

Many other conditions may cause spinal malsegmentation with normal limbs.







? O.E.I.S complex

Associated major visceral malformations appear to be more common in **sporadic** cases of spinal malsegmentation rather than familial cases.

Craniofacial Dysostoses

Mandibulofacial dysostosis
Treacher-Collins syndrome (TCS)

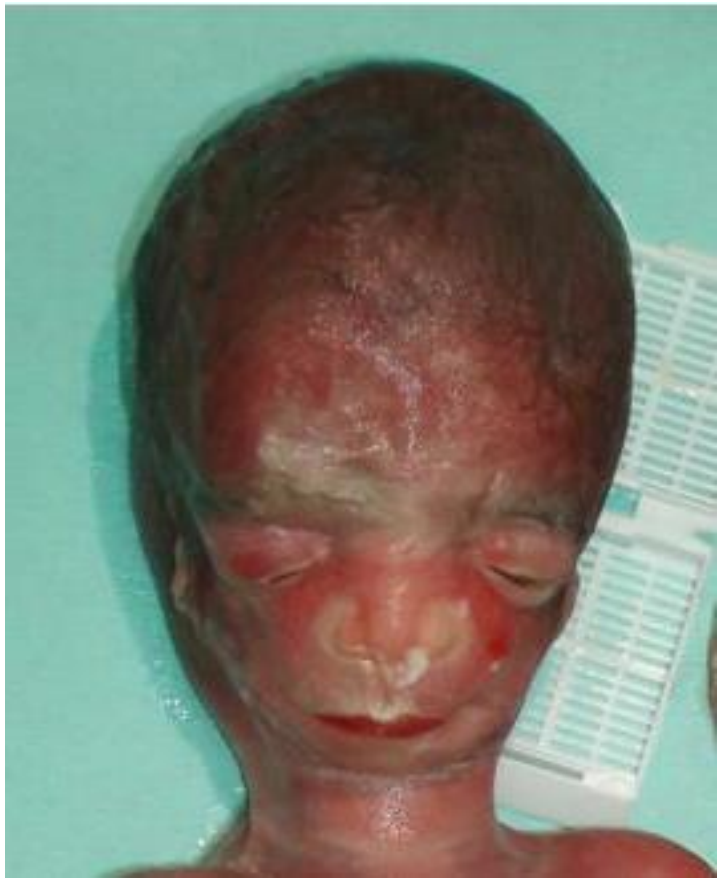
Treacher Collins syndrome is the most common mandibulofacial dysostosis.

Autosomal Dominant character in **types 1 and 2** (TCS1, TCS2)
Autosomal Recessive character in **type 3** (TCS3)

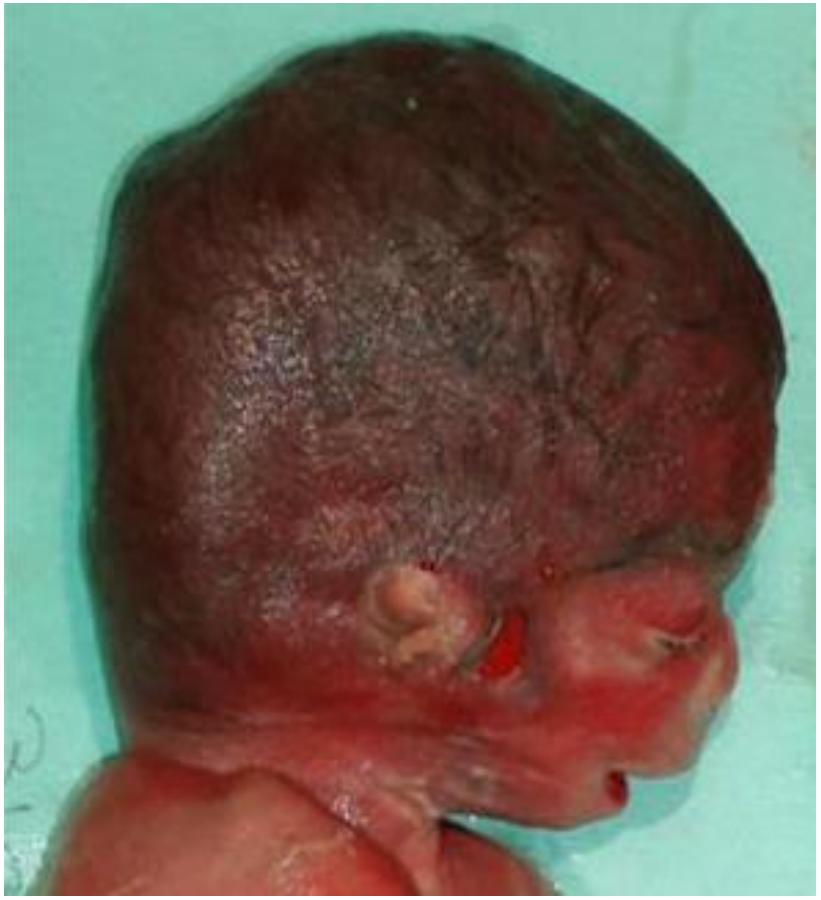
TCS1: 95% of TCS ***TCOF1*** gene mutations

There is an extreme inter- and intrafamilial **phenotypic variation**, ranging from cases with **perinatal death** due to airway obstruction by severe orofacial malformations to those that remain **clinically undiagnosed**.

- At present there is no clear genotype–phenotype correlation to discern between dominant and recessive types, sporadic and familial mutations or to predict disease



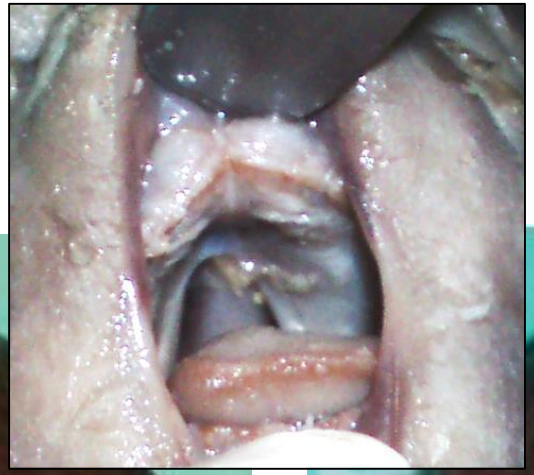
TSC 1



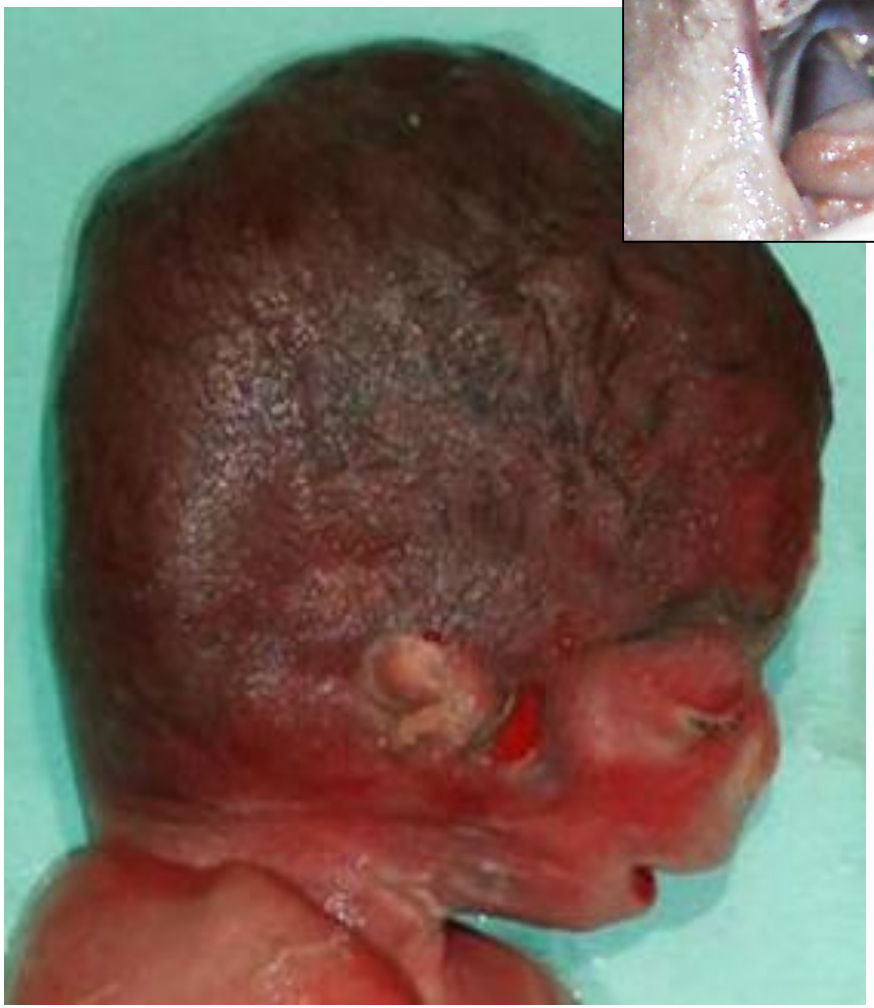
Mandibular hypoplasia (severe retromicrognathia)
Midface hypoplasia
Large frontal vault
Hypertelorism – Protruding eyes
Down slanting palpebral fissures
Flat nose

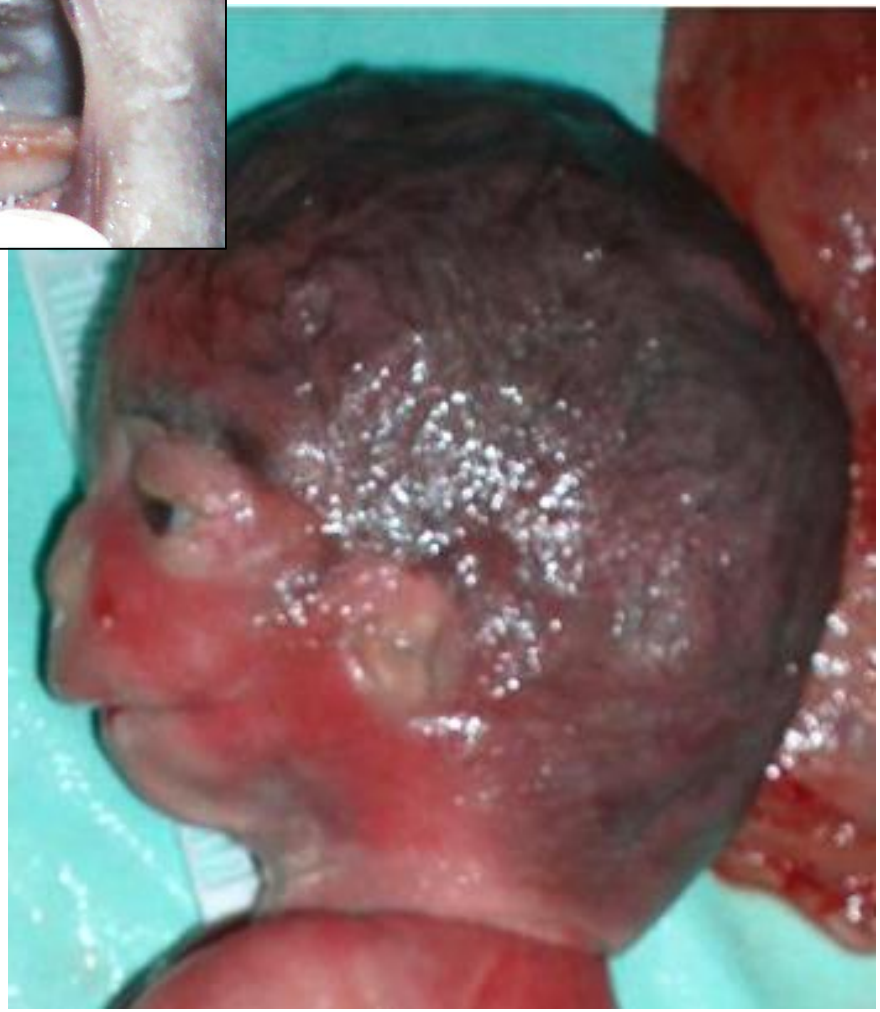
Bilaterally malformed ear lobes
Atresia of external auditory canal

Flat face
Flat occiput



U-shaped soft palate cleft

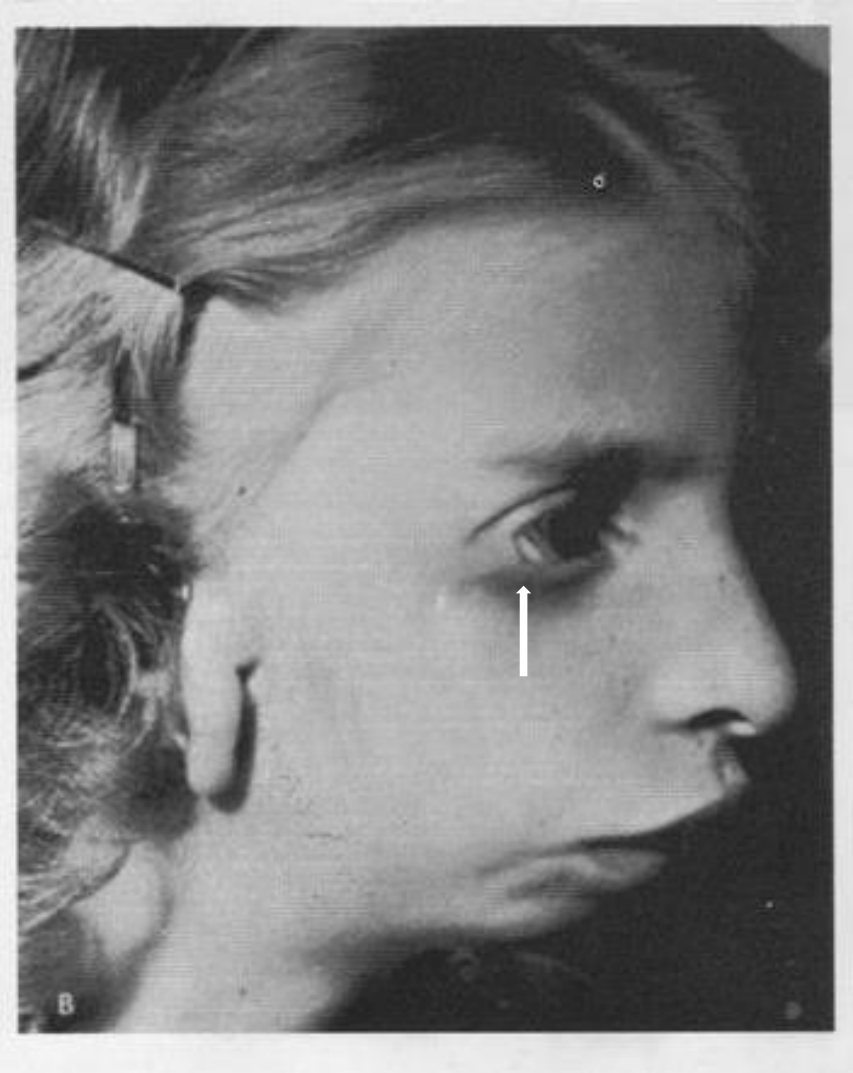




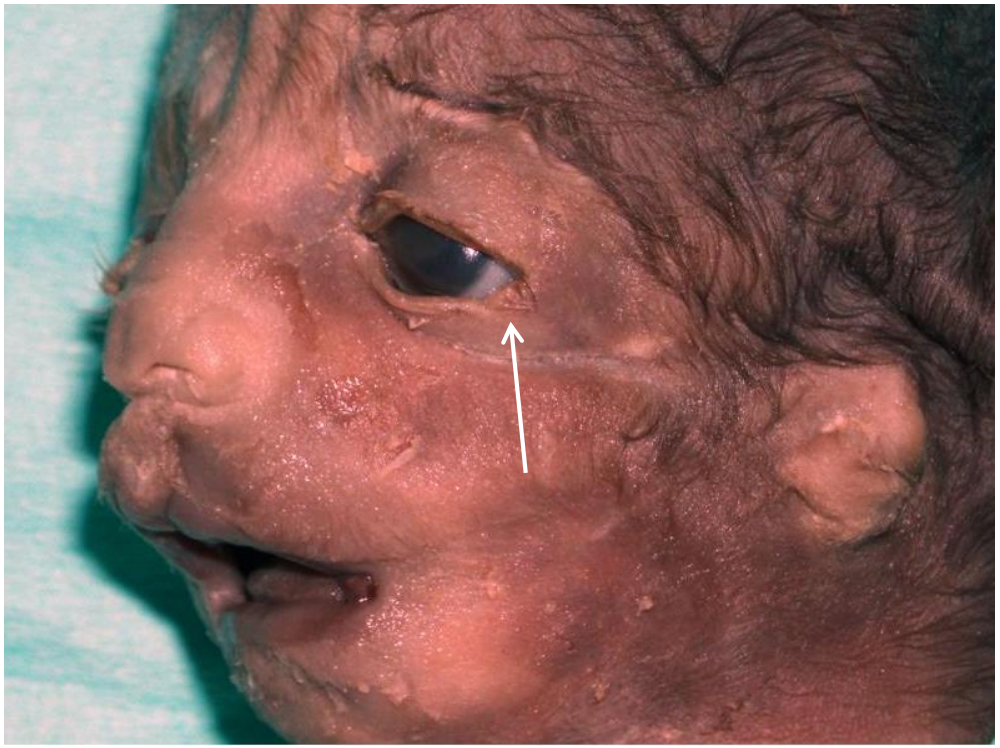
bilaterally malformed ears

- ***Pierre-Robin sequence:*** Severe retromicrognathia + U-shaped cleft of the soft palate

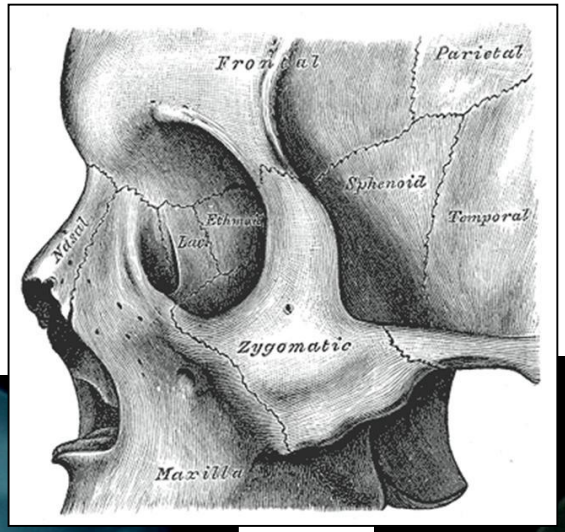
coloboma of the lower lid



Smith's
Recognizable Patterns
of Human Malformations



Konstantinidou et al.
Mandibulofacial Dysostosis (Treacher-Collins Syndrome) in the Fetus: Novel Association with Pectus Carinatum in a Molecularly Confirmed Case and Review of the Fetal Phenotype
Birth Defects Research (Part A): 97:774–780 (2013)



Patient 25w

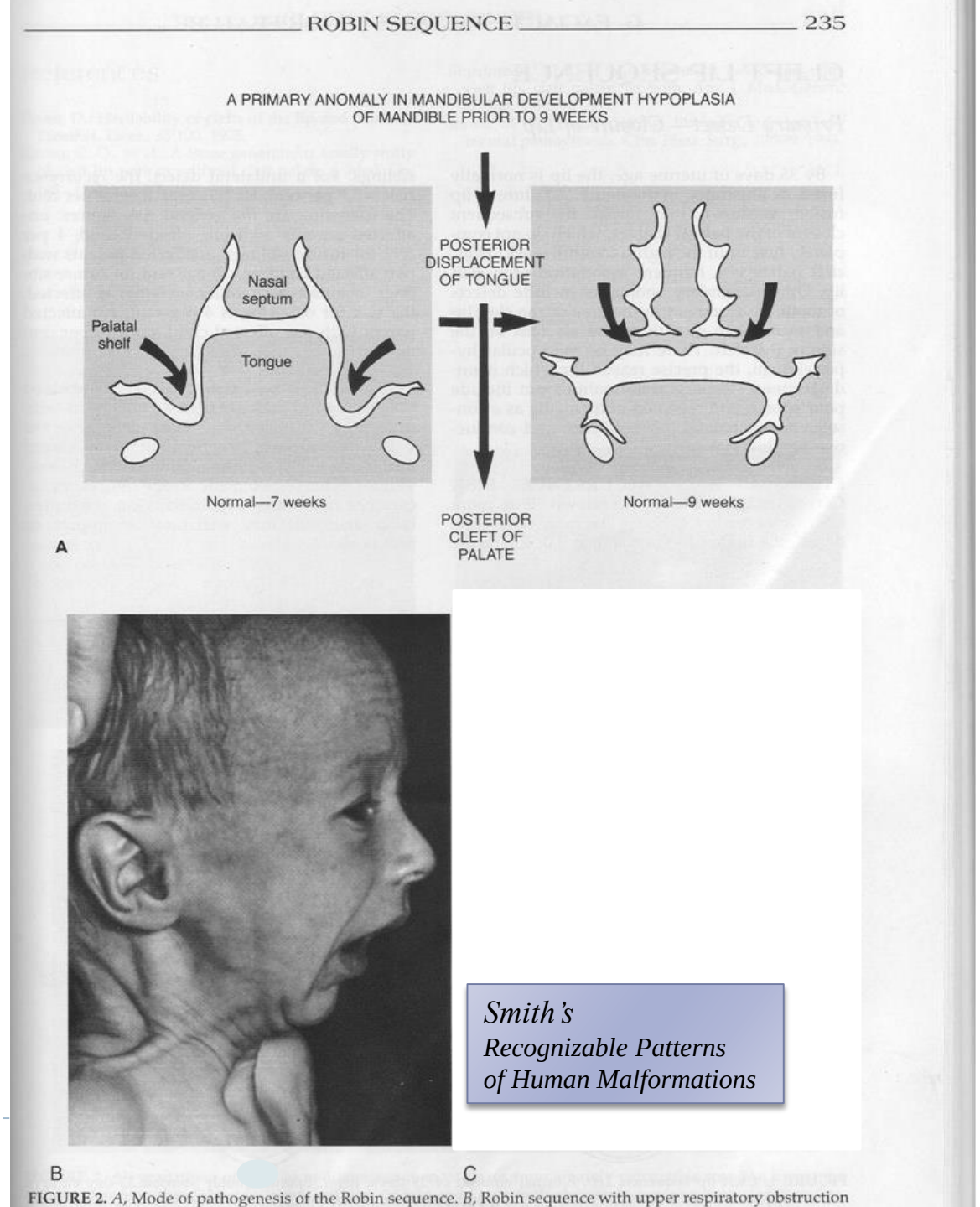
Control 25w

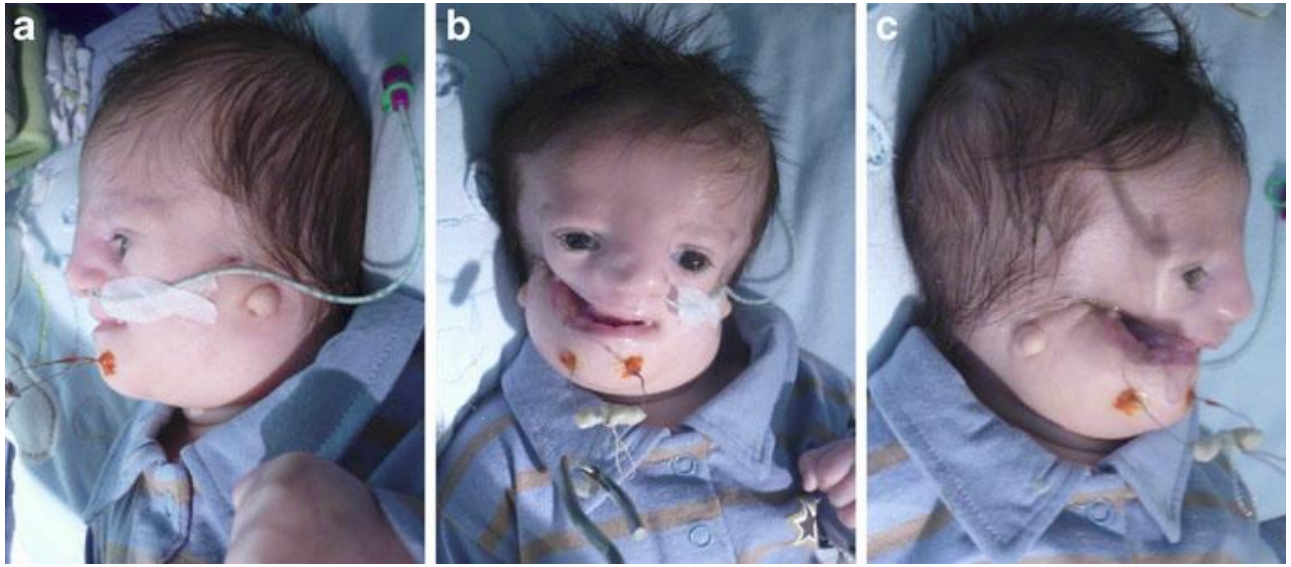
Midface hypoplasia: hypoplastic zygomatic and maxilla

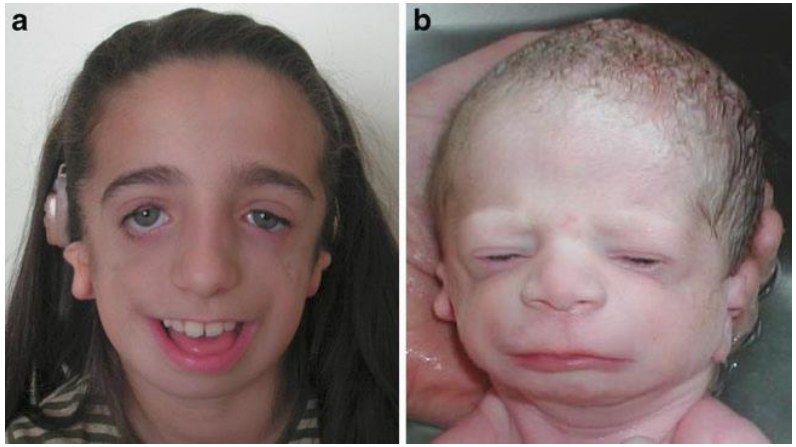
Pierre-Robin sequence

The primary anomaly is that in the development of the mandible that causes mandibular hypoplasia and consequently a displacement of the tongue towards the posterior part of the oral cavity that causes in turn the clefting of the palate.

These babies suffer respiratory distress due to the obstruction of upper airways caused by glossoptosis.







"TCS presenting in its severest manifestation, may be a primary cause of infant mortality and have serious lifetime functional, aesthetic and social consequences that are devastating to both children and parents alike".

Schlump JU, et al. Treacher Collins syndrome: clinical implications for the paediatrician. Eur J Pediatr 2012

- There is an extreme inter- and intrafamilial **phenotypic variation**, ranging from cases with **perinatal death** due to airway obstruction by severe orofacial malformations to those that remain **clinically undiagnosed**.

Craniofacial Dysostoses

Hemifacial microsomia

Goldenhar syndrome
Oculo-auriculo-vertebral spectrum

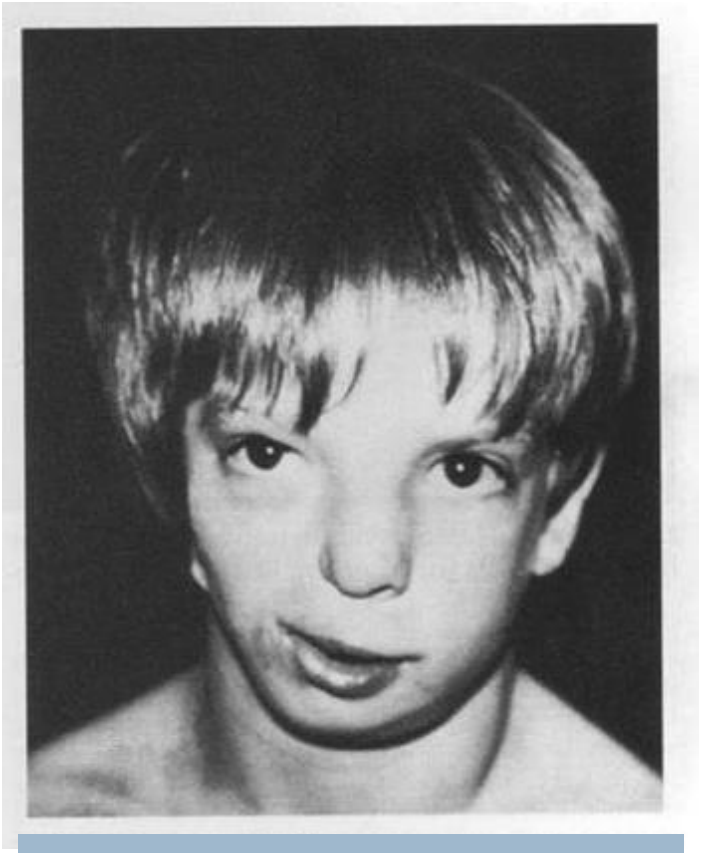
Hemifacial microsomia is a common birth defect involving first and second branchial arch derivatives.

Genetically heterogeneous SP / AD

Phenotype highly variable

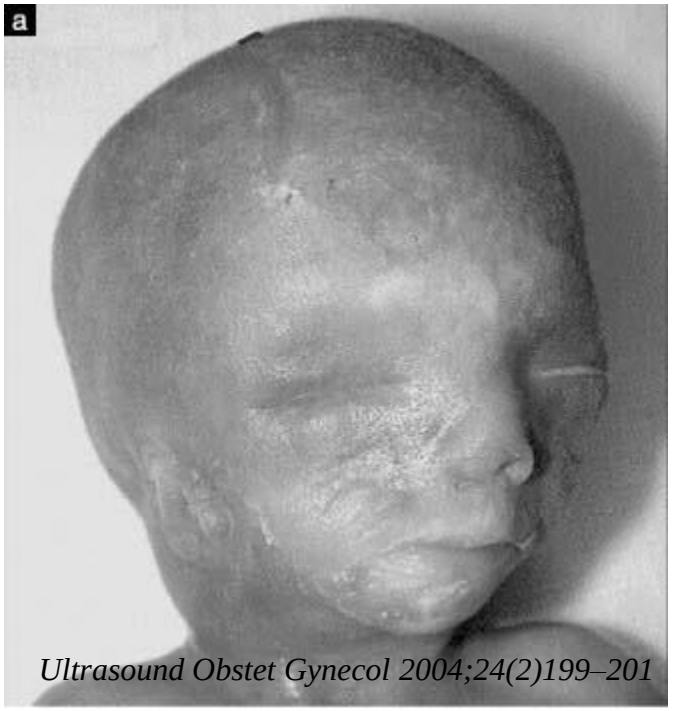
Craniofacial anomalies
(Vertebral malsegmentation)

Cardiac defects
CNS defects



Smith's
Recognizable Patterns of Human Malformations

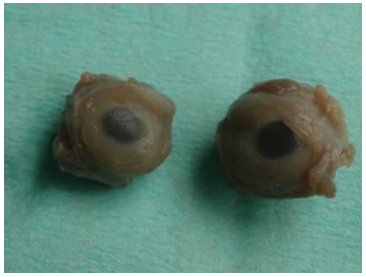
Hemifacial microsomia
Goldenhar syndrome
Oculo-auriculo-vertebral spectrum



Ultrasound Obstet Gynecol 2004;24(2)199–201

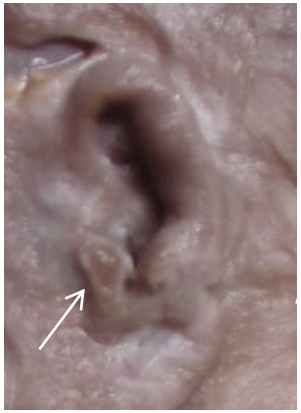
Facial asymmetry:

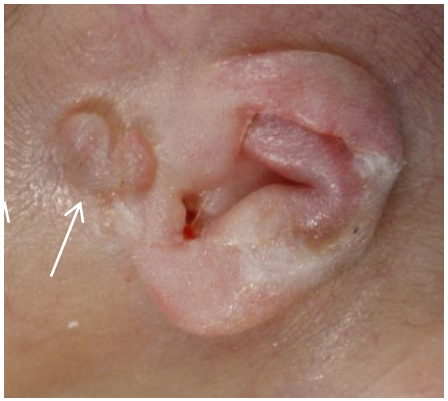
Unilateral midface hypoplasia with ipsilateral deformity of the auricle



- asymmetrical microphthalmia
- coloboma of the upper eyelid

Ears
- preauricular tags (ipsi- or contralateral)
- atresia of the external auditory canal
- anomalies in the size and shape of the auricle





End of Part 2 of Skeletal Stuff

Rome - Cemetery of the Capuchins - 5th chapel