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CILIOPATHIES and SKELETAL DYSPLASIA

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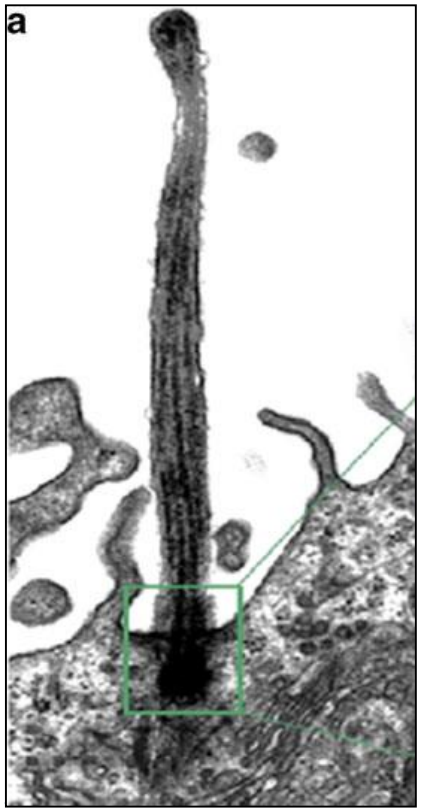
Ciliary Skeletal Dysplasias

The term “ciliary skeletal dysplasias” summarizes inherited conditions
resulting from cilia malfunction affecting skeletal development in mammals.

Cilia are hair-like organelles projecting from the surface of cells.

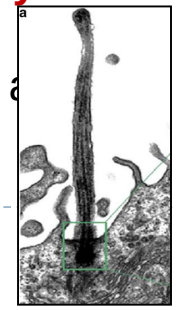


Cilia can be divided into two main subgroups:

motile cilia - occuring in bundles of hundreds
distinguished by their **ability to beat rhythmically**
Restricted to:
the **respiratory** tract, **brain ventricles**, **reproductive** tract, organizing fluid flow across the cell surface and mucociliary clearance,
and the **embryonic node** in mammals,
producing a leftward fluid flow so that the embryo knows Left from Right.

Gene defects encoding for proteins of the ciliary motile apparatus lead to a cystic fibrosis-like disease named Primary Ciliary Dyskinesia (including Kartagener syndrome) presenting with bronchiectasis, infertility, and laterality defects, which are due to impaired motile ciliary function in the embryonic node.

non-motile (primary) cilia - single structures
Primary cilia can be found **on nearly every cell** throughout the organism.
They have chemosensory, osmosensory a
phototransduction functions.



An expanding group of syndromic genetic conditions with a broad range of phenotypes are linked to malfunction of primary cilia:

Bardet-Biedl syndrome
Polycystic Kidney Disease,
Nephronophthisis
Joubert syndrome - Meckel syndrome
……
and the ciliary osteochondrodysplasias.

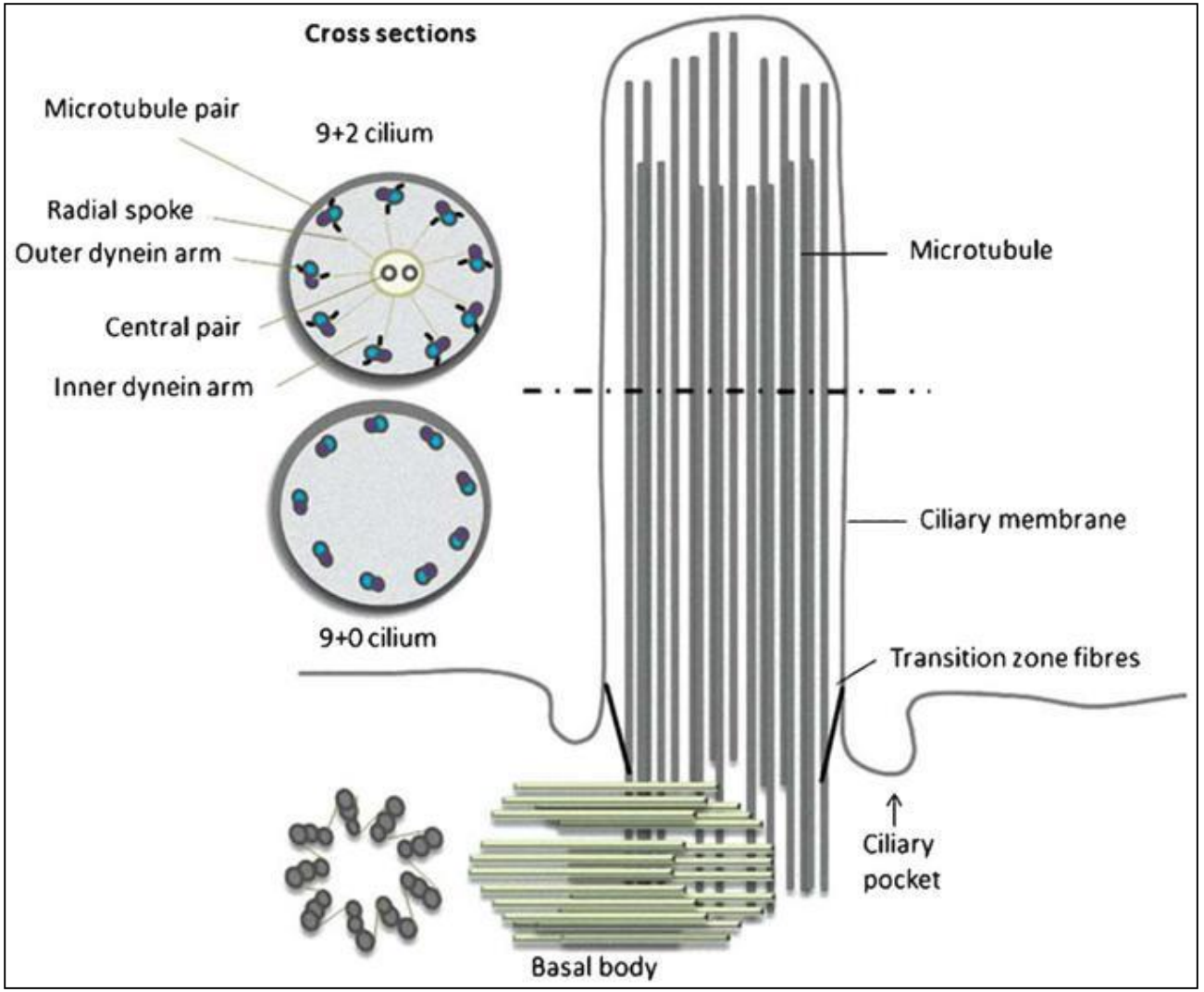
Ciliary ultrastructure

Primary cilia consist of nine pairs of microtubules (9+0).
Motile cilia display an additional central pair (9+2). These motile cilia also contain other proteins necessary for the motile apparatus such as dynein arms and radial spokes, not observed in primary cilia.

The ciliary axoneme extends from the **basal body** which is formed from centrioles, complex microtubule-based structures, and
directs the trafficking of vesicles and organelles.

Transition zone fibers connect ciliary membrane with the cilium and are thought to form a barrier towards the cellular cytoplasm.

The **ciliary pocket** has been identified as a hub for **cell signaling pathways** and it is thought that proteins produced within the cell body are transported to the ciliary pocket within vesicles.



J Pediatr Genet 2014;3(2): 46–94

Ciliary proteins are thought to be transported to the cilium within vesicles that merge with the ciliary membrane in the ciliary pocket area. Delivery of ciliary cargo involves assembly of cilia from the ciliary base to the tip.

Anterograde intraflagellar transport (IFT) from the ciliary base to the tip is facilitated by IFT complex B, while retrograde transport back the base requires IFT complex A.

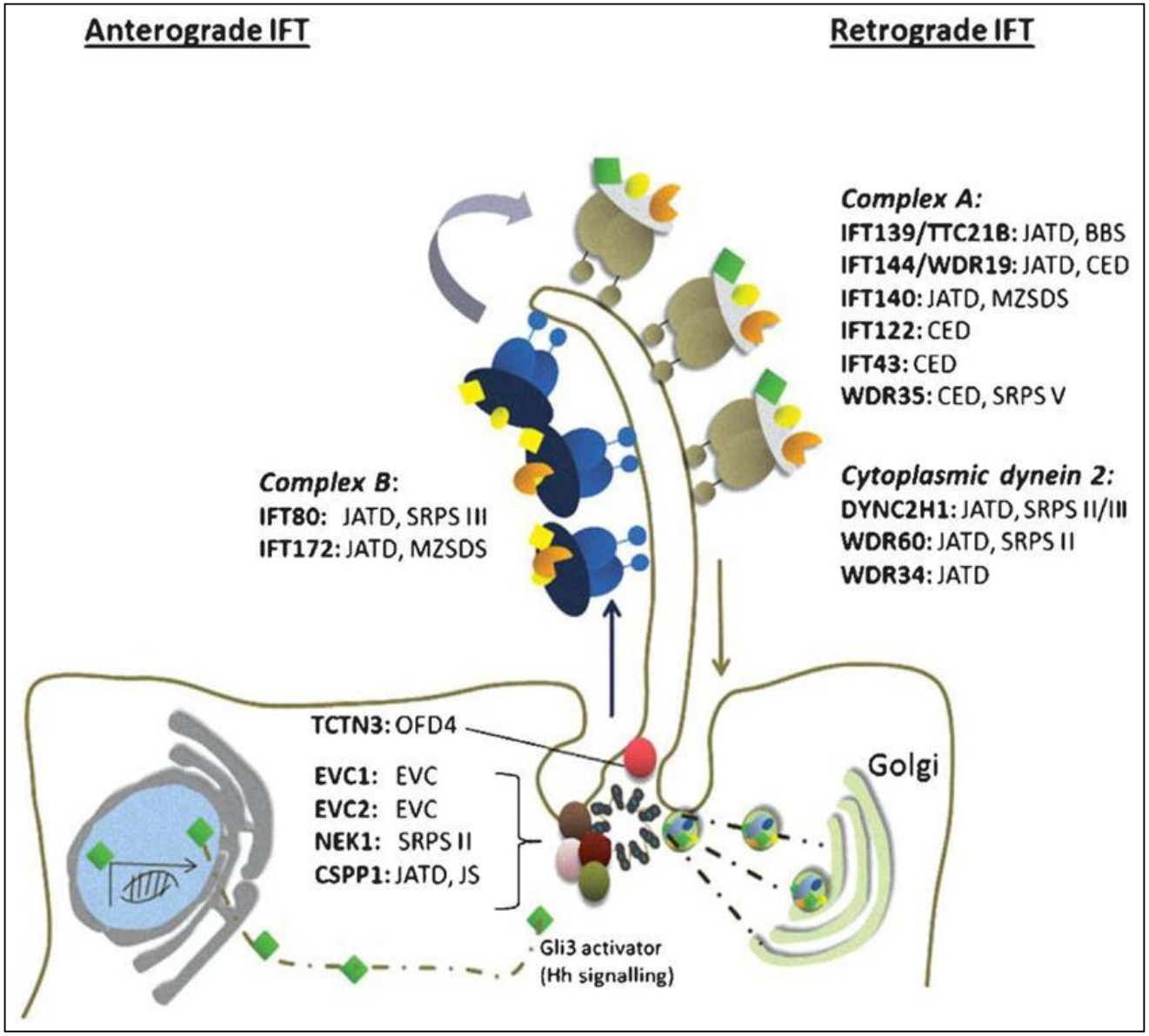
Most **genes** found to be **involved in ciliary chondrodysplasias** encode for proteins of **complex A** and the **associated motor complex, cytoplasmic dynein-2,** which provides the power for ciliary assembly.

However, EVC/EVC2, CSPP1 and NEK1 localize to **the base of the cilium** and TCTN3 is found at the ciliary transition zone.

To date, no human mutations have been identified in the motor for complex B, kinesin-2.

Hedgehog (Hh) signaling is essential to maintain a balance between cell proliferation and differentiation at the growth plates. In Hh signaling, activated GLI proteins (transcription factors) finally translocate to the nucleus where they influence gene expression. IFT mutant mice as well as mice lacking Evc function

Intraflagellar Transport (IFT)



J Pediatr Genet 2014;3(2): 46–94

In the ciliary chondrodysplasias :

Abnormal primary ciliary structure or function

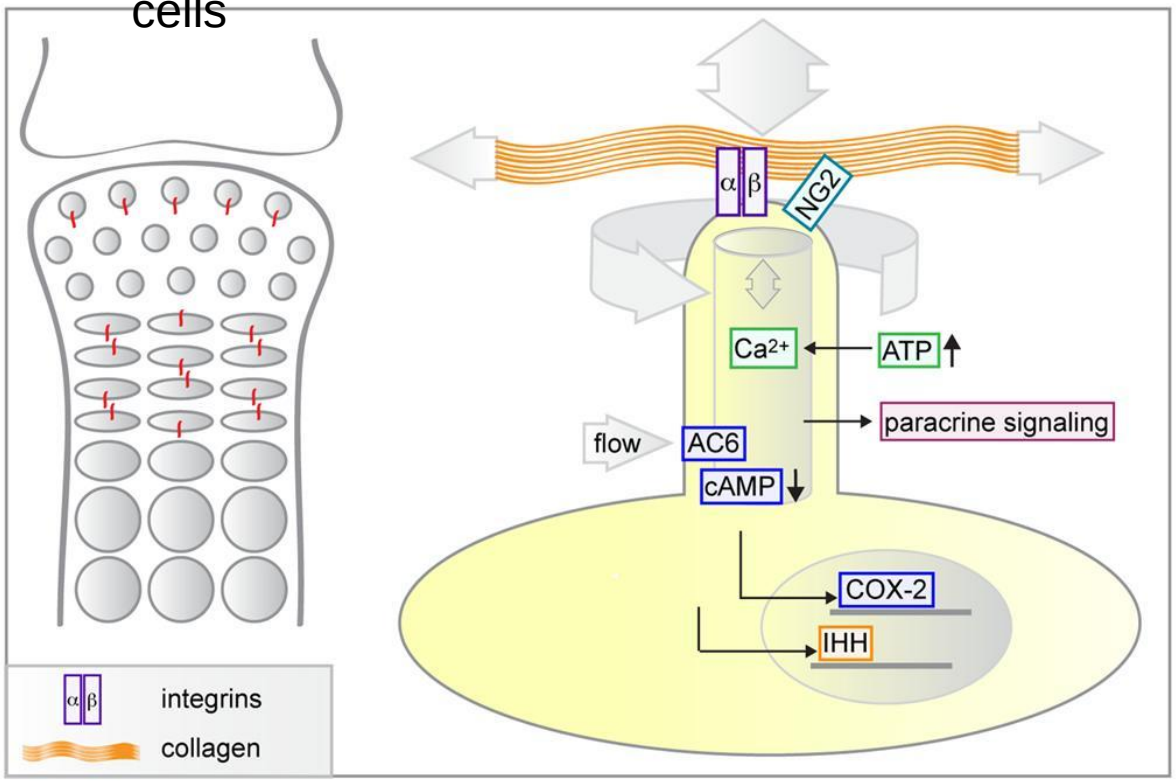
The causative gene product is localized to the ciliary apparatus or to associated complexes and pathways.

Many of the disease-related proteins are not expressed in the cilium itself, but rather at its base, in the basal body (transition zone or centrosome).

> “ The ciliopathies form a class of genetic disease whose etiology purportedly lies not with dysfunction in a single-gene product but with dysfunction in an integrated aspect of cellular physiology. ”

Baker K, Beales PL. 2009. Making sense of cilia in disease: The human ciliopathies. Am J Med Genet Part C Semin Med Genet 151C:281–295.

Ciliary signaling in cartilage and bone cells



Extensive signaling dialog between cilia and extracellular matrix

The primary cilium protrudes like an antenna from the cell surface, sensing mechanical and chemical cues provided in the cellular environment.
In the bone, ciliary protrusion into the extracellular matrix (ECM) allows response to compression forces.

Articular chondrocytes sense mechanical forces including shear stress, rotation, pressure, and tension in part through interactions of the ECM with ciliary proteins (integrins and NG2 chondroitin sulfate proteoglycan).

Hydrostatic loading of growth plate chondrocytes increases Indian hedgehog (IHH) signaling, governing chondrocyte proliferation and differentiation in the growth plate, dependent on intact cilia.

- Cilia are required for osteogenic and bone resorptive responses to fluid flow.

Curr Opin Cell Biol. 2012 October ; 24(5): 652–661

CILIARY CHONDRODYSPLASIAS (known to date)

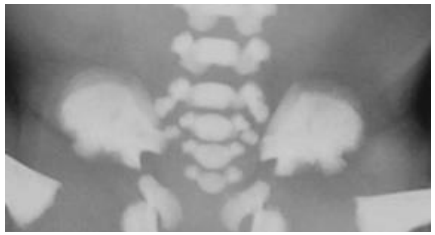
A group of phenotypically and genetically related disorders,
inherited in an **autosomal recessive** fashion.

- Short-Rib-Polydactyly (SRP)
  - SRP type 1/3 (Saldino-Noonan / Verma-Naumoff)
  - SRP type 2 (Majewski)
  - SRP type 4 (Beemer-Langer)
  - SRP type 5 WDR35
- Asphyxiating Thoracic Dystrophies (ATD; Jeune)
- Chondroectodermal dysplasia (Ellis-van Creveld)
- Mainzer-Saldino syndrome (MZSD) 'conorenal syndrome'
- Oral-facial-digital syndrome 4 (OFD4)
- Cranioectodermal dysplasia (CED; Sensenbrenner syndrome)
- Weyers Acrodental Dysostosis (WAD)

Short Rib Thoracic Dystrophies (SRTD 1-12)

Autosomal Dominant does not affect the

CILIARY CHONDRODYSPLASIAS



The **skeletal phenotype** is predominant.

- shortened limbs
- shortened ribs
- 'trident' acetabulae (horizontal acetabular roofs with spur-like projections at the lower margins of the sciatic notches)
- polydactyly - variably present (postaxial in SRP types 1, 2, 3, and EvC), preaxial or combined preaxial and postaxial in SRP type 2, rare in SRP type IV)
- (craniofacial malformations such as craniosynostosis)

Extraskeletal involvement may be additionally present :

cleft lip/palate
kidneys, liver,
brain, eye,
heart,
pancreas, intestines,
genitalia
laterality defects

Within each organ, diseases can be developmental
phenotypes presenting in utero, at birth or later in childhood.

Often this may depend on the severity of the underlying mutation in addition to the number of defective proteins encoded where more than one mutation in a ciliary gene occurs.

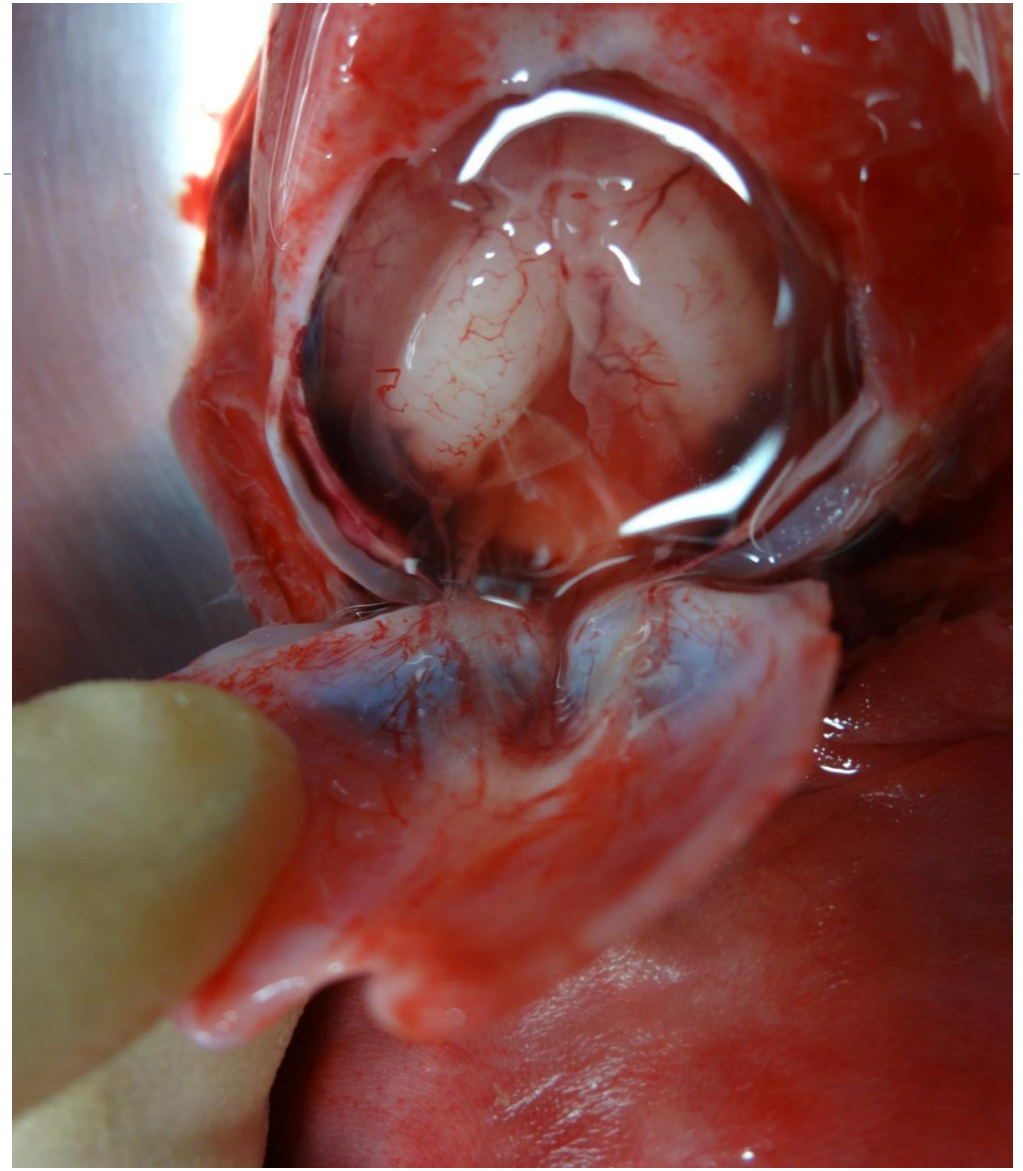
EVC and **CED** show **ectodermal** involvement (nails, hair, teeth, eccrine gland abnormalities).

Phenotype severity varies significantly between the different conditions, but also between patients with the same condition.

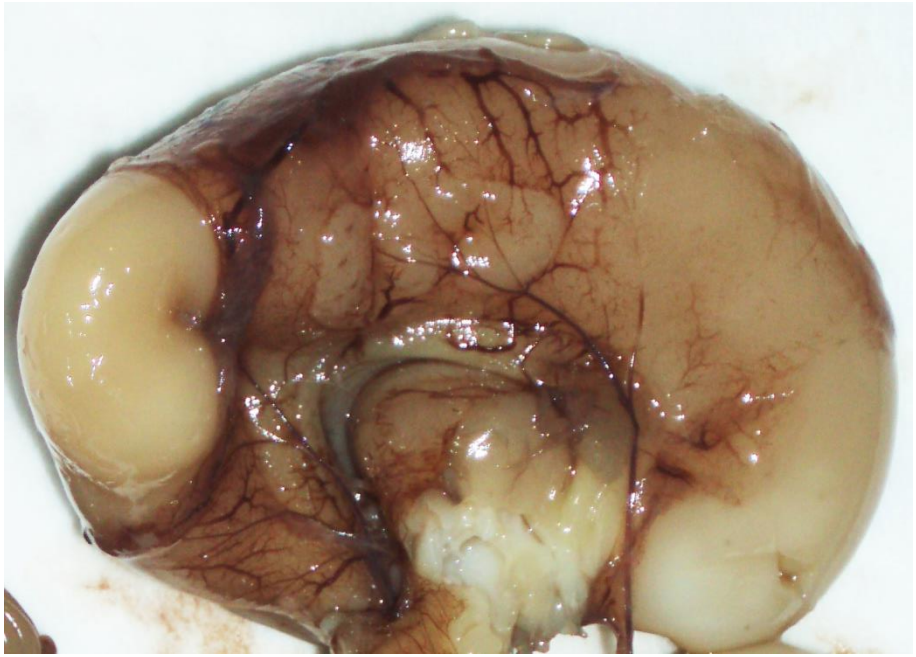
Badano et al. in their review of ciliopathies [2006] had weighted 9 phenotypic features, according to their likely relevance to predict ciliary involvement :

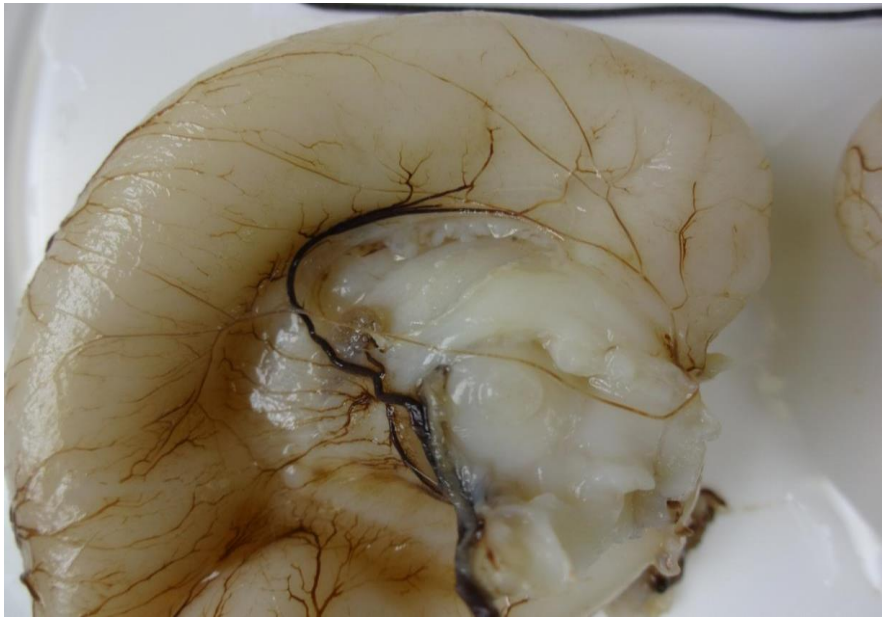
	Phenotypic features likely to predict ciliary involvement (in descending order)
1.	Dandy-Walker malformation
2.	Agenesis of Corpus Callosum
3.	Situs inversus
4.	Posterior encephalocele
5.	Multicystic renal disease
6.	Post-axial polydactyly
7.	Hepatic disease
8.	Retinitis pigmentosa
9.	Mental retardation
	Additional ciliopathy-related features
10.	Cardiac defects
11.	Skeletal dysplasia

Badano JL, Mitsuma N, Beales PL, Katsanis N. 2006. The ciliopathies: an emerging class of human genetic disorders. Annu Rev Genomics Hum Genet 7:125-148.

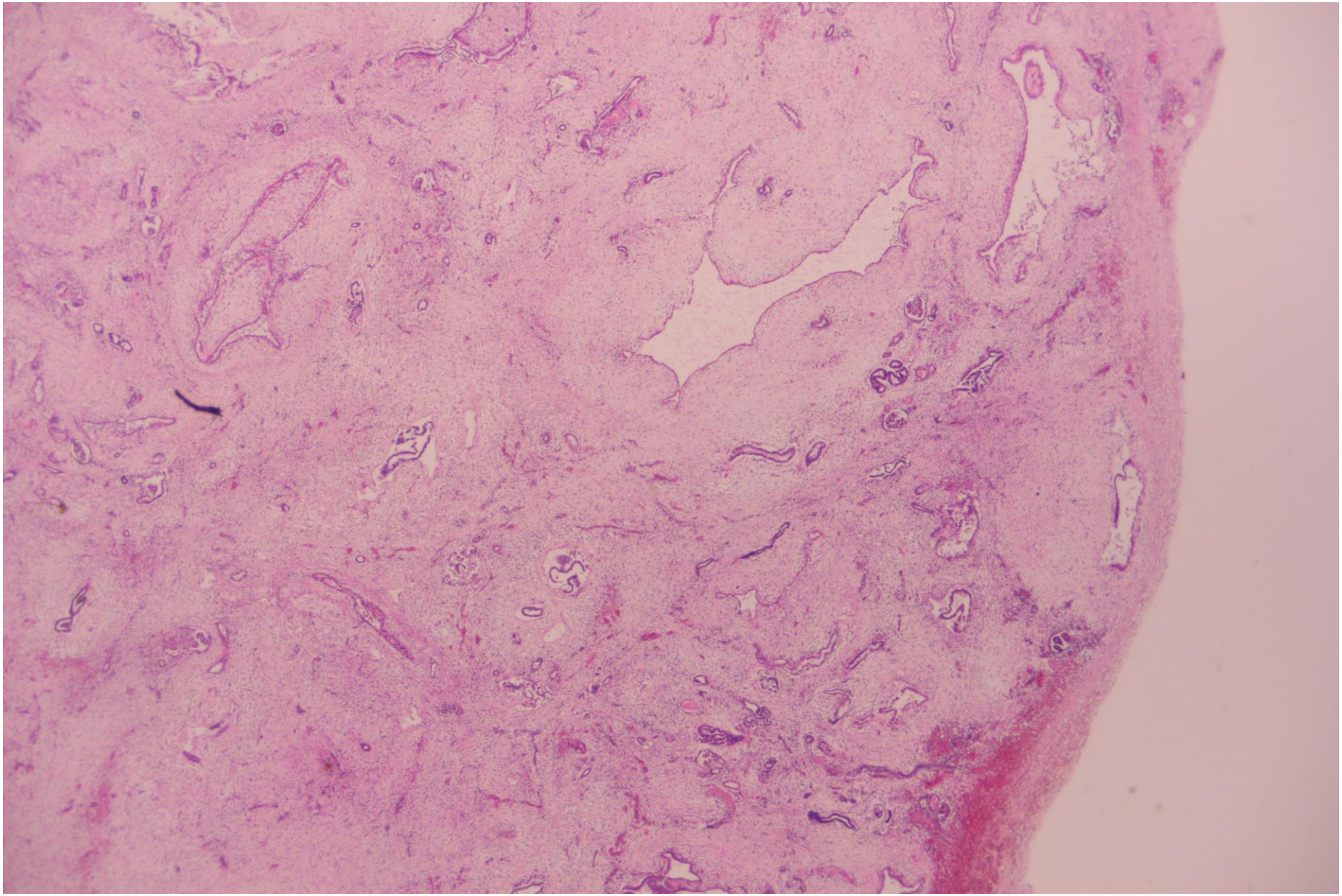


D-W

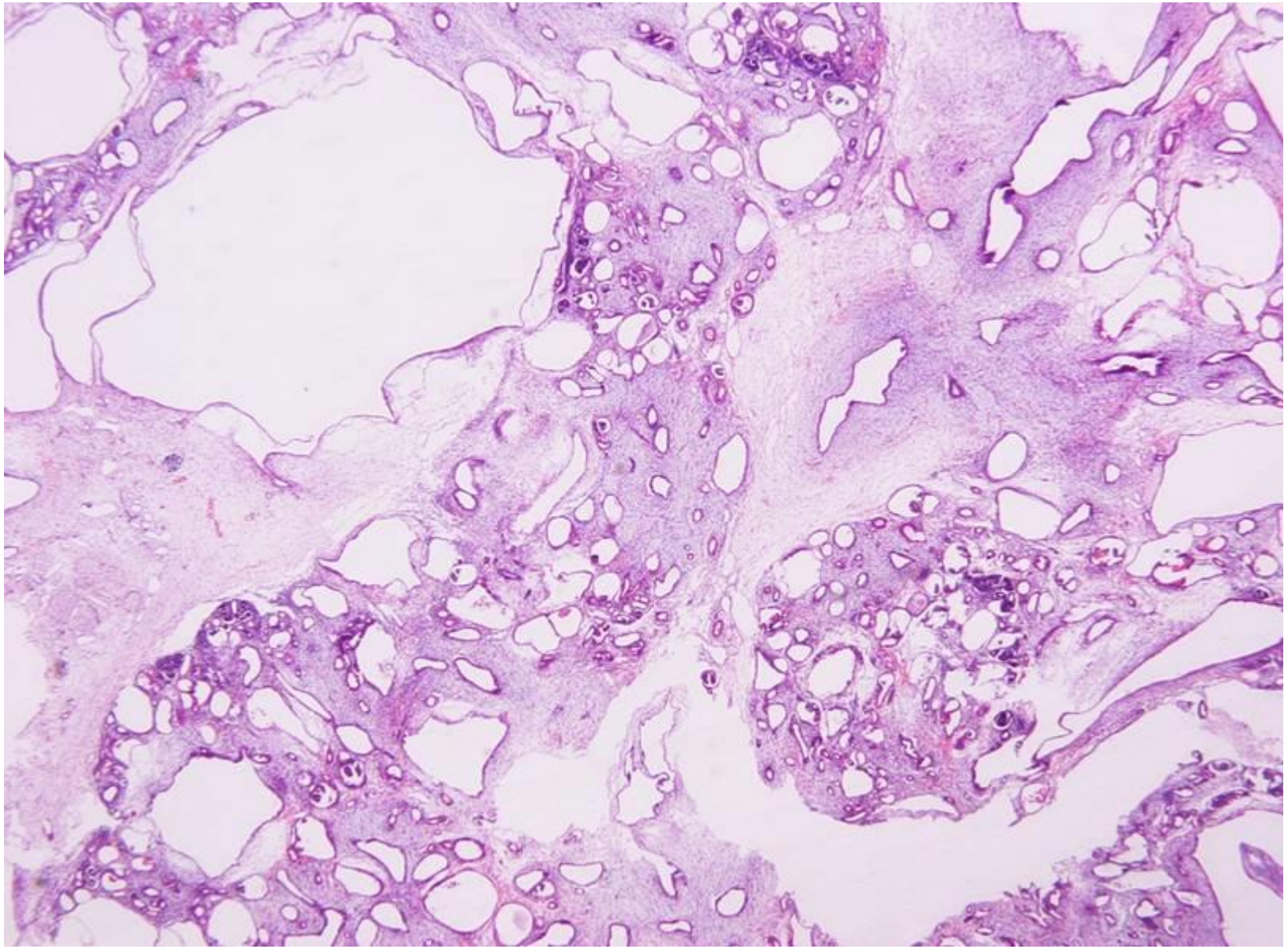


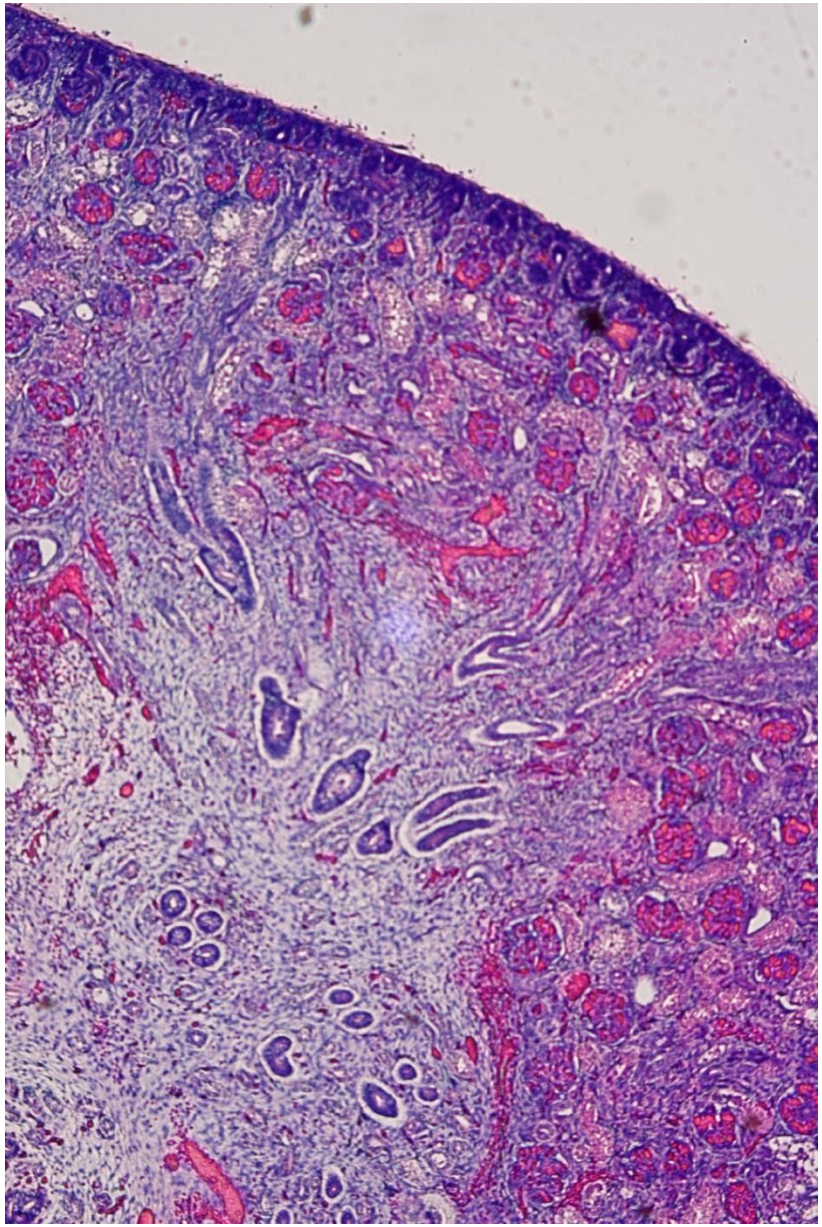


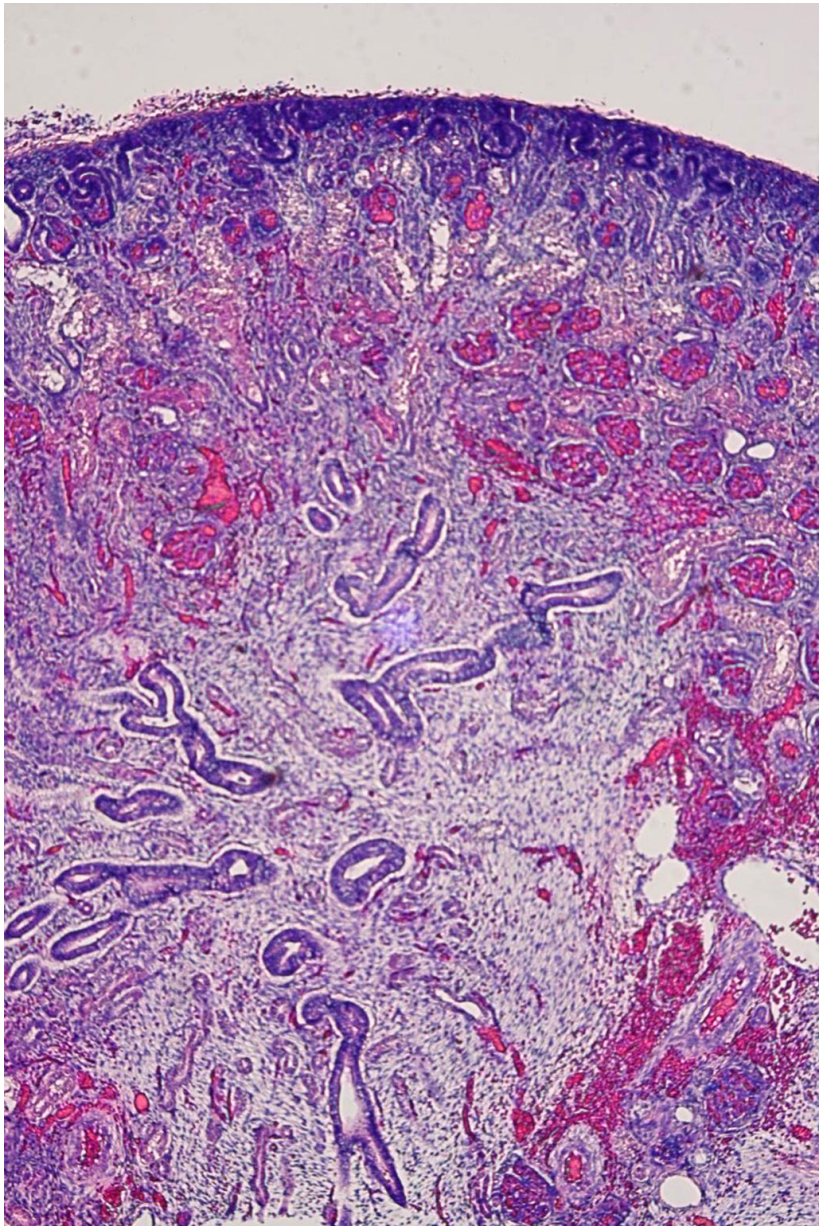
- CC agenesis

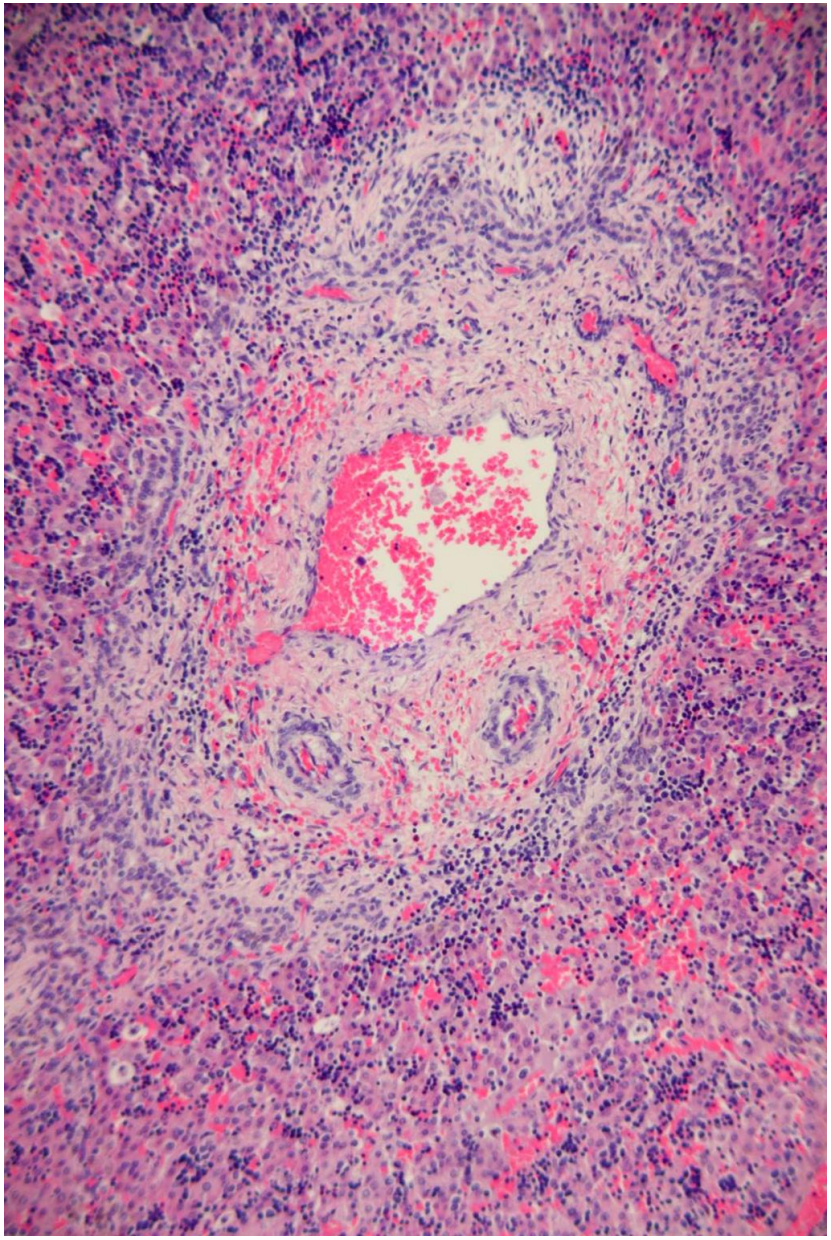


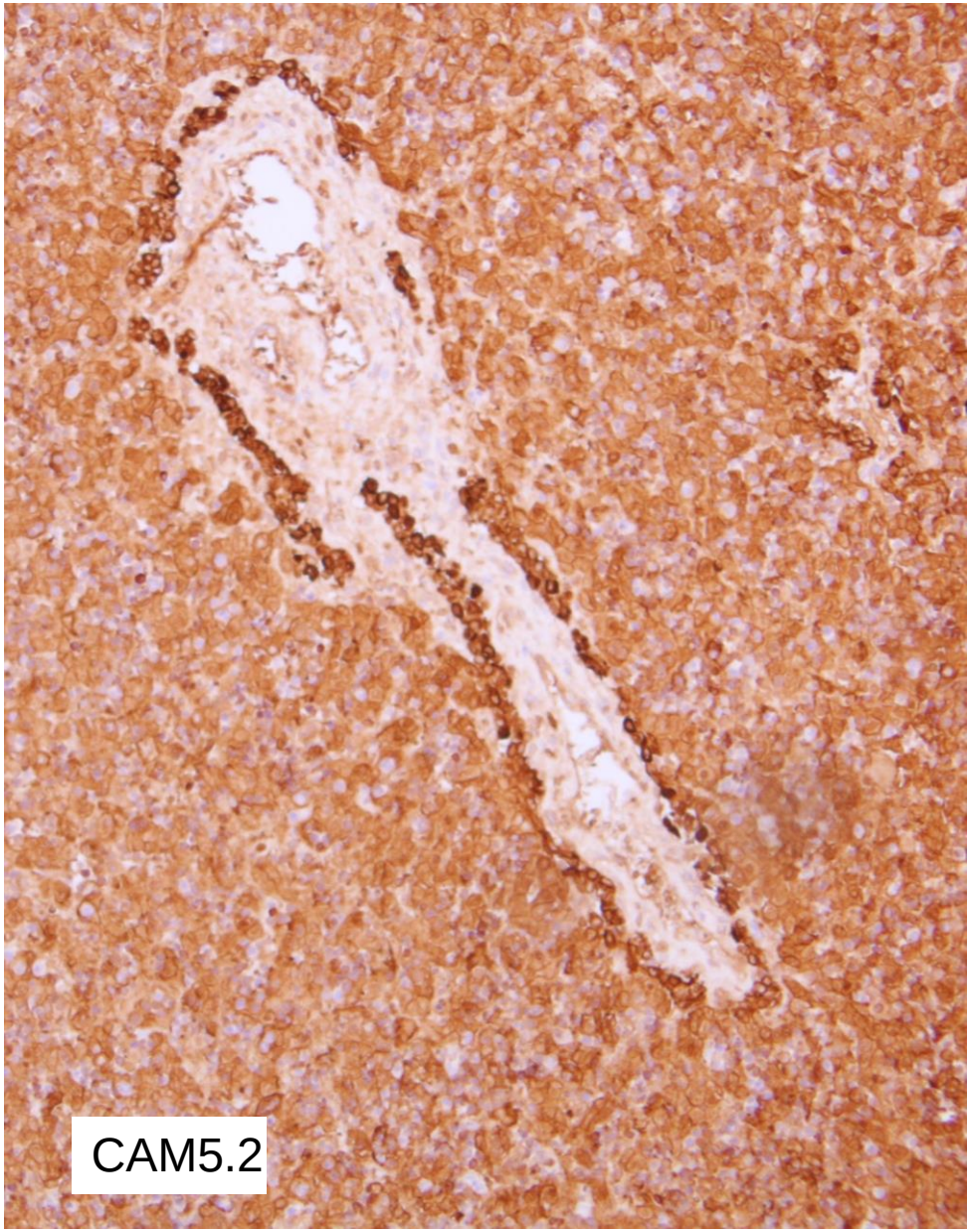
Renal dysplasia



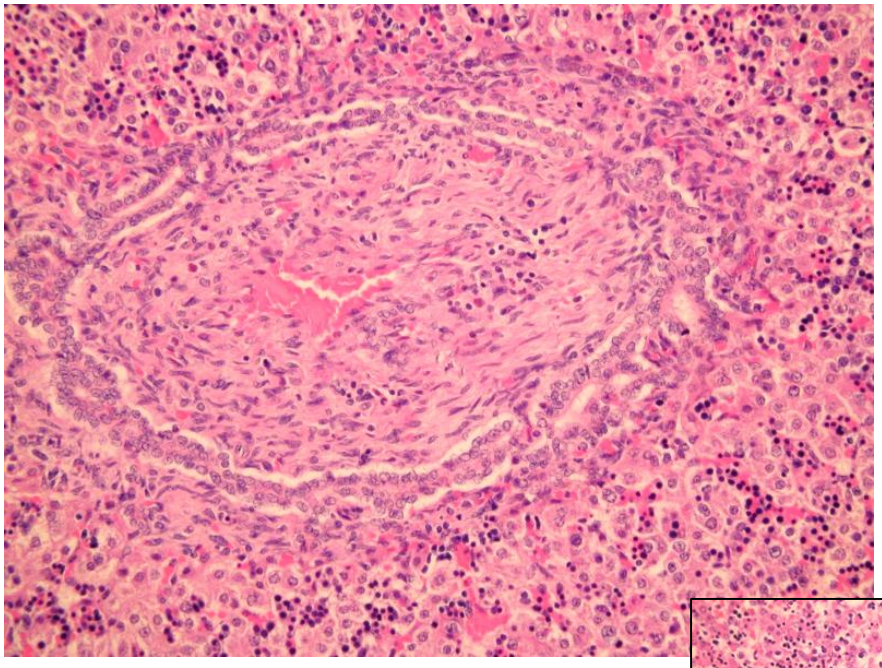


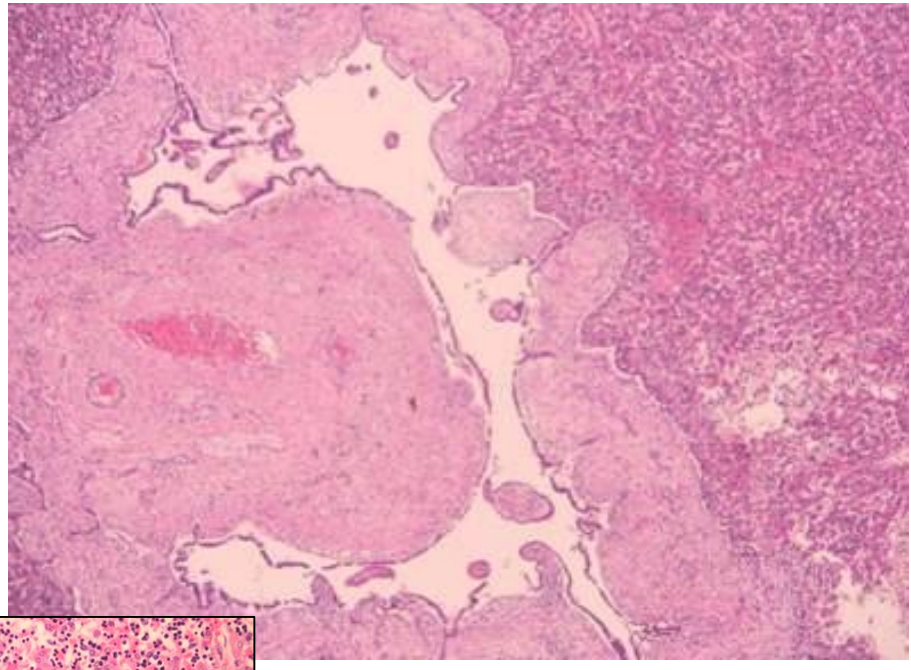


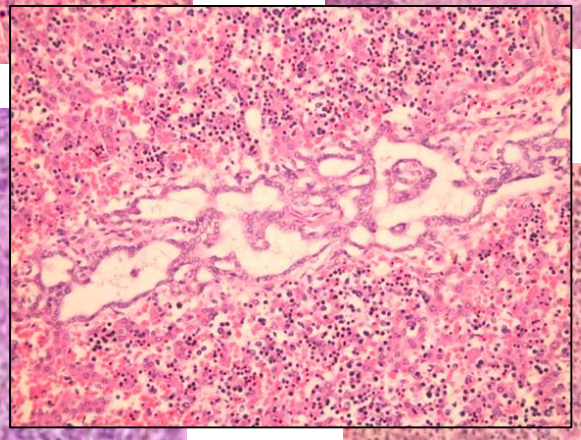




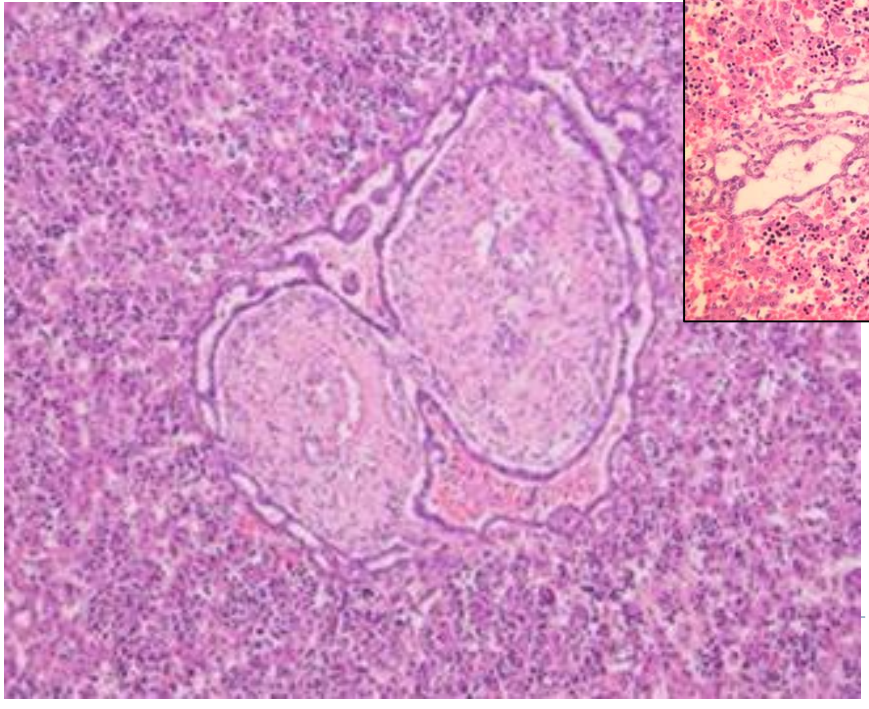
Persisting Ductal

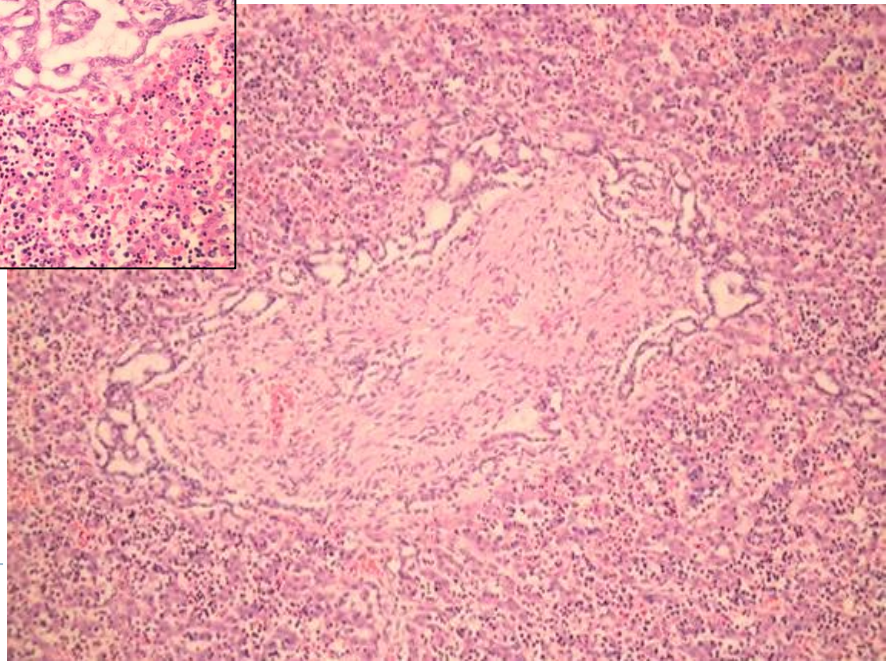


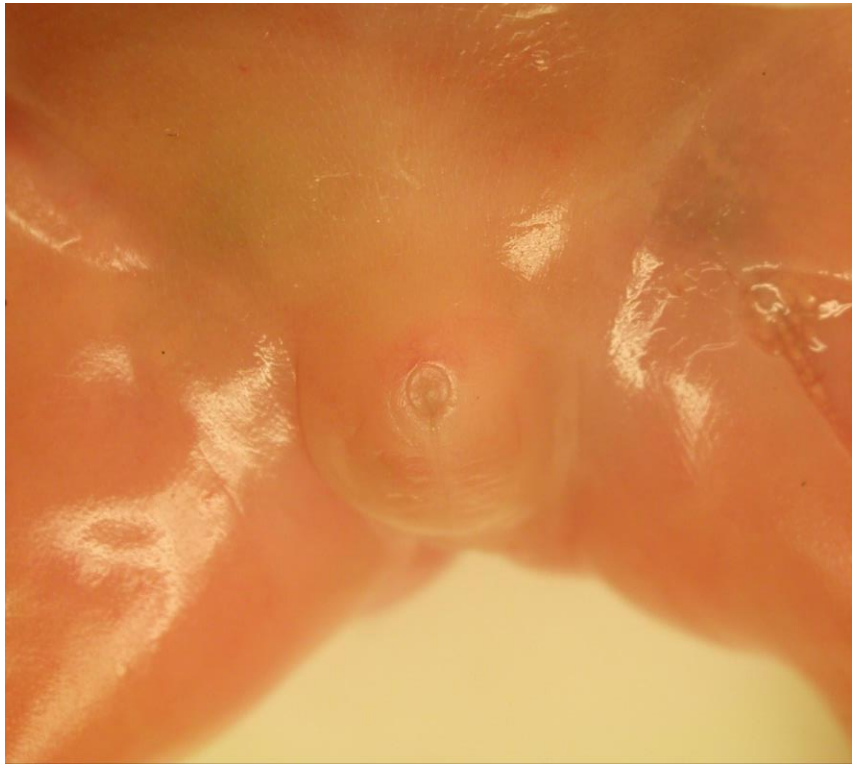


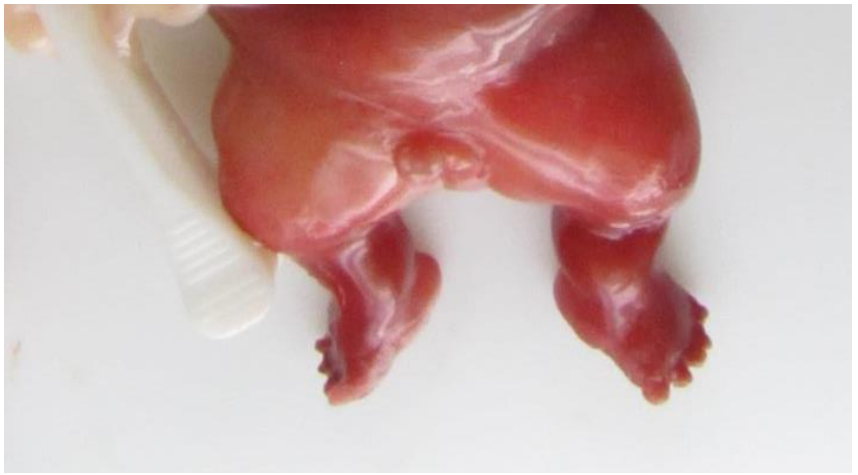


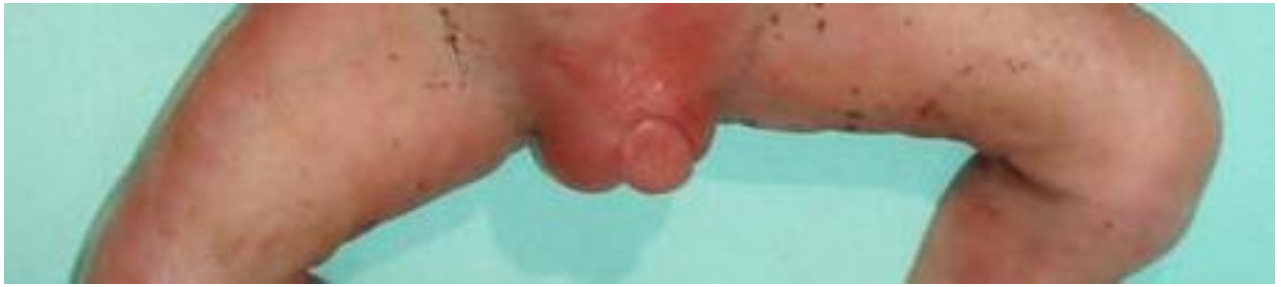
Ductal Plate Malformation



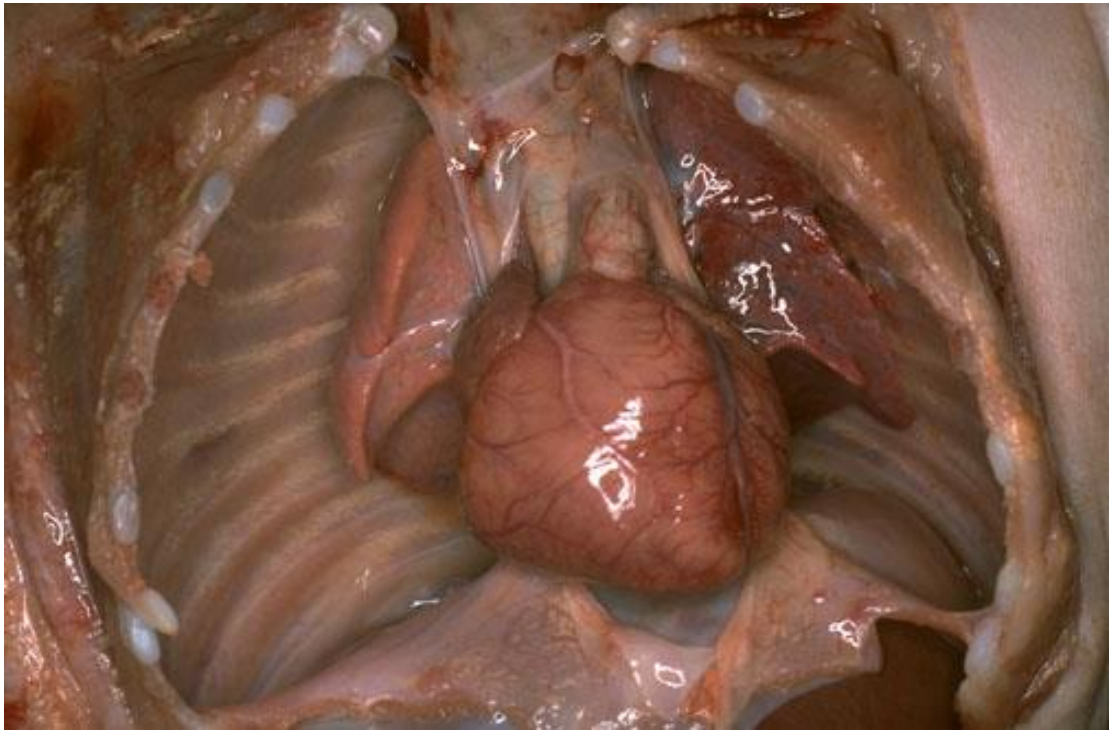








Abnormal genitalia



Pulmonary hypoplasia

CILIARY CHONDRODYSPLASIAS

Prognosis

The most severe **thoracic constriction** is usually seen in SRPs and Jeune-ATD.

SRPs are always lethal, due to cardiorespiratory failure.

ATD-Jeune shows 60% perinatal mortality.

Ellis van Creveld may be compatible with life, but frequently shows severe heart defects.

MZSDS and CED have a milder thoracic constriction but a higher rate of **renal, retinal and liver disease** that may lead to severe morbidity or mortality in childhood.

SHORT-RIB ± POLYDACTYLY SYNDROMES (SRP)

SHORT-RIB THORACIC DYSTROPHIES (SRTD)

	Gene locus
SRP type 1/3 (Saldino-Noonan / Verma-Naumoff)	*DYNC2H1, IFT80, WDR34?*
SRP type 2 (Majewski)	*NEK1, DYNC2H1*
SRP type 4 (Beemer-Langer)	--
SRP type 5 similar to type 3 with acromesomelic hypomineralization and camptomelia	*WDR35*

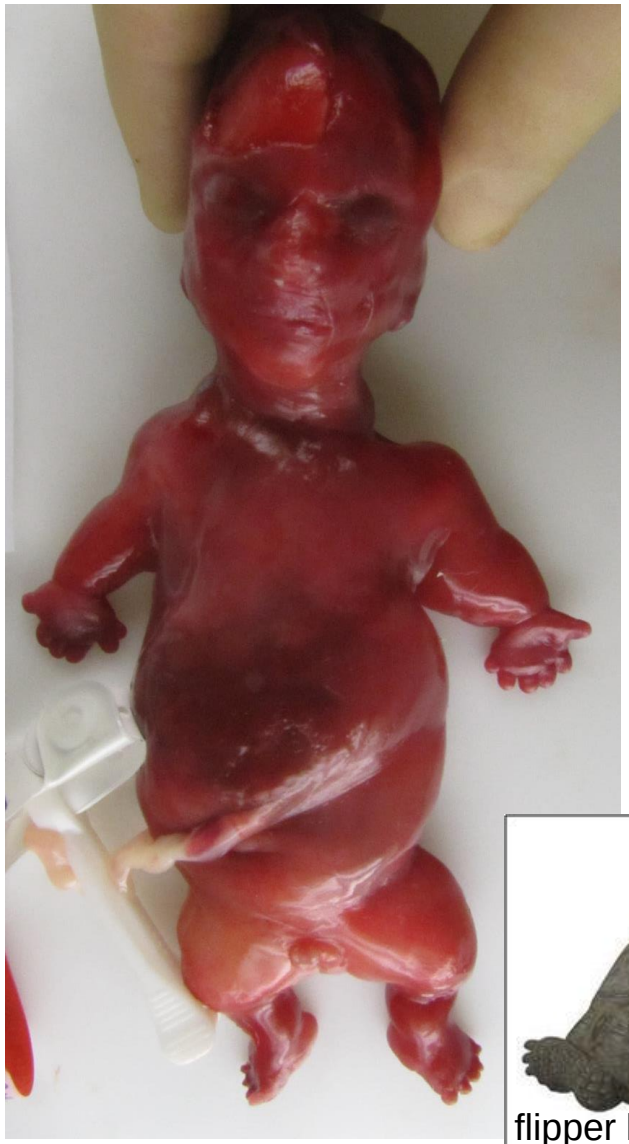
The various phenotypic forms of SRTDs differ by **visceral malformation** and **metaphyseal** appearance.

Overlapping phenotype between all types – Cases that could not fit in one particular type

Severe thoracic constriction
Lethal in the early neonatal period

characteristic of ciliary diseases

SRP-I Saldino-Noonan



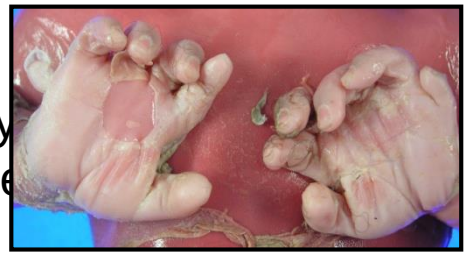
SRP 1

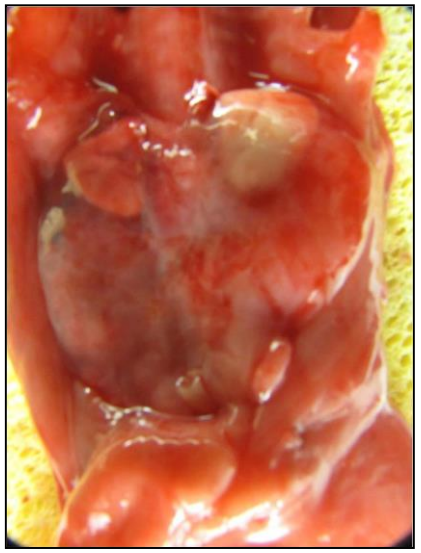
postaxial polydactyly

hydropic appearance

small thorax

micromelia



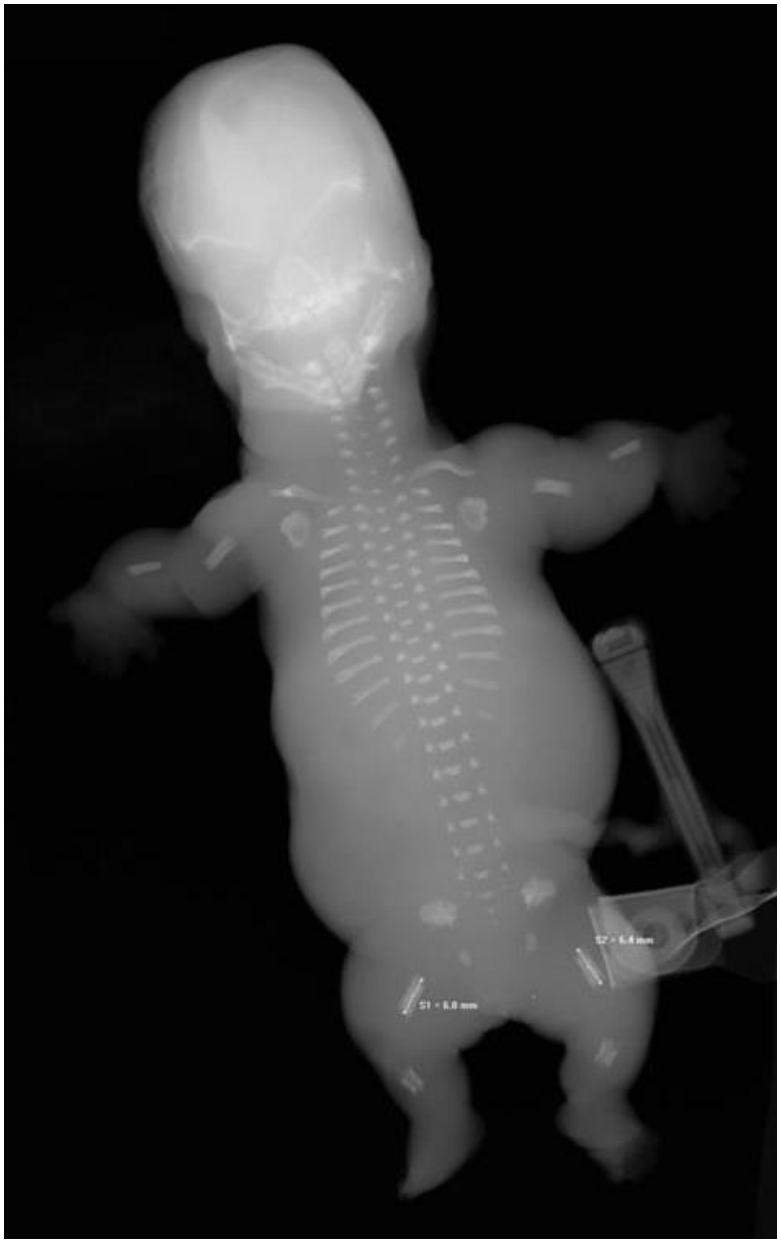


- polycystic kidneys, liver DPM
- cardiac and gastrointestinal defects
- genital defects common

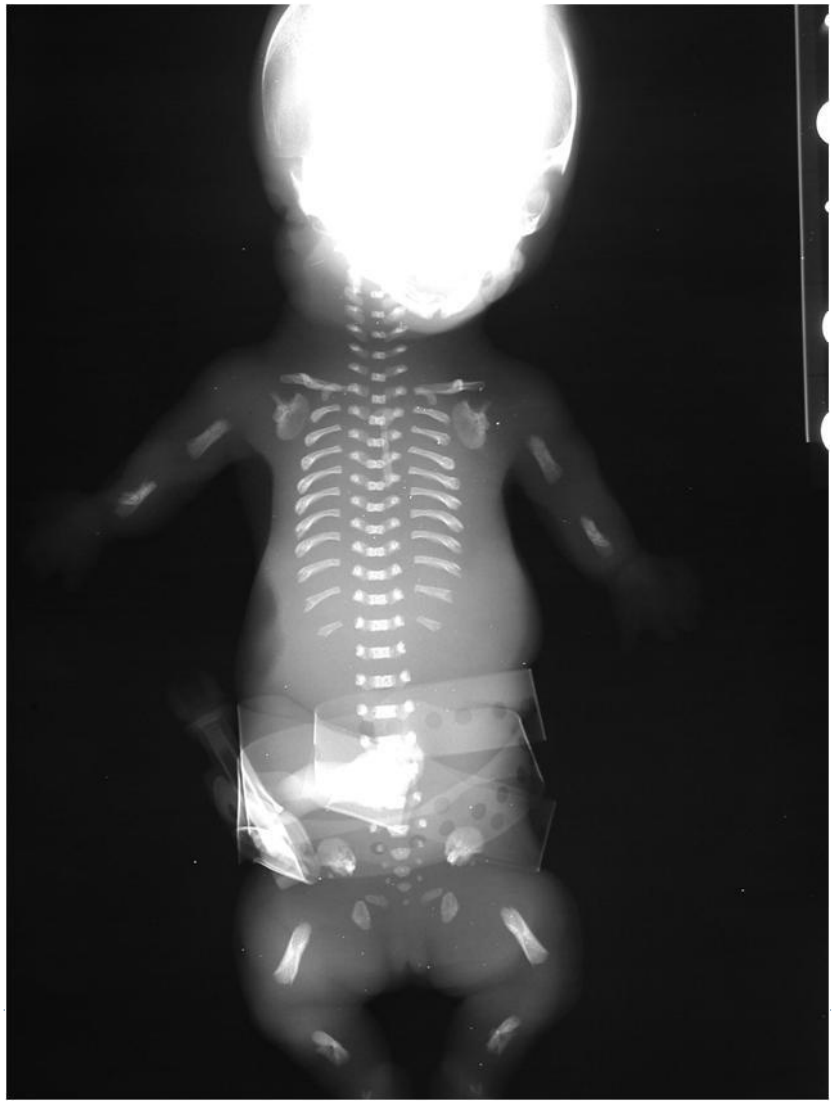
flipper limb

- The typical hallmark of SRPS-I is extreme micromelia resulting in ‘flipper-like’ limbs

SRP-I Saldino-Noonan

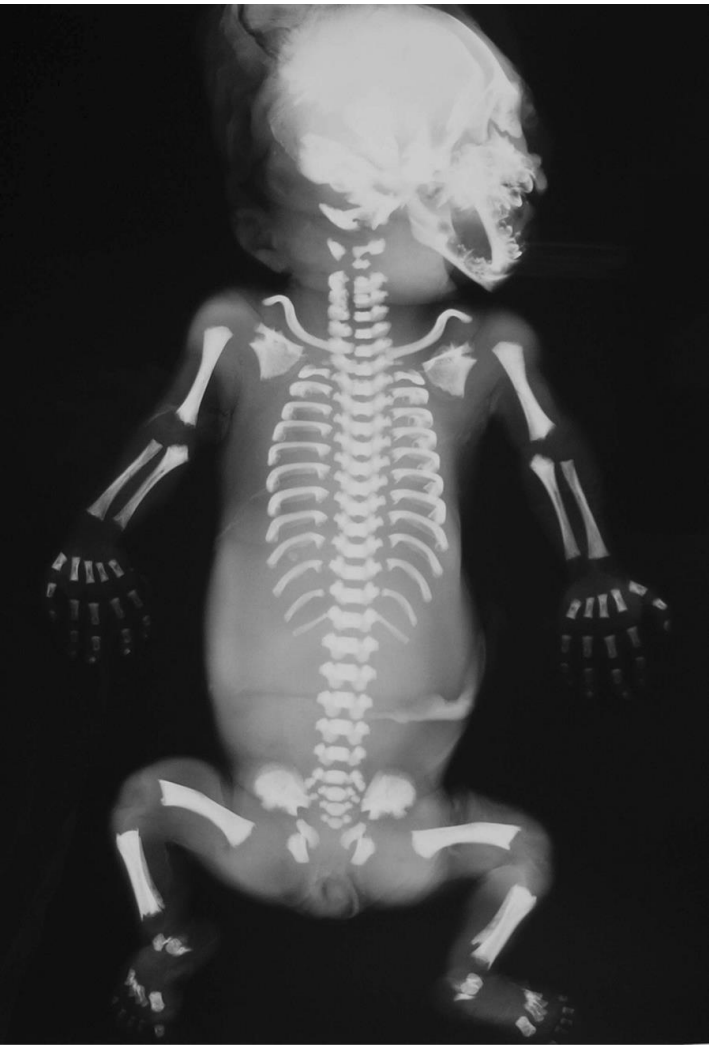


- short horizontal ribs
- platyspondyly
- very short tubular bones with metaphyseal spurs
- ossification defects of hands and feet
- small ilia with flattened, trident acetabular roofs



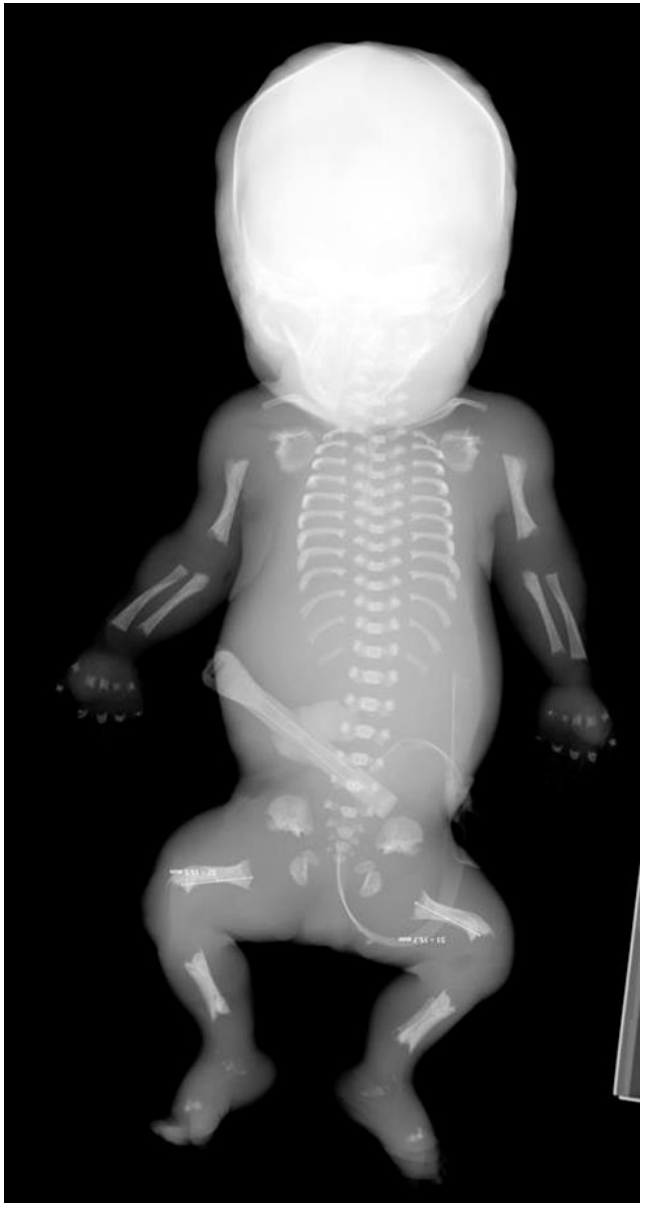
- extremely short tubular bones

SRP-3 Verma-Naumoff



- cleft lip/palate
- urogenital defects less common than SRP-1

SRP-3 with brachydactyly (STD8



Skeletal Dysplasias. In: The Pediatric and Perinatal Autopsy Manual. MC Cohen, I Scheimberg, Eds. Cambridge University Press 2014

Micromelia is less severe than

marked longitudinal metaphyseal spurs

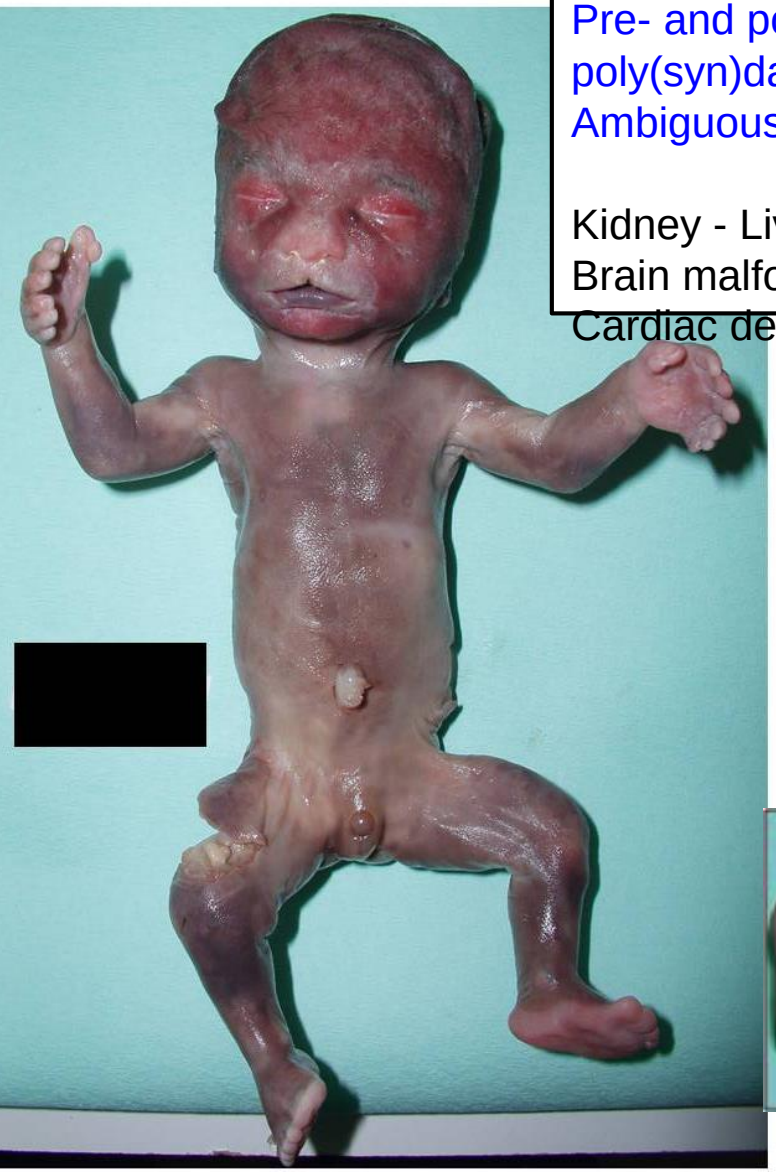
SRP-2 Majewski overlapping with OFD-4 (Mohr-Majewski)

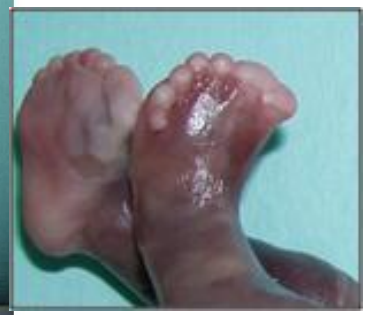
Cleft or pseudo-cleft lip/palate
Pre- and postaxial poly(syn)dactyly
Ambiguous genitalia common

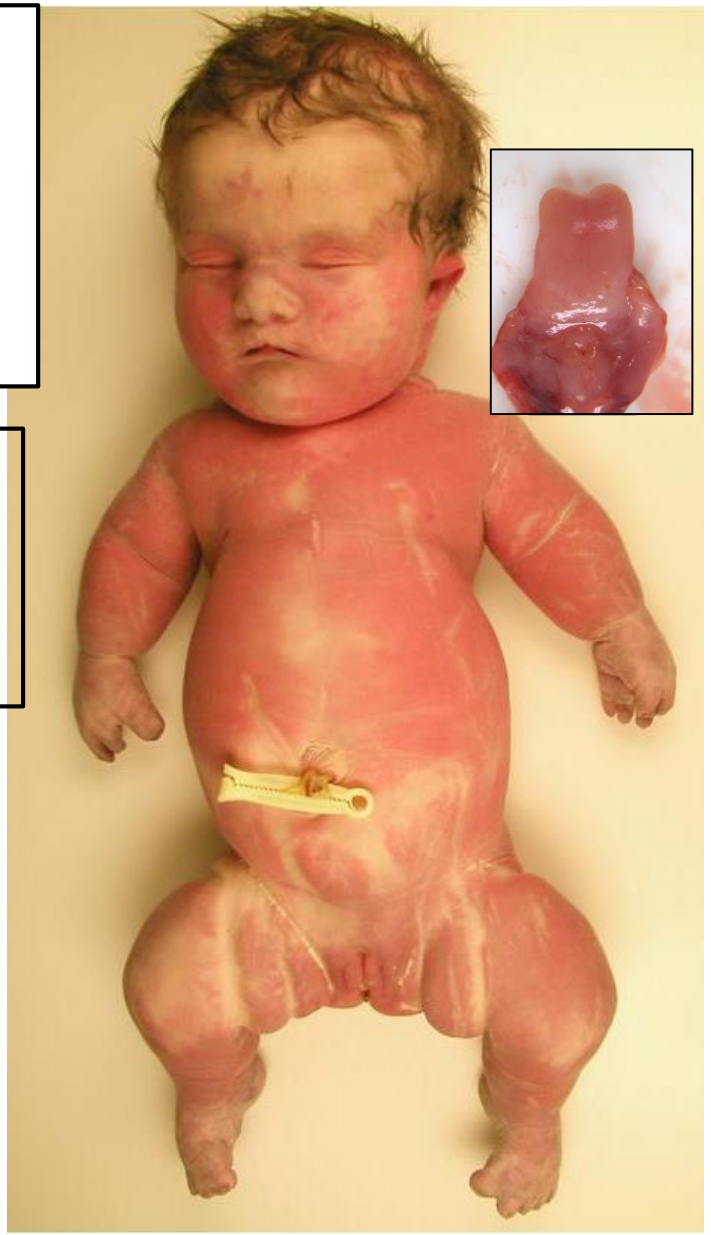
Kidney - Liver involvement
Brain malformations
Cardiac defects

laryngeal malformations

bifid tongue or frenula

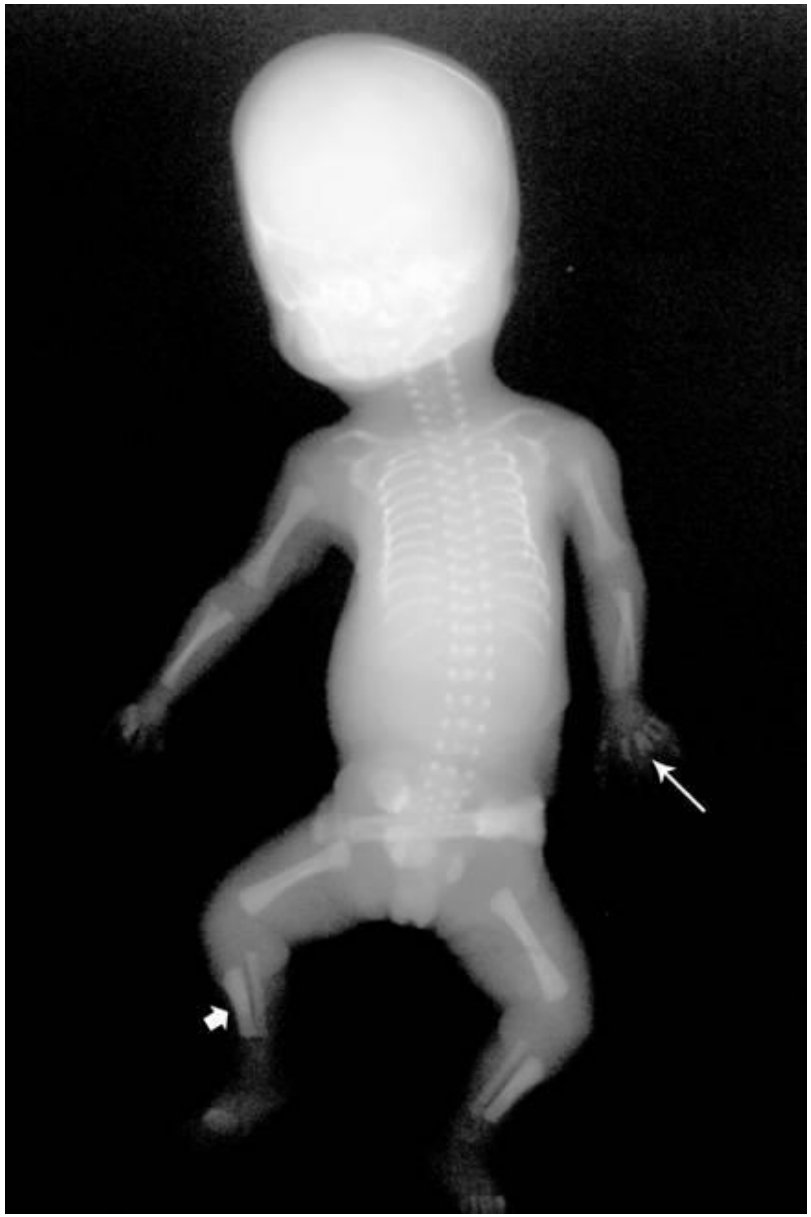






in OFDs: bifid or lobulated tongue

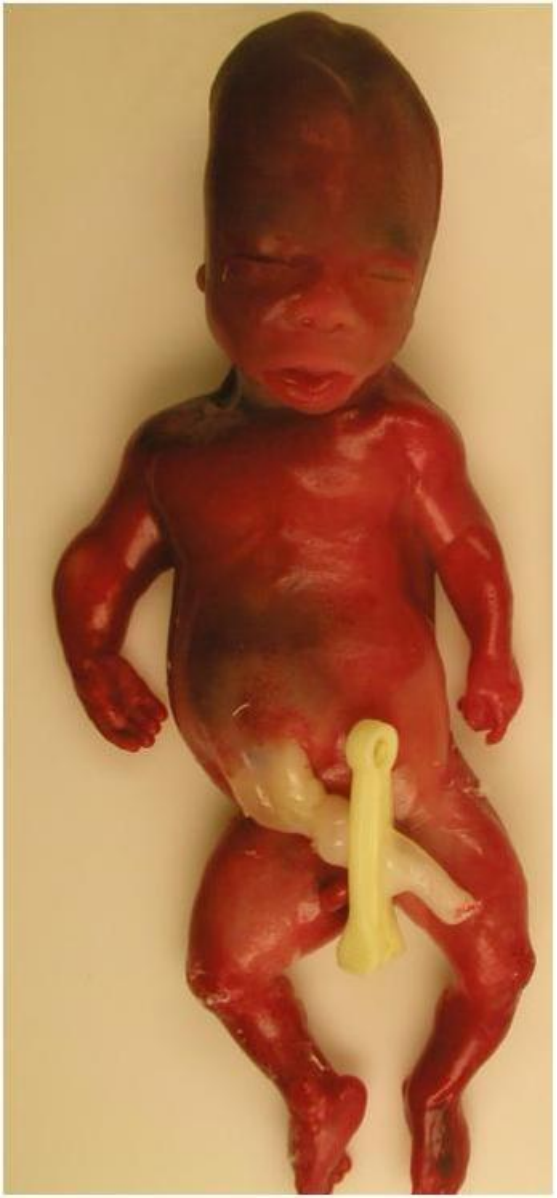
SRP-2 Majewski



V-shaped metacarpals
(osseous syndactyly)

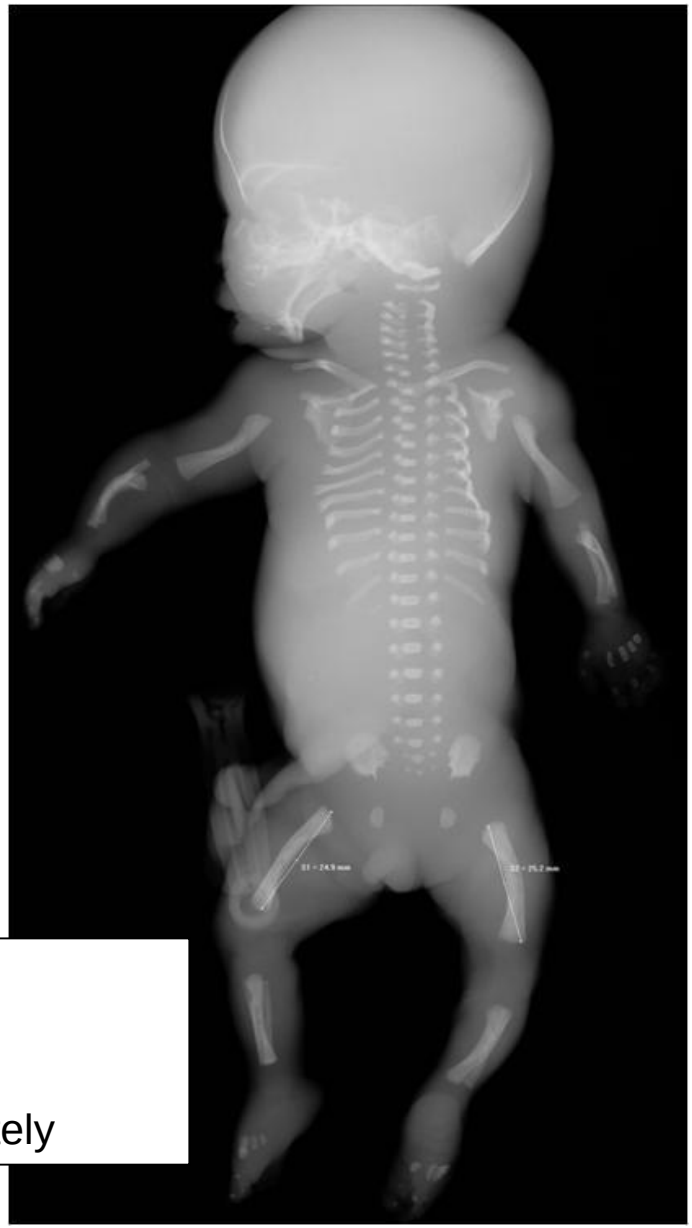
Smooth metaphyses
The tibia is shorter than the fibula.

SRP-4 Beemer-Langer



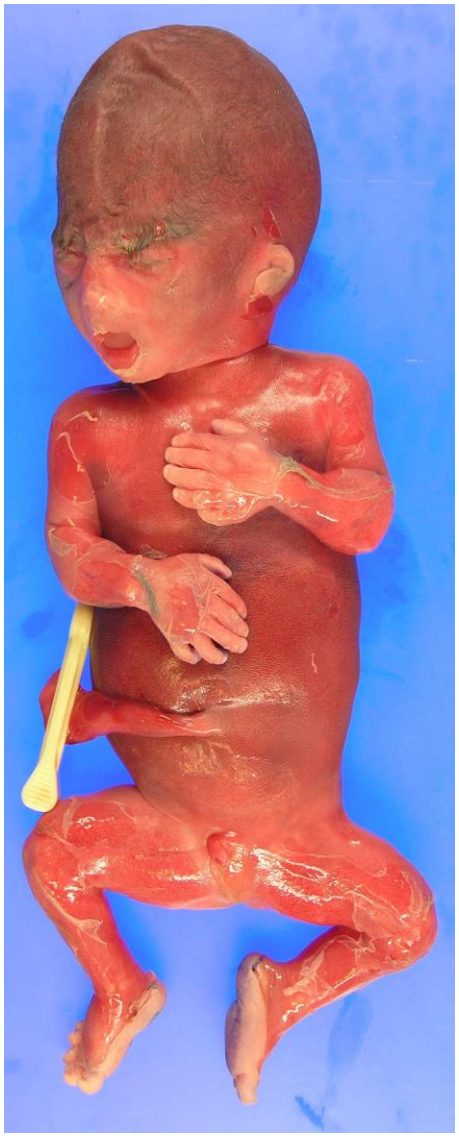
polydactyly often absent

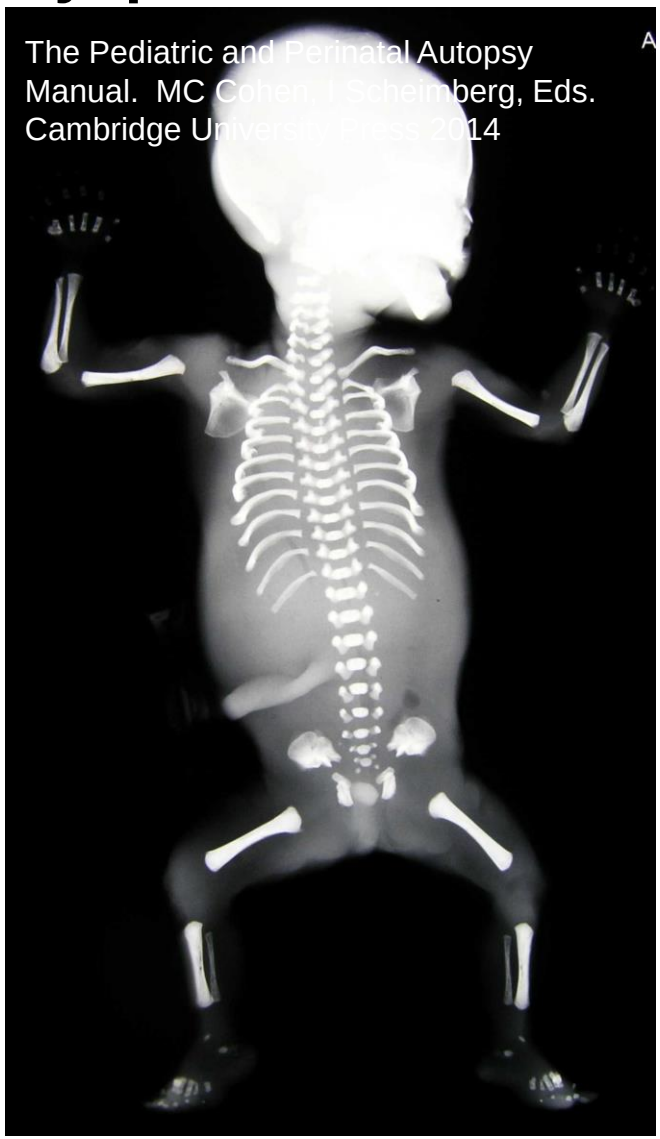
orofacial clefts
kidney - liver involvement
brain malformations
cardiac defects

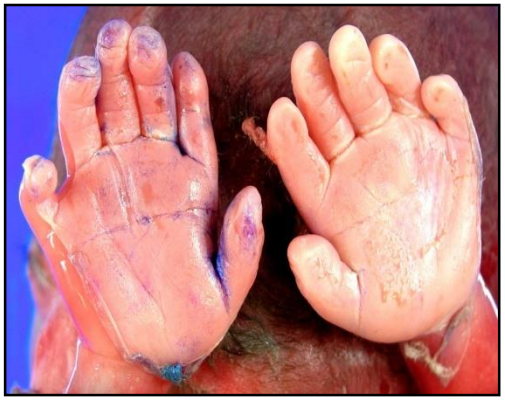


X-ray
Smooth metaphyses
Bowed radius and ulna
The tibia is **not** disproportionately short.

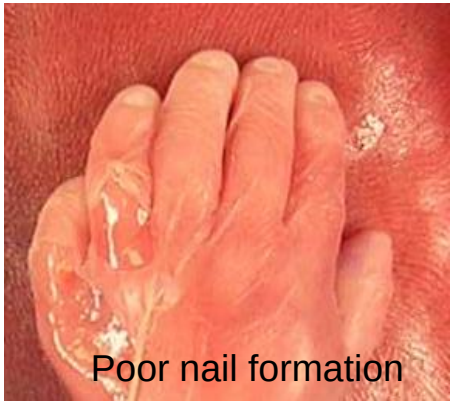
Ellis van Creveld Chondroectodermal Dysplasia



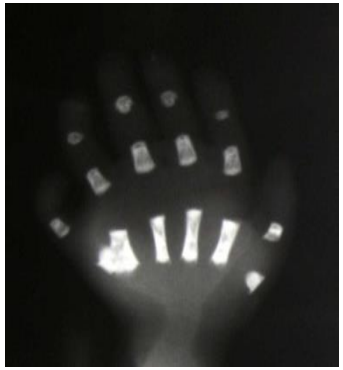




Postaxial hexadactyly is constan



Poor nail formation



- Cardiac defects are common.

V-shaped metacarpals common in EvC and SRP-2

JEUNE ATD

IFT80, IFT40, IFT172
DYNC2H1
WDR19, WDR60, WDR34
TTC21B
CEP120

Genetically heterogeneous disorder.

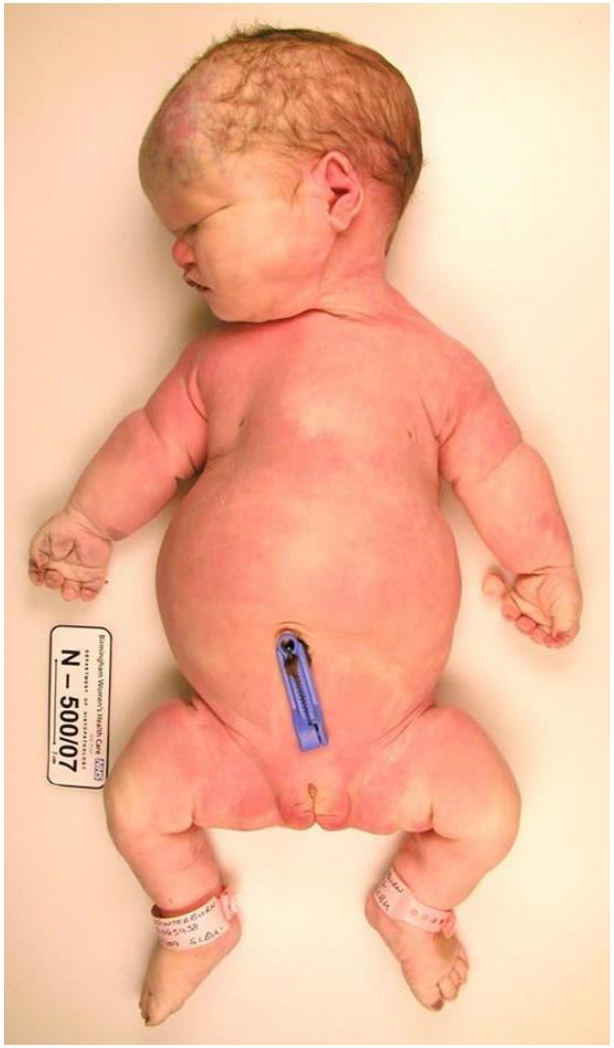
Compared to SRPs, the phenotype is less severe.

Respiratory problems account for most of the mortality in JATD ranging from 20–60%,
but patients seem to somewhat “grow out” of the respiratory phenotype.

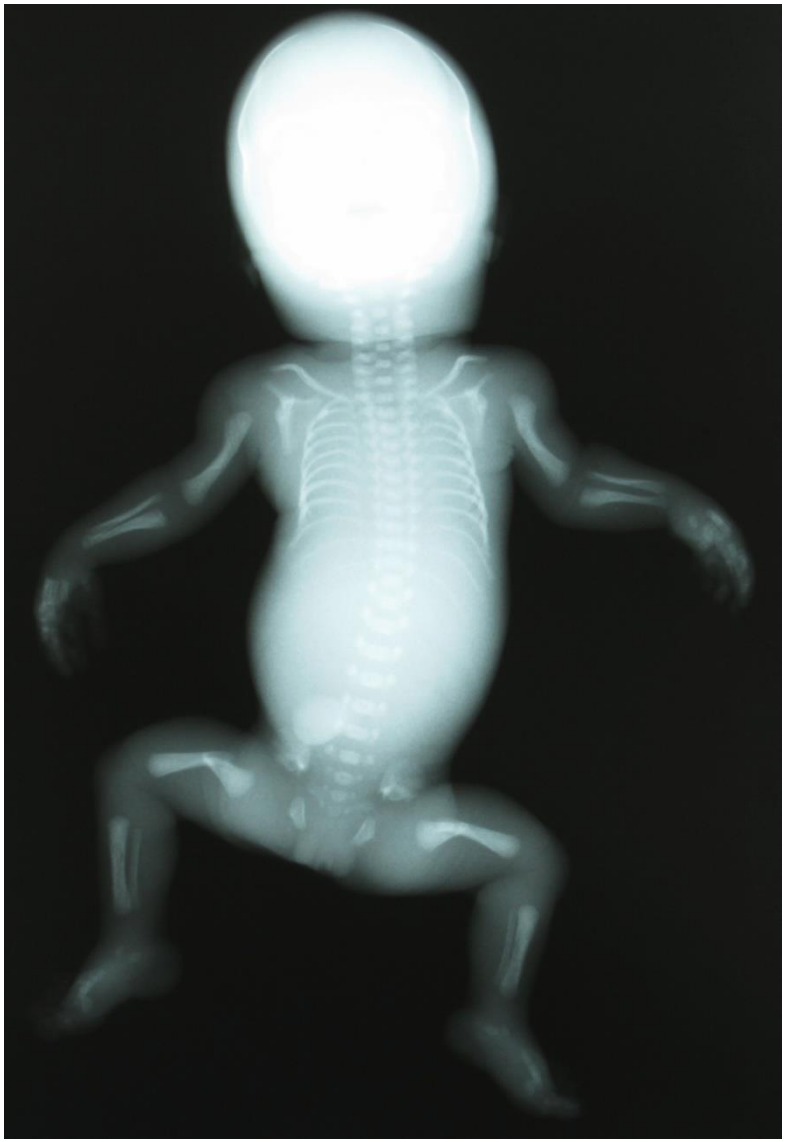
End-stage renal disease in childhood due to NPHP-like (and rarely cystic) kidney involvement affects less than 20% of all JATD.
IFT140 and *IFT172* mutations can predict this phenotype with nearly 100% probability.

Patients with mutations in one of those two genes also develop retinal degeneration.

Pancreatic lesions, elevated liver enzymes and brain malformations can also occur in JATD.



JEUNE ATD



Bell-shaped thorax
Less severe restriction than SRPs

Normal vertebrae
Trident acetabulae
Smooth metaphyses

Polydactyly is infrequent.

- Note: the femurs are frequently angulated.

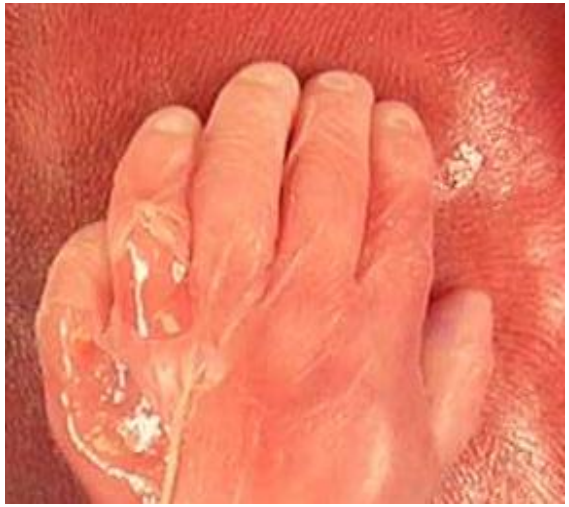
JATD vs **EvC**

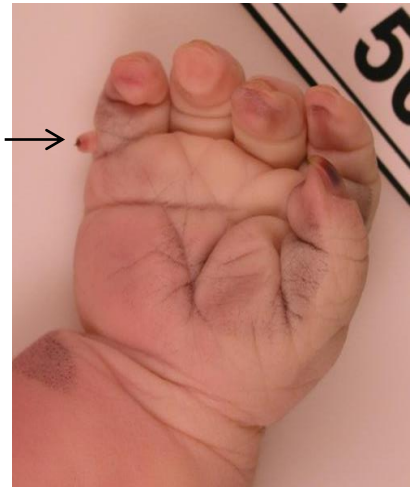
In JATD cases with polydactyly, differentiation from Ellis-van Creveld syndrome may not be possible on radiologic grounds alone.

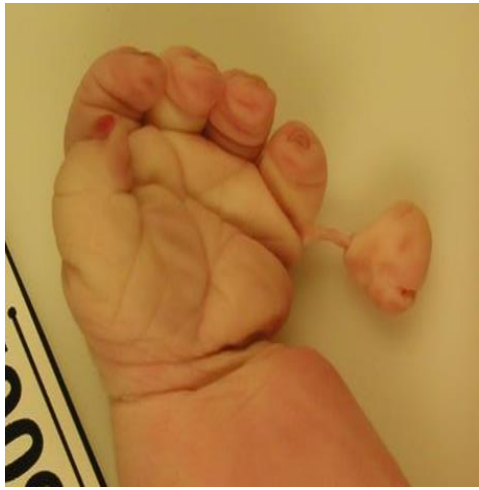
Polydactyly is an inconstant feature of JATD and, when present, usually also affects the feet. In contrast, polydactyly of the hands is a constant feature in EVC, but the feet are uncommonly affected.

The main visceral abnormality in JATD is renal, whereas it is cardiac in EVC.

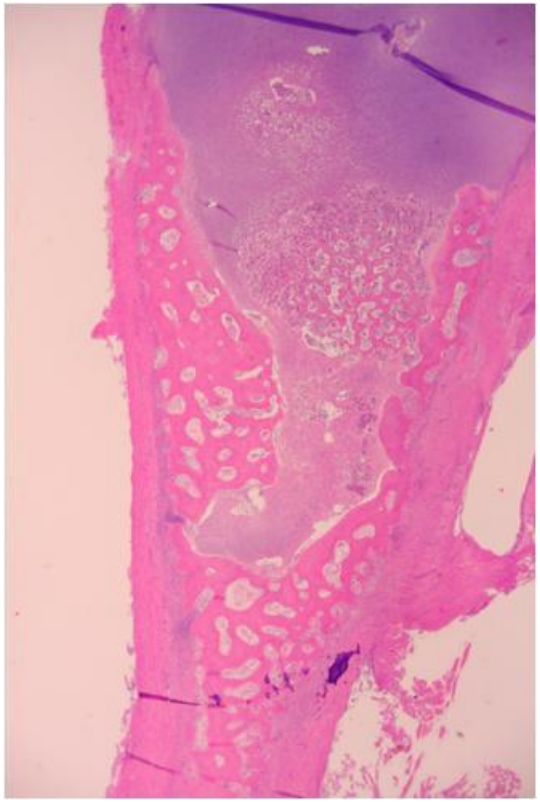
Ectodermal defects are common in EVC and not a feature of JATD.

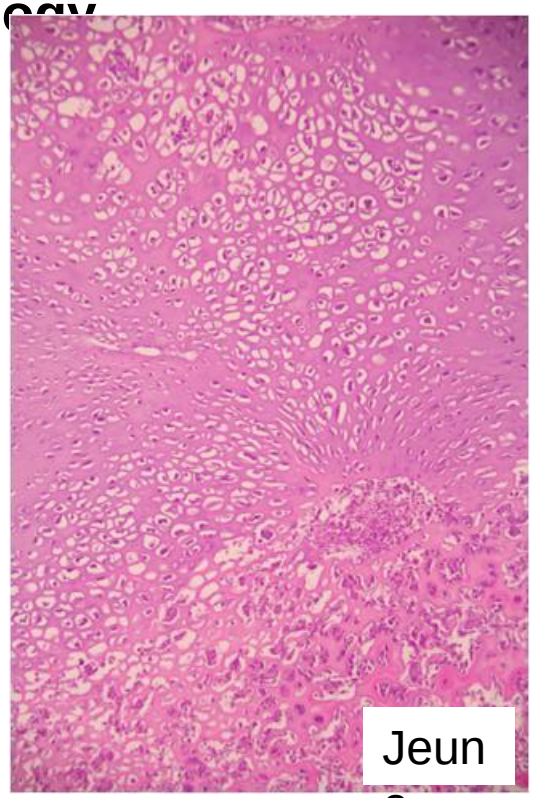




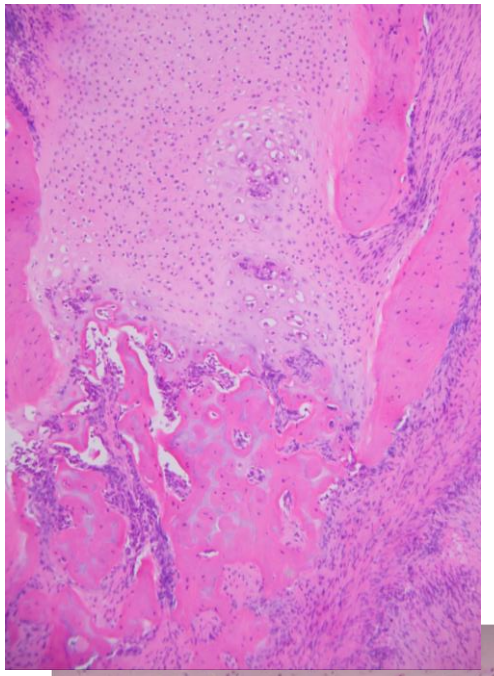


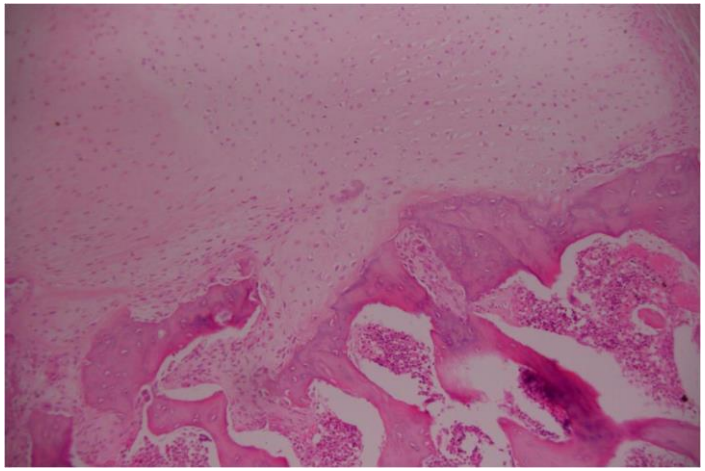
Short Rib syndromes: **Histology**

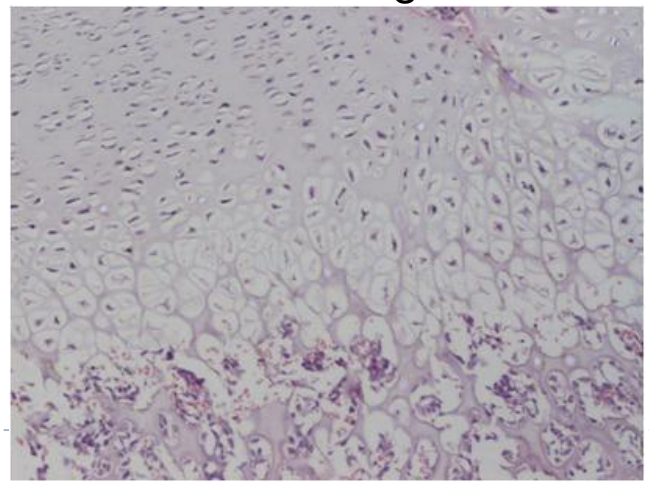


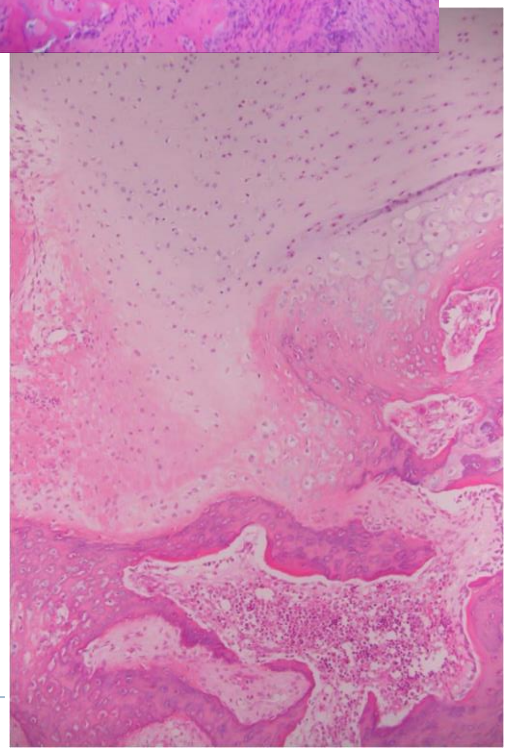


Jeune







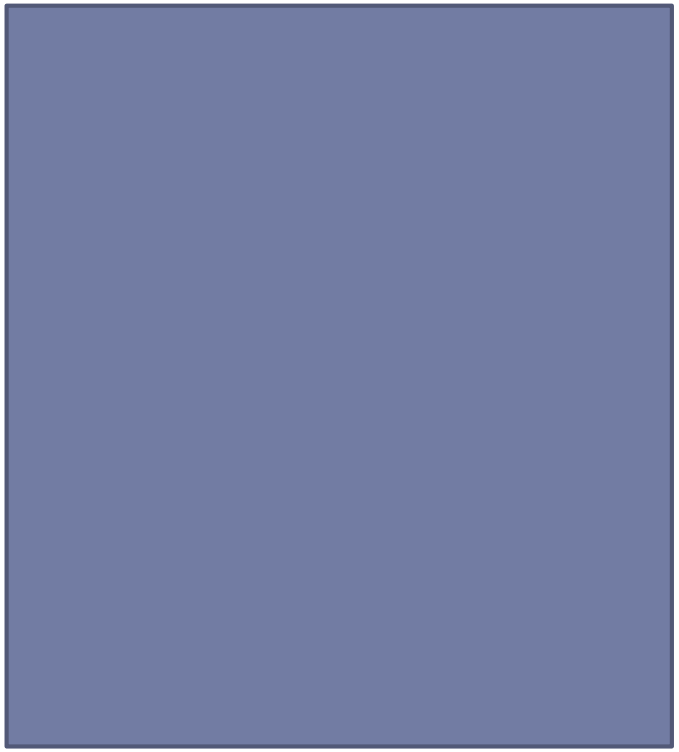


- Variably:
  abnormal physeal border; retardation, disorganisation of the growth plate; disordered

CRANIOECTODERMAL DYSPLASIA (CED)
Sensenbrenner syndrome

Patients with CED present characteristic craniofacial dysmorphic features and ectodermal defects including nail, hair and teeth abnormalities.

Dolichocephalus and frontal bossing resulting from **craniosynostosis** of the sagittal suture, present at birth.



The disease allows survival to childhood but is often complicated by early onset renal insufficiency due to a Nephronophthisis-like renal phenotype with the histological picture of tubulointerstitial nephritis and microscopic glomerular and tubular cysts.

Heart defects and retinal dystrophy are less frequent .

CED: FAMILY CASE

TOP of 2 female fetuses – 23 wk and 19wk

for U/S findings and family history

USS findings:

- Increased nuchal tranlslucency - Narrow thorax
- Short long bones [< 5th c] - Mesomelic [< 3rd c]
- Posterior fossa cyst
- Small kidneys with echogenic heterogeneity

Family history:

1 affected 5 yr-old female child

At birth: "acromesomelic dysplasia" with craniosynostosis

severe renal insufficiency

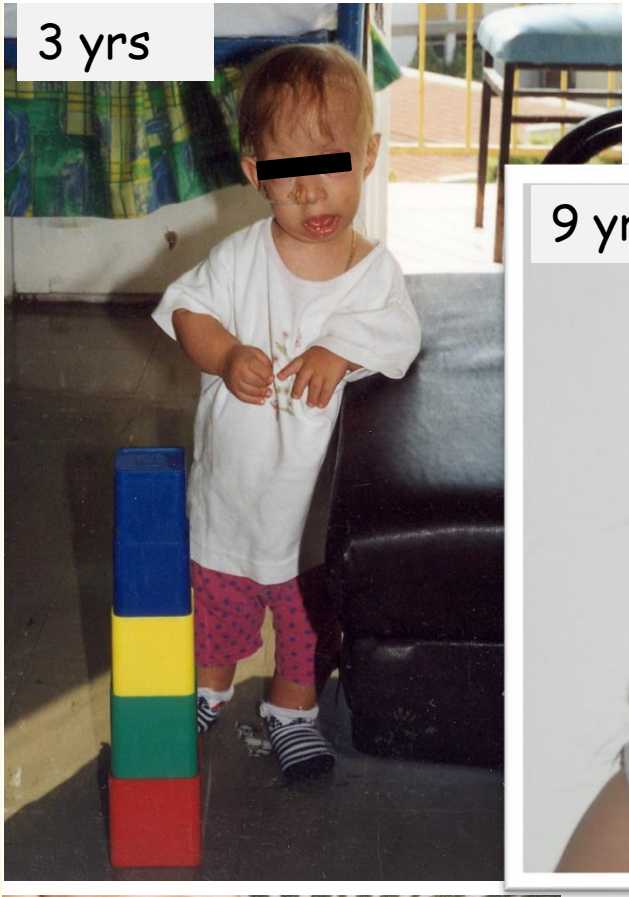
- Growth restricted
- Short limbs

- Frontal bossing and protruding eyes (craniosynostosis)
- Retrognathia
- Brachydactyly
- 2-3 partial toe-syndactyly

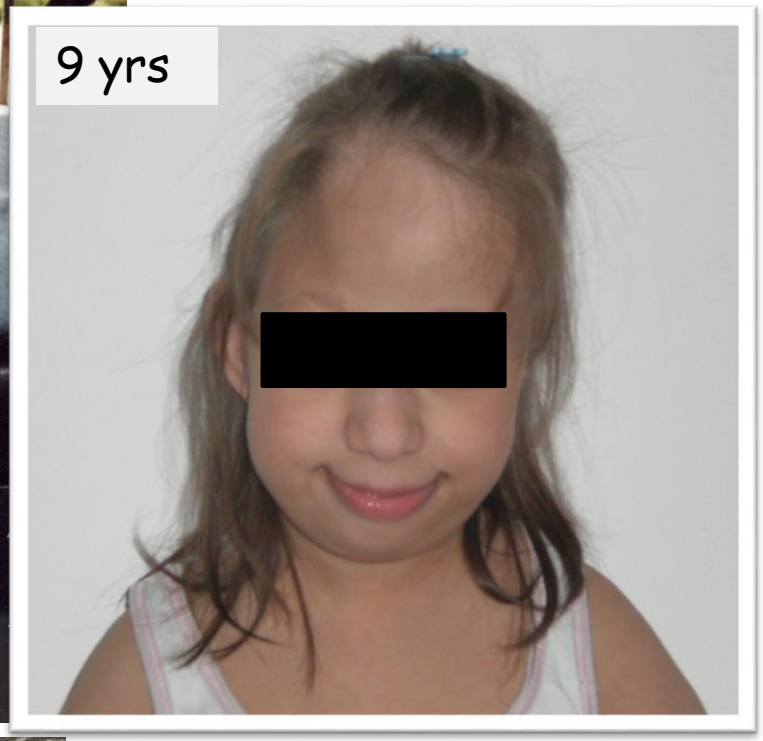
- Fine sparse hair
- Hypodontia
- Reduced sweating

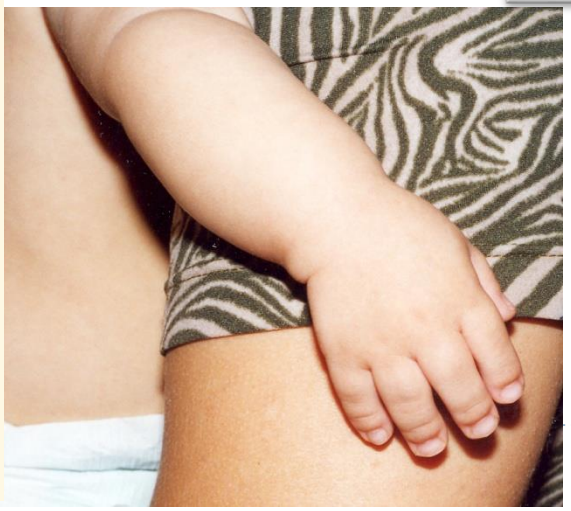
- Large cisterna magna on MRI

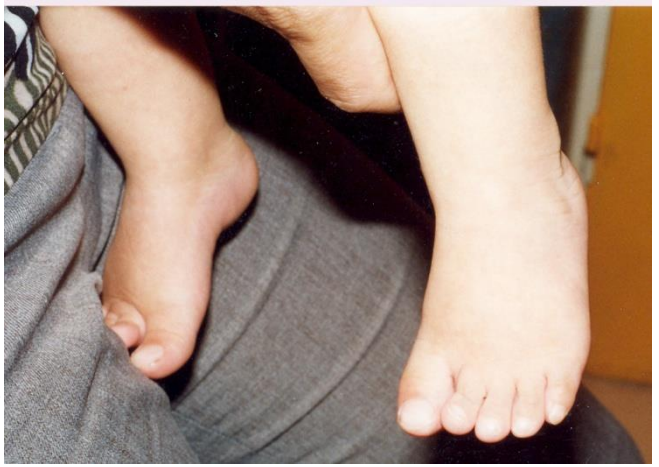
- Chronic renal failure on dialysis



46, XX

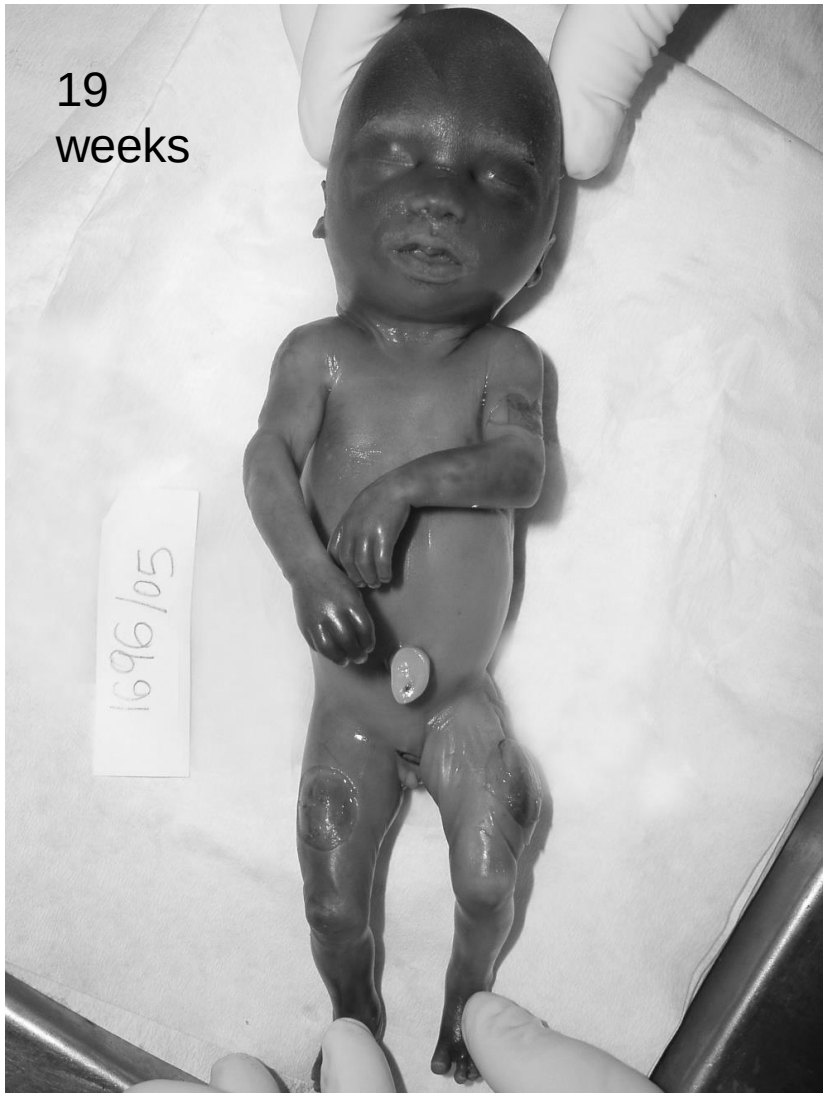


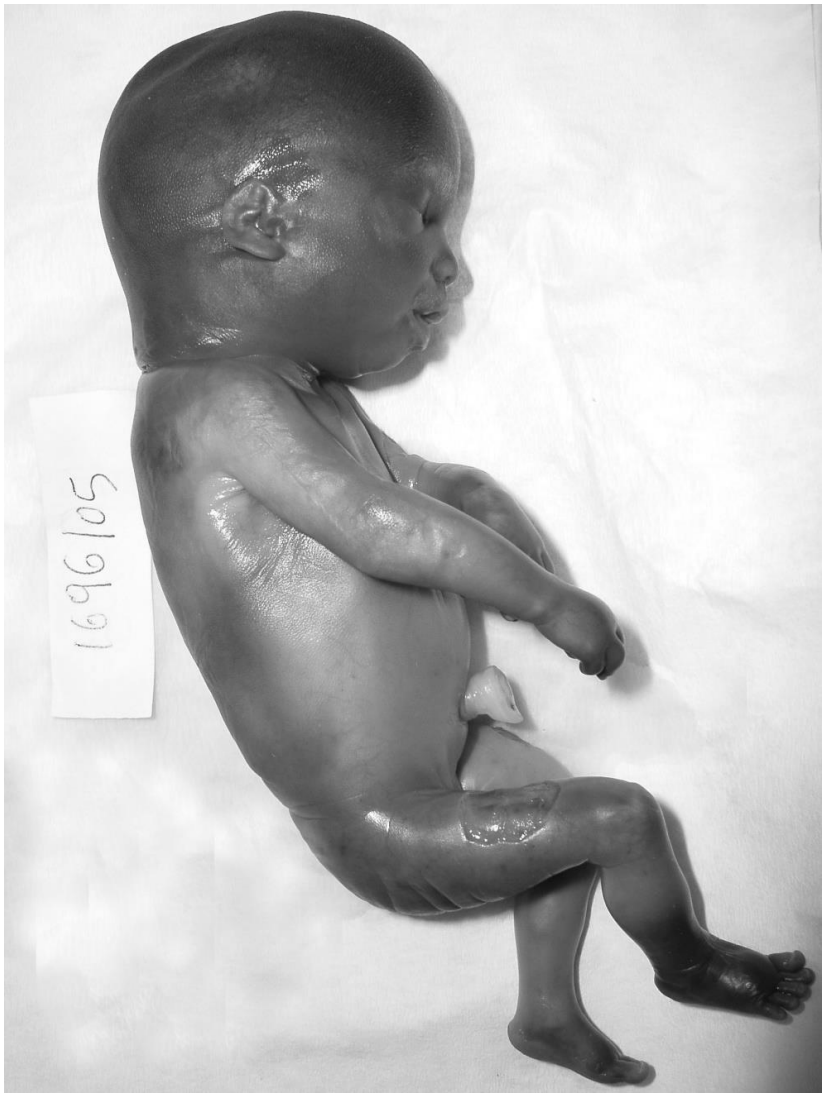




CED

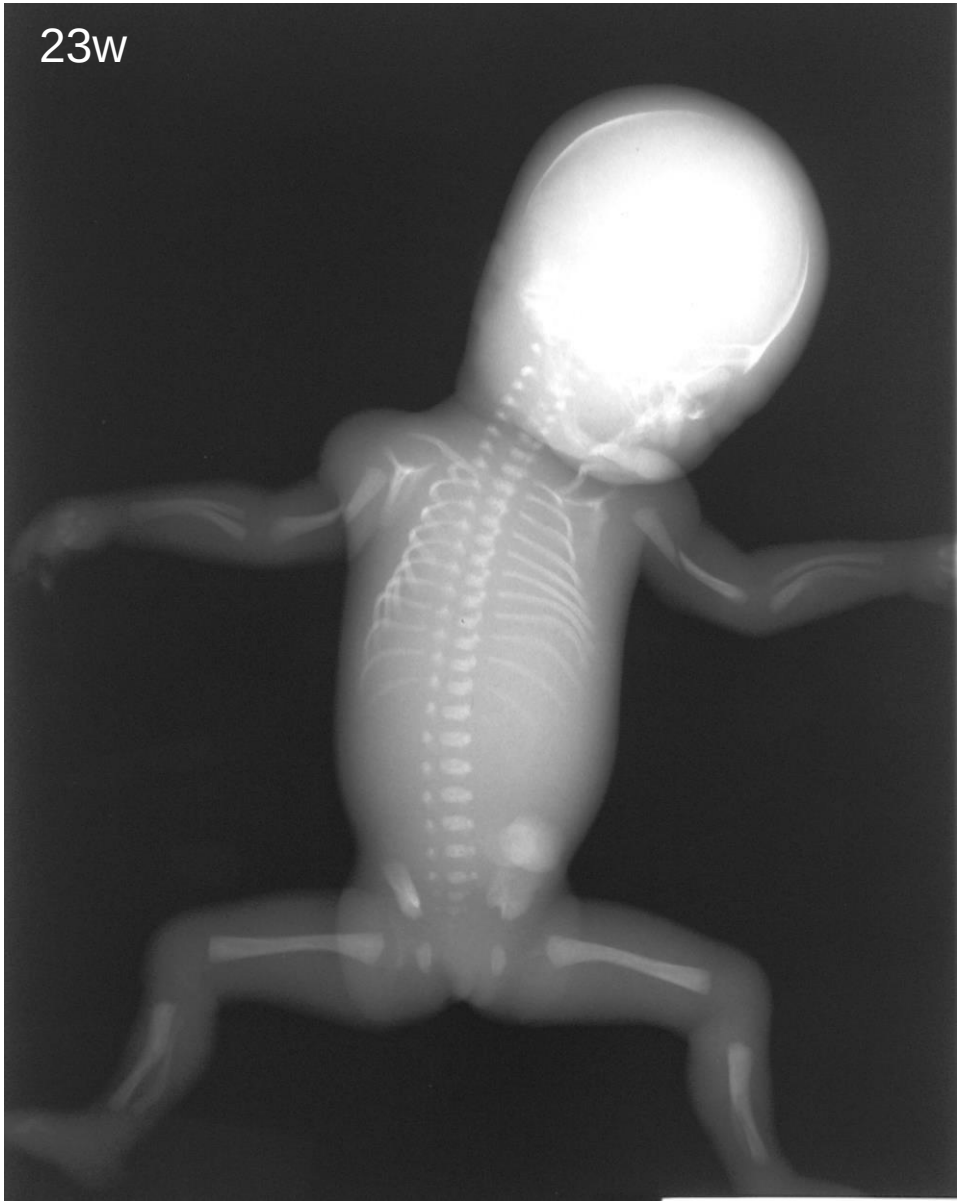
TOP of two female fetuses at 23 and 19 weeks

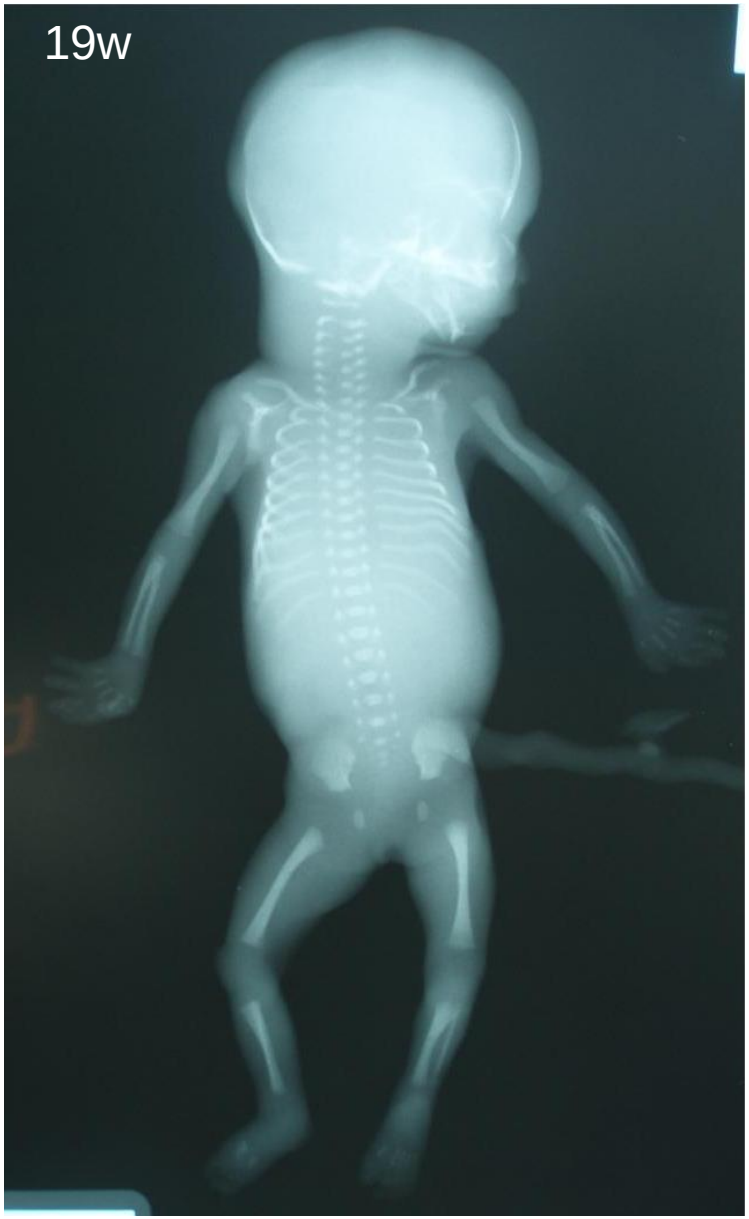




- Micrognathia - Large lips
- Wide neck
- Large klitoris

- Narrow thorax
- Mesomelic shortening
- **NO CRANIOSYNOSTOSIS**

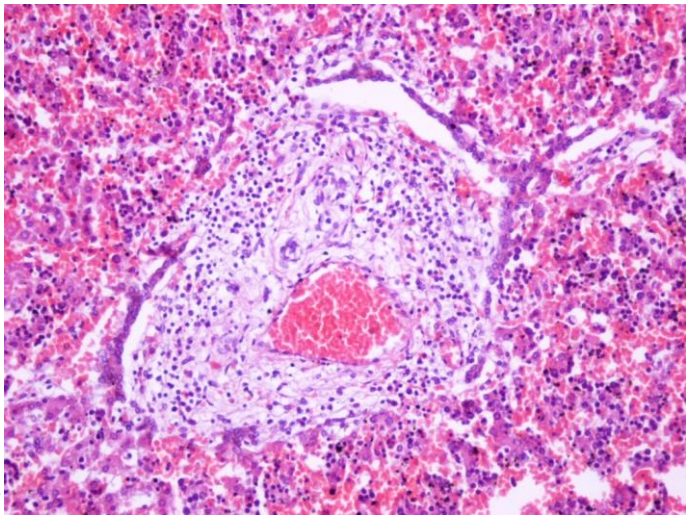




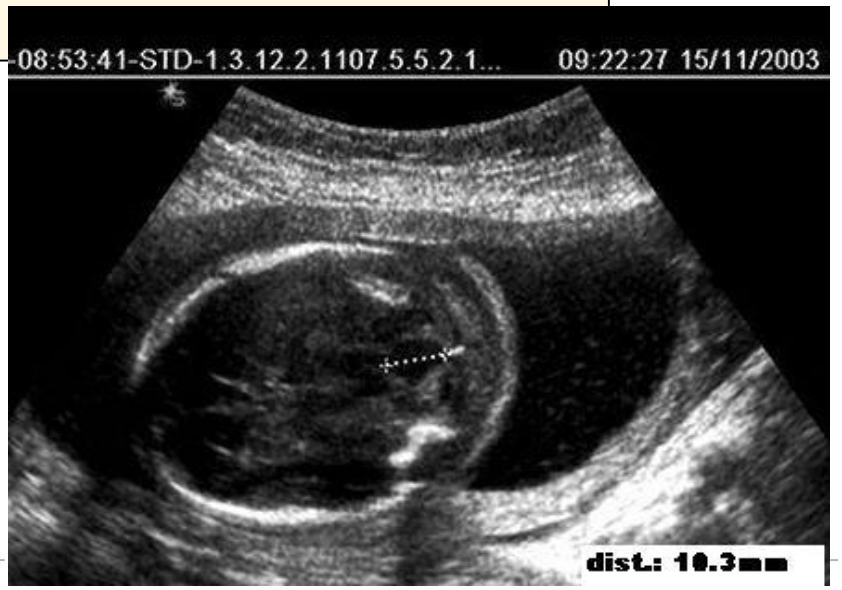
- narrow thorax
  mesomelic shortening and benting

Extraskeletal findings

- Posterior fossa cyst
- Lung hypoplasia (lung : body weight ratio 0.012 < 0.015)
- Atrial septal defect
- Renal microcysts (mostly tubular)
- Persisting ductal plate

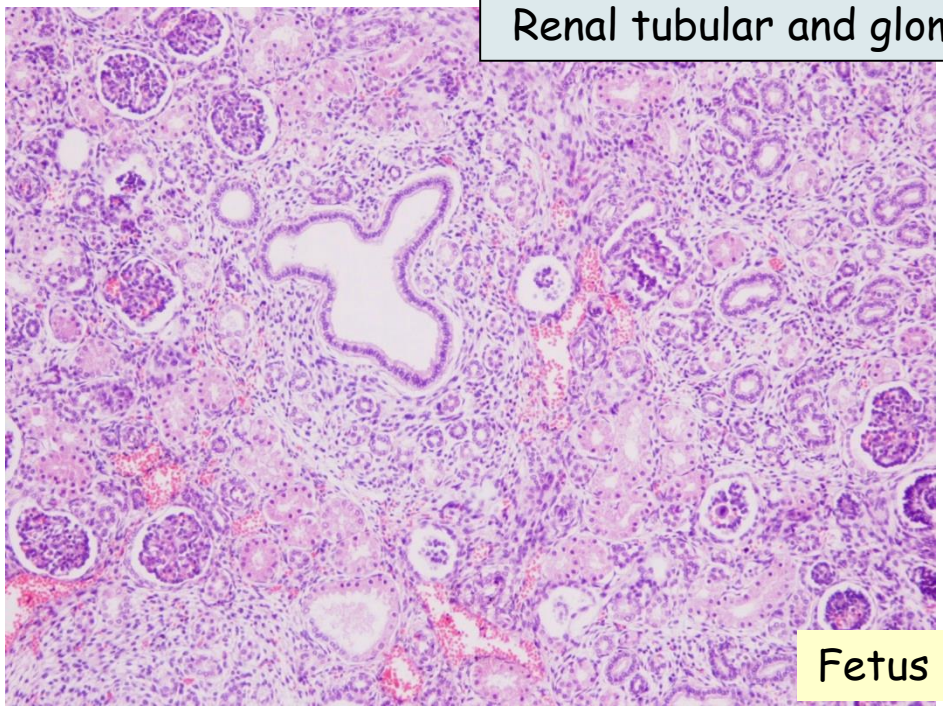


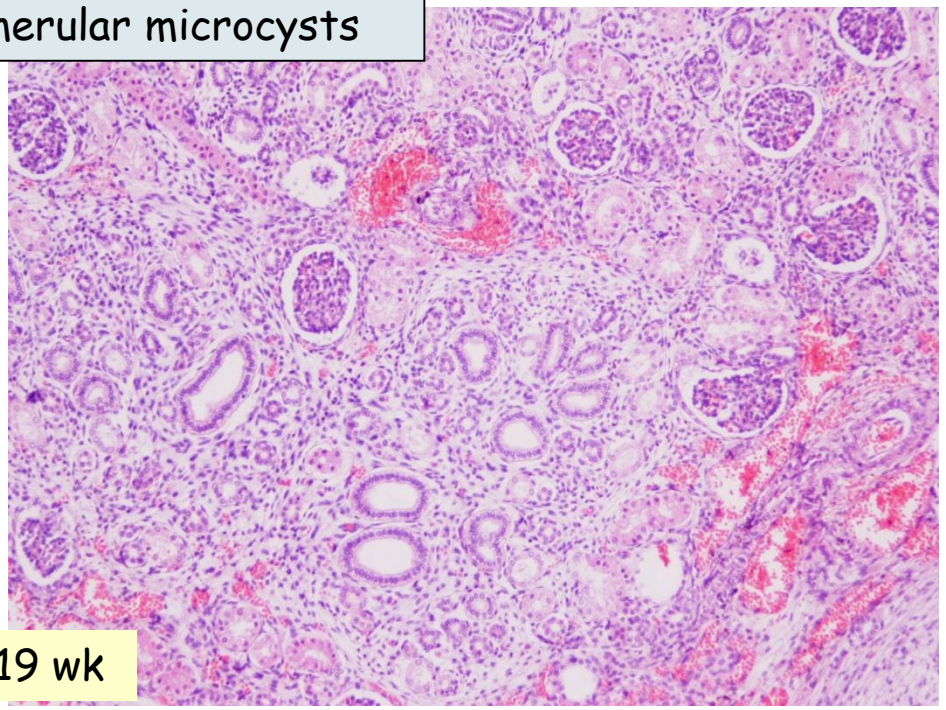
persisting ductal plate



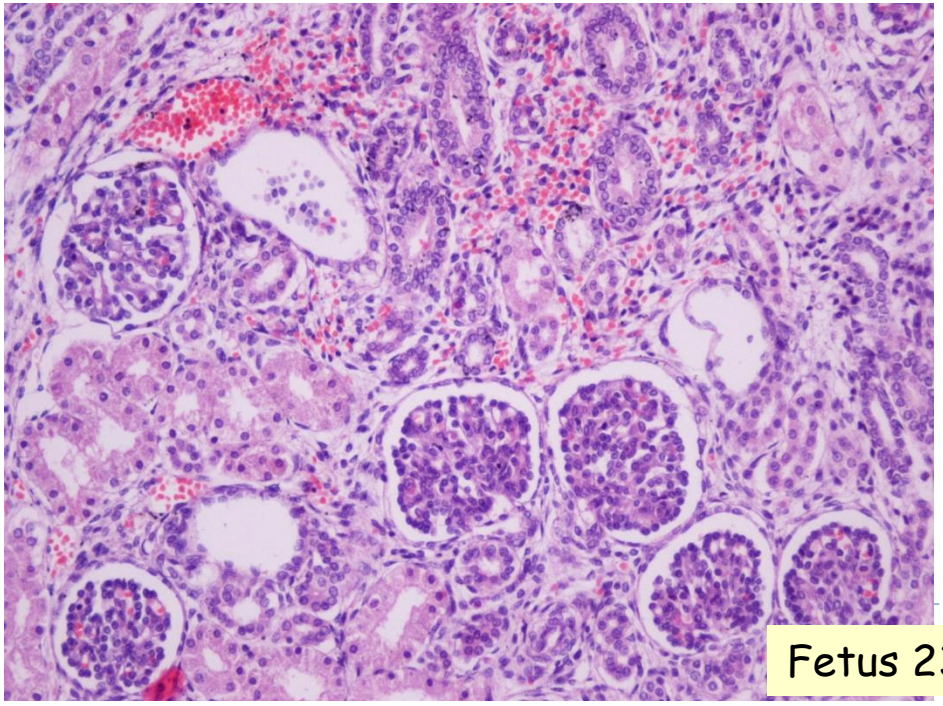
posterior fossa cyst

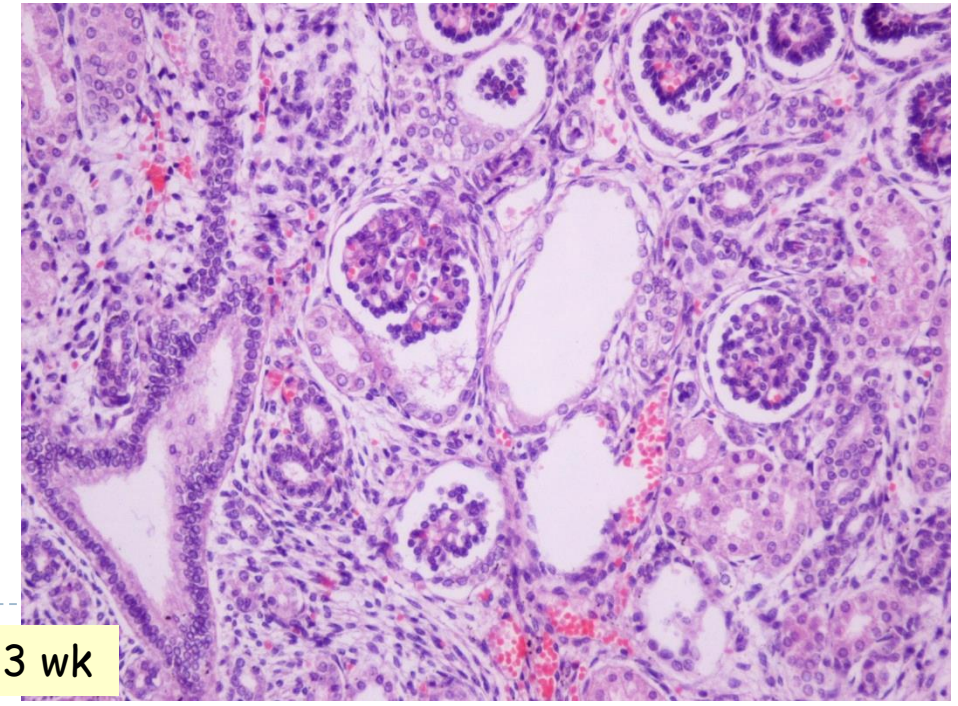
Renal tubular and glomerular microcysts





Fetus 19 wk

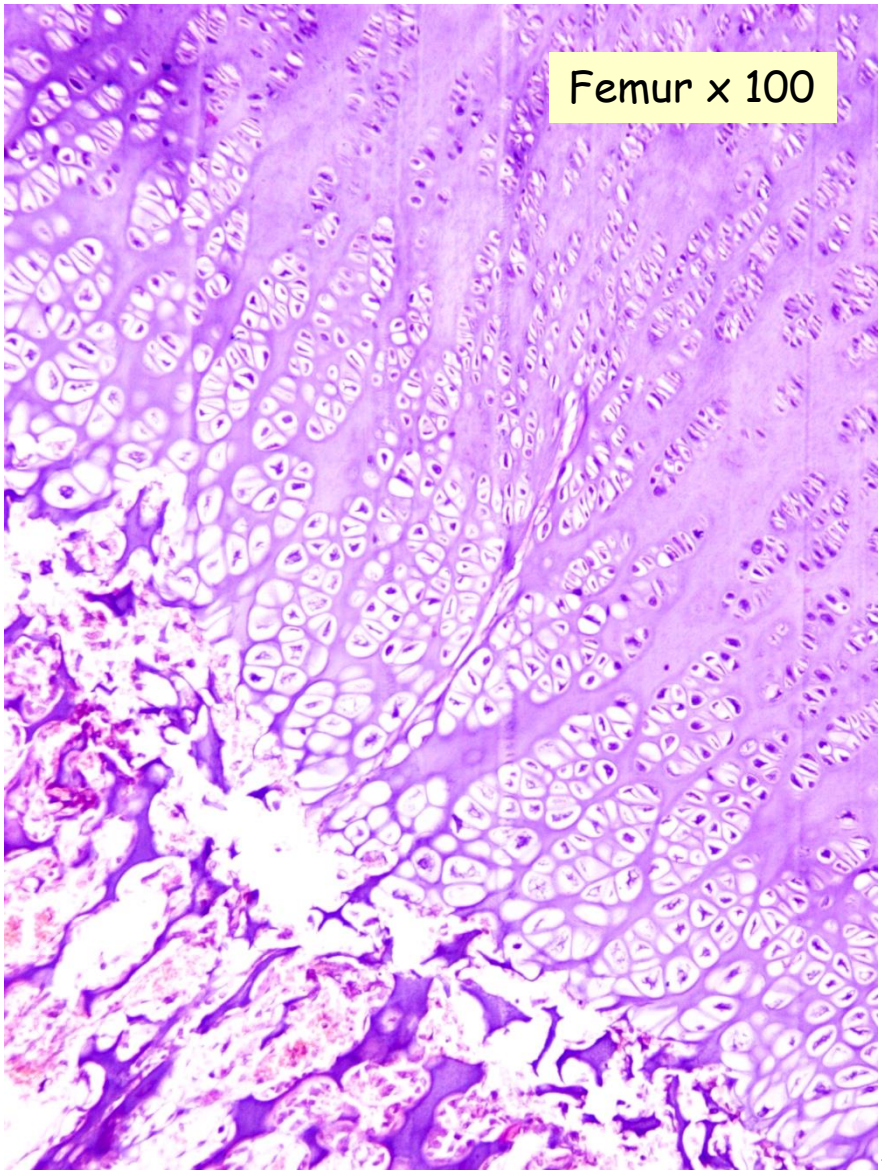


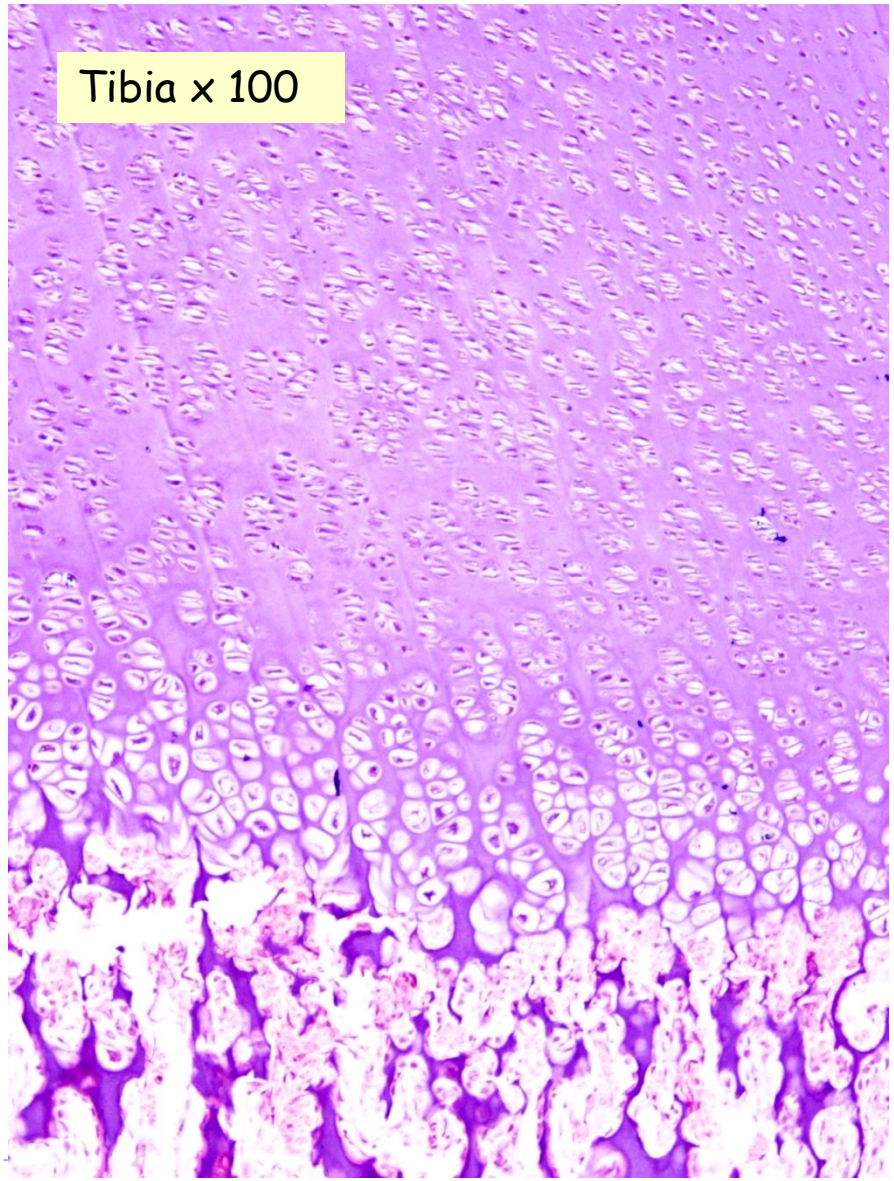


Fetus 23 wk

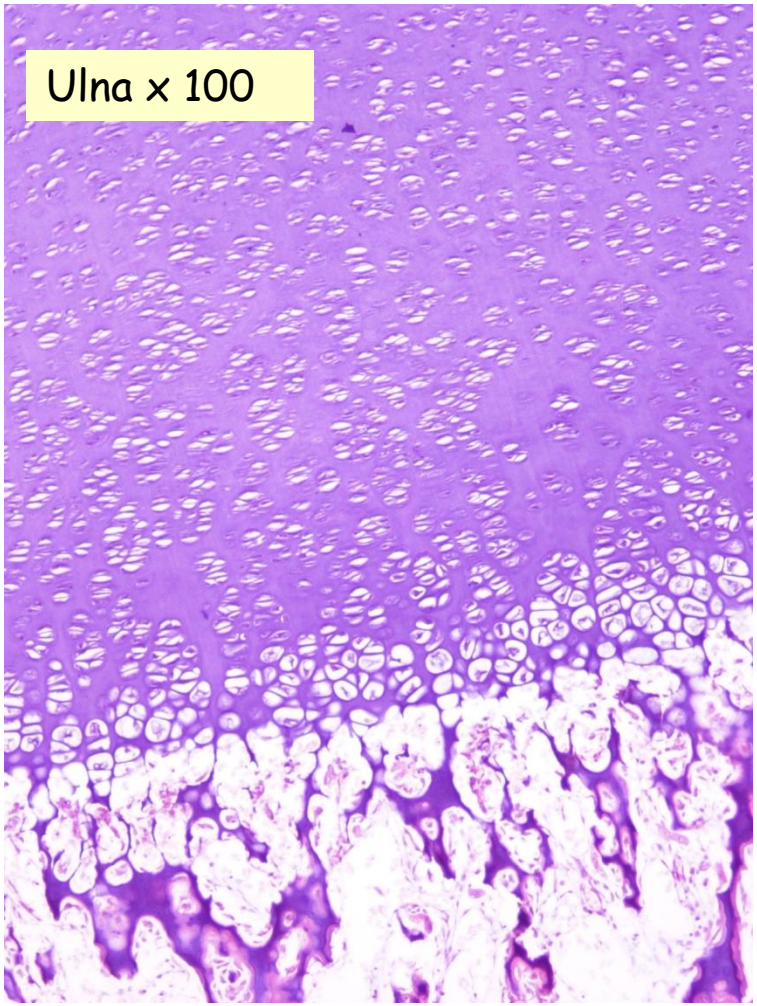
Growth plate

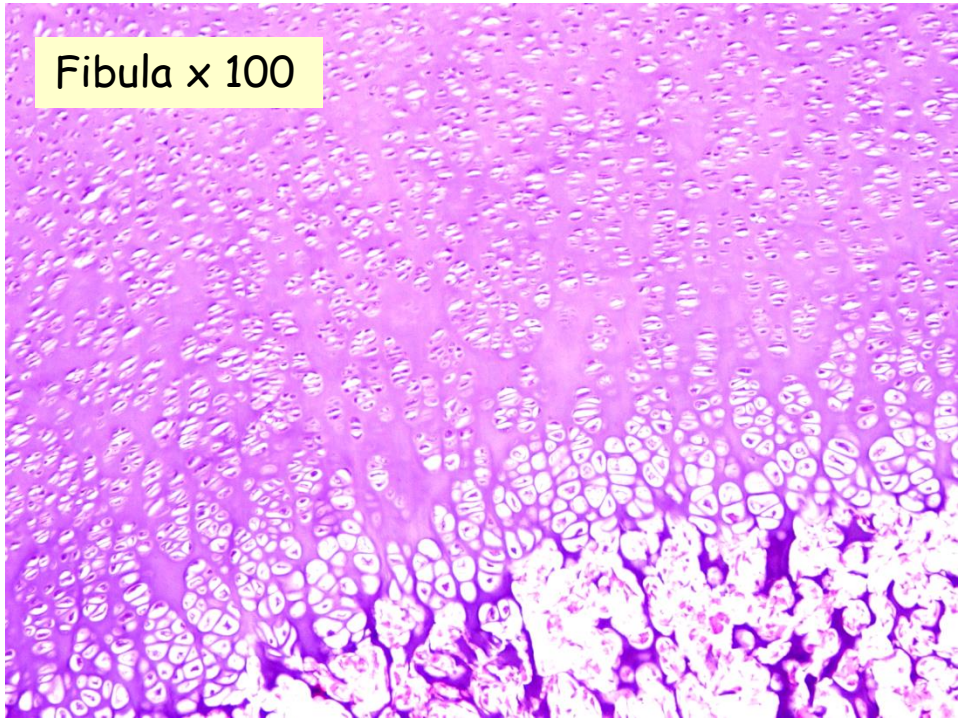
Fetus 23 wk

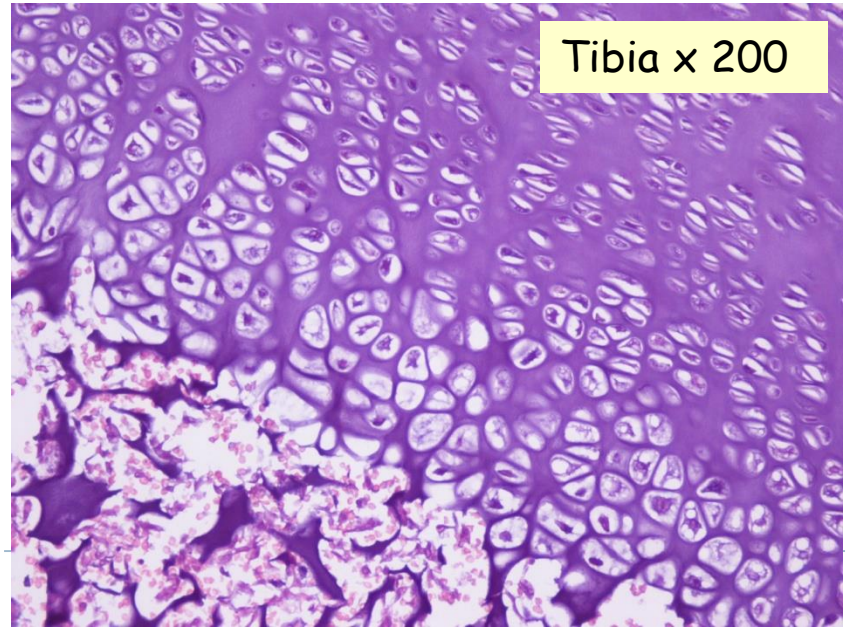




Fetus 19 wk







Cranioectodermal dysplasia

Sensenbrenner syndrome

Levin Syndrome I

IPPA COURSE 2007

Salzburg

Reviewed by *Tamai et al. (2002)*
15 individuals reported
(5 pairs of sibs + 5 individual cases)

Autosomal Recessive

no gene identified
(2007)

- Poor prognosis
(follow-up of 2 sibs)
- death before 6yrs
(renal or cardiac failure)

Constant findings

- Dolichocephaly
(with sagittal craniosynostosis)
- Brachymelia

Variable findings

- Ectodermal dysplasia
- Short narrow thorax
- Cardiac defect
- Renal failure
(tubulointerstitial nephropathy)
- Photoreceptor dystrophy

Badano et al. in their review of ciliopathies [2006] had weighted 9 phenotypic features, according to their likely relevance to predict ciliary involvement :

	Phenotypic features likely to predict ciliary involvement (in descending order)	
1.	Dandy-Walker malformation	Posterior fossa cyst - Large cisterna magna
2.	Agenesis of Corpus Callosum	
3.	Situs inversus	
4.	Posterior encephalocele	
5.	Multicystic renal disease	Renal microcysts
6.	Post-axial polydactyly	
7.	Hepatic disease	Persisting ductal plate
8.	Retinitis pigmentosa	
9.	Mental retardation	
	Additional ciliopathy-related features	
10.	Cardiac defects	ASD
11.	Skeletal dysplasia	+

Badano JL, Mitsuma N, Beales PL, Katsanis N. 2006. The ciliopathies: an emerging class of human genetic disorders. Annu Rev Genomics Hum Genet 7:125-148.

Cranioectodermal Dysplasia: A Probable Ciliopathy

AE Konstantinidou*, H Fryssira, et al.

Am J Med Genet **2009**;149A:2206-11

Cranioectodermal dysplasia is a ciliopathy caused by mutations in the IFT122 gene.

J Walczak-Sztulpa, J Eggenschwiler, et al.

Am J Hum Genet **2010**;86(6):949-56

Novel WDR35 mutations in patients with Cranioectodermal Dysplasia (Sensenbrenner syndrome)

J Hoffer, AE Konstantinidou, et al.

Clin Genet 2013 Jan;83(1):92-5. Epub **2012** Apr 9.

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Tamina Seeger-Nukpezah and Erica A. Golemis. The extracellular matrix and ciliary signaling. Curr Opin Cell Biol. 2012 October ; 24(5): 652–661.

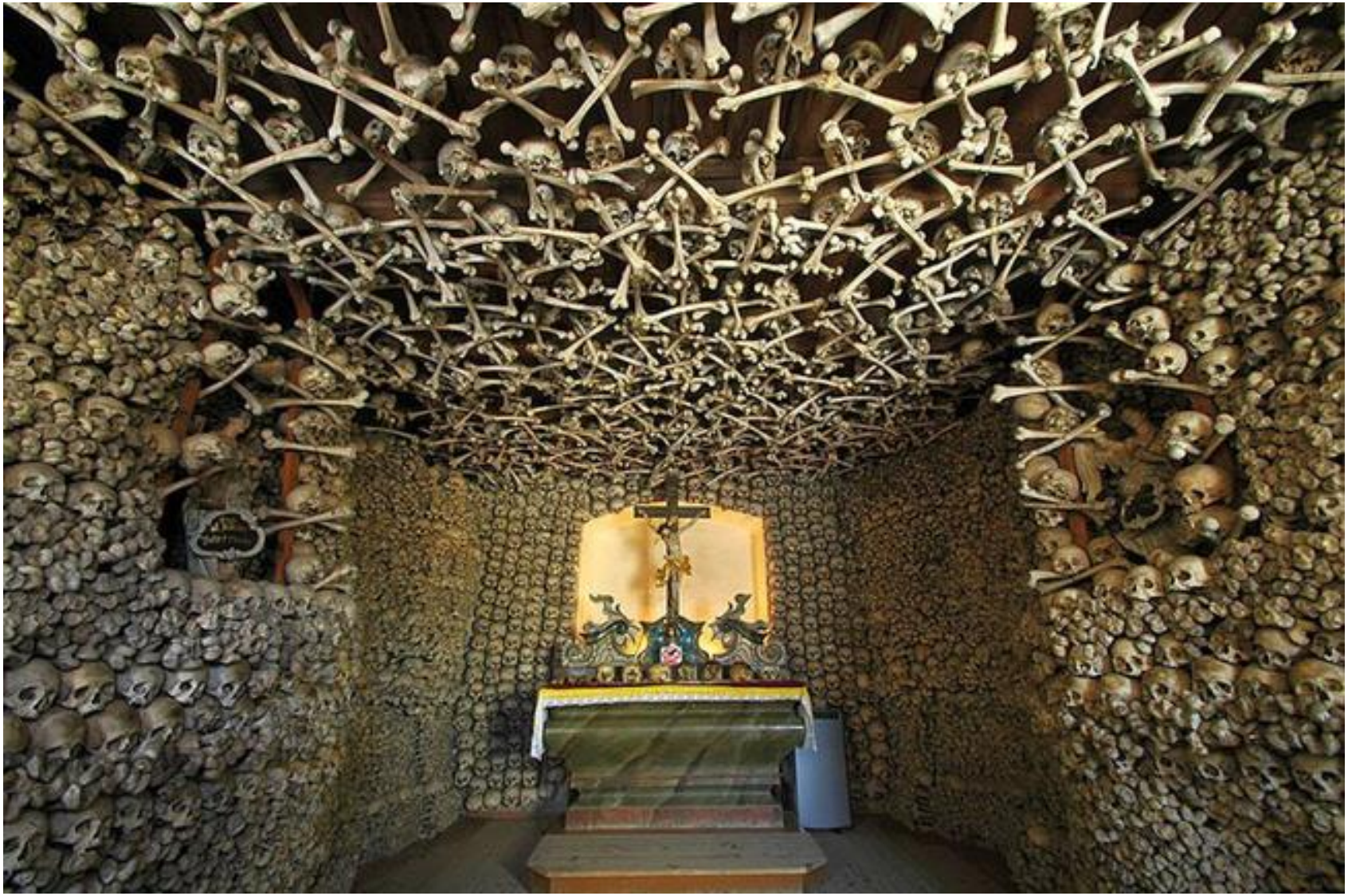
Aoife M. Waters & Philip L. Beales. Ciliopathies: an expanding disease spectrum. Pediatr Nephrol (2011) 26:1039–1056.

Baker K, Beales PL. 2009. Making sense of cilia in disease: The human ciliopathies. Am J Med Genet Part C Semin Med Genet 151C:281–295.

AE Konstantinidou, H Fryssira, et al. Cranioectodermal Dysplasia: A Probable Ciliopathy. Am J Med Genet 2009;149A:2206-11

Badano JL, Mitsuma N, Beales PL, Katsanis N. 2006. The ciliopathies: an emerging class of human genetic disorders. Annu Rev Genomics Hum Genet 7:125-148.

END OF BONES. THANK YOU !



Rome – Cimetière des Capucins

I wish to aknowledge:

the patients demised before time
and their parents for giving consent for teaching.