SoFFœt
Société Française de Fœtopathologie

34-year-old primigravida – Non consanguineous couple
Pregnancy obtained by In Vitro Fertilization – ICSI
Prenatal USS (12 and 16 WG)

- increased nuchal translucency measurement /cystic hygroma >5 mm
- Fetal subcutaneous œdema
- IntraUterine Growth Retardation <5p

Chorionic villus sampling : normal Karyotype, normal CGH array
TOP at 20 WG

SERVICE DE BIOLOGIE DU DÉVELOPPEMENT
FŒTOPATHOLOGIE

Biometry

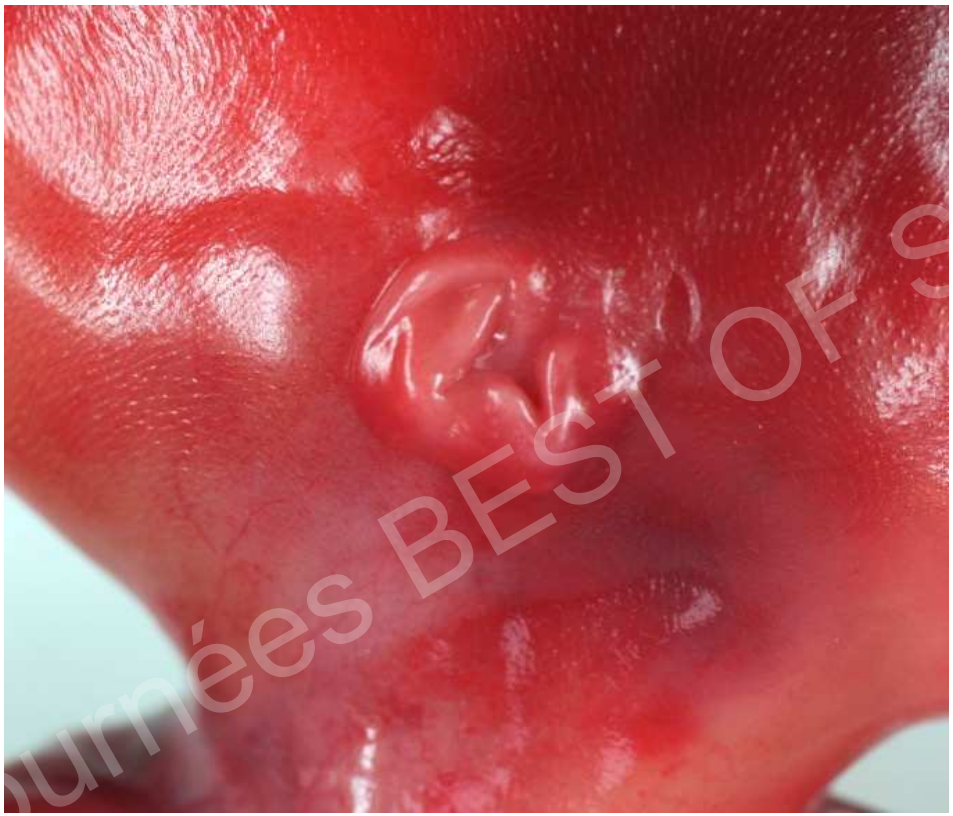
Body Weight= 155 g (<5p 20GW – 50p 17 GW)

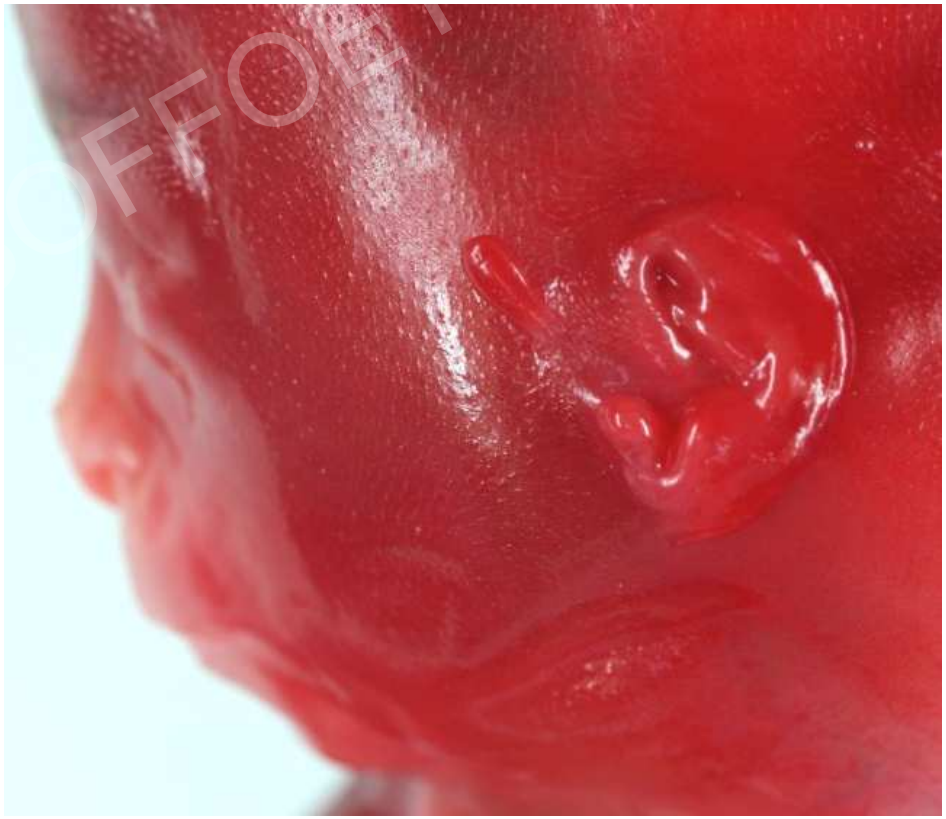
CR Lenght = 13,5 cm (<5p 20GW – 50p 17,5 GW)

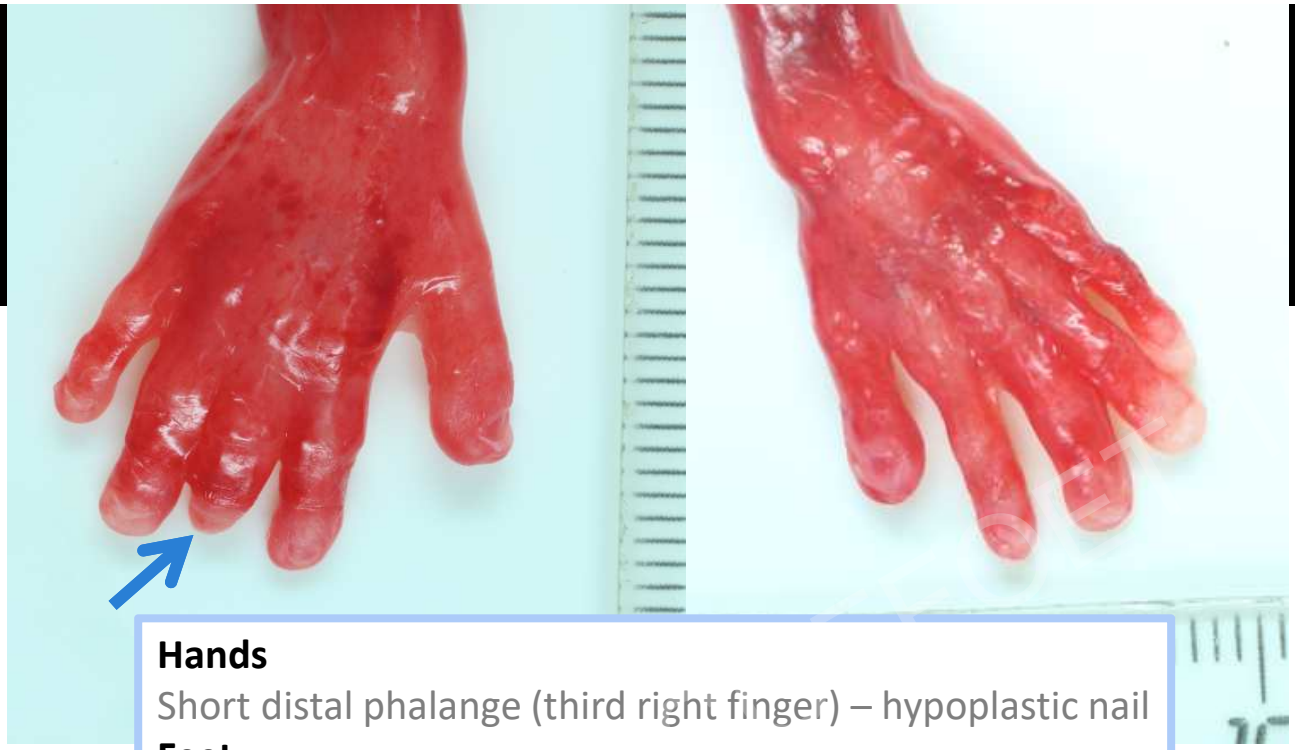
CH Lenght = 21 cm (<5p 20GW – 50p 18 GW)

Head circumference =14,5 cm (<5p 20GW – 50p 17,5 GW)

Microretrognatia
Asymmetric ears
Pre auricular tags





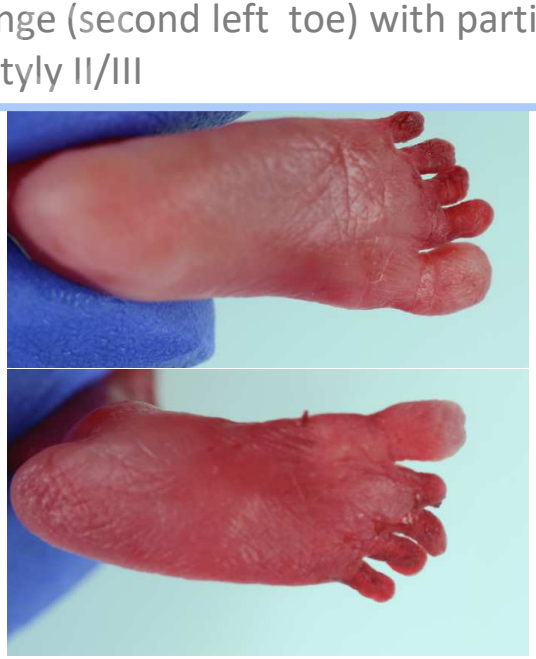


Hands

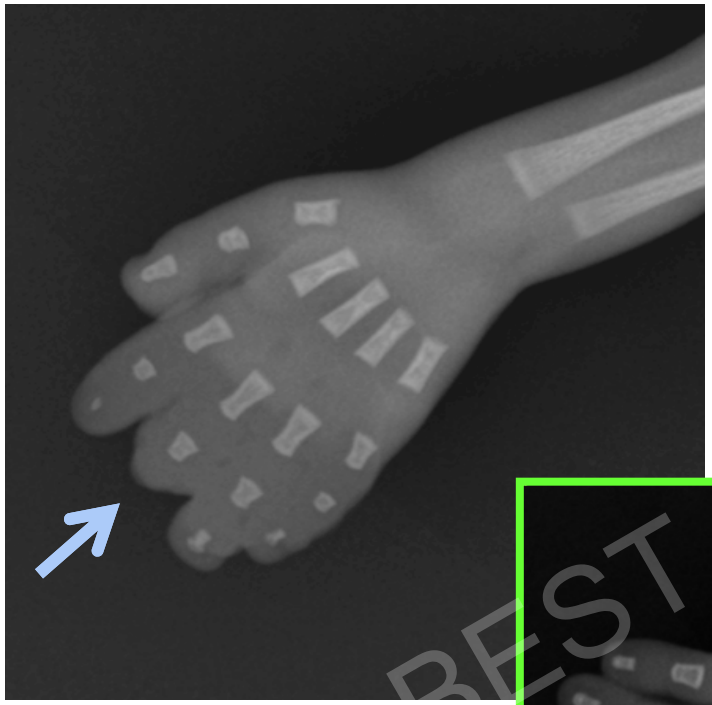
Short distal phalange (third right finger) – hypoplastic nail

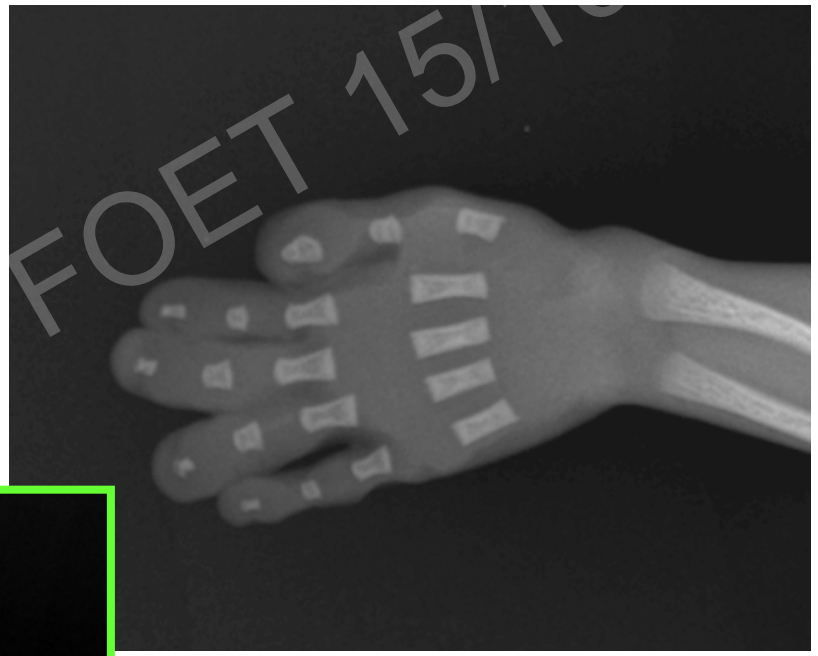
Feet

Short distal phalange (second left toe) with partial cutaneous syndactyly II/III

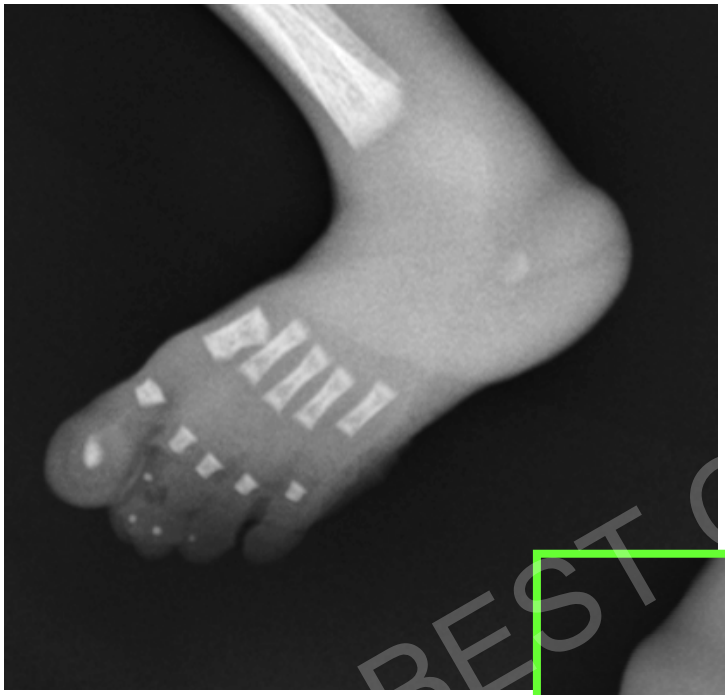


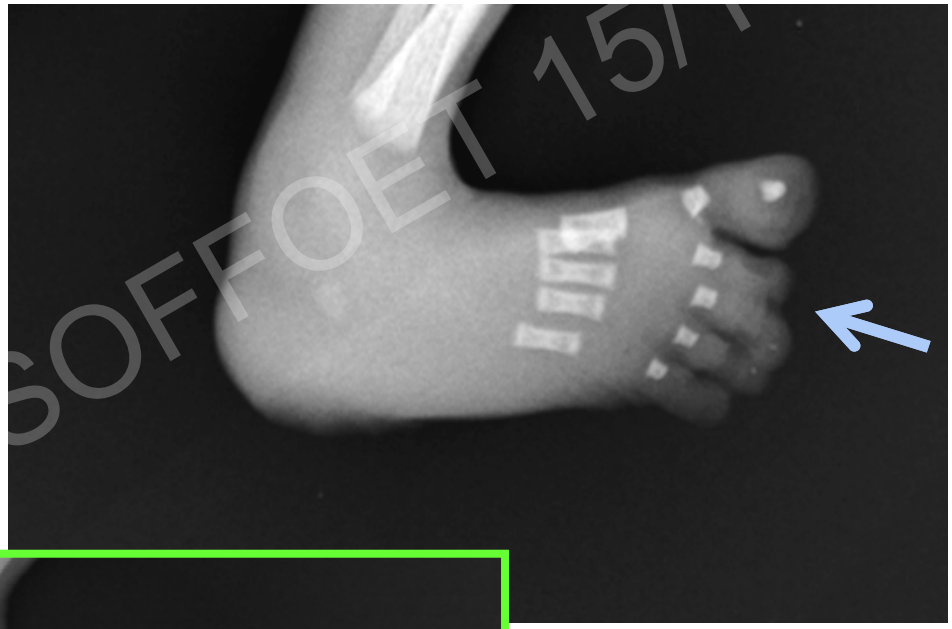
X-Rays

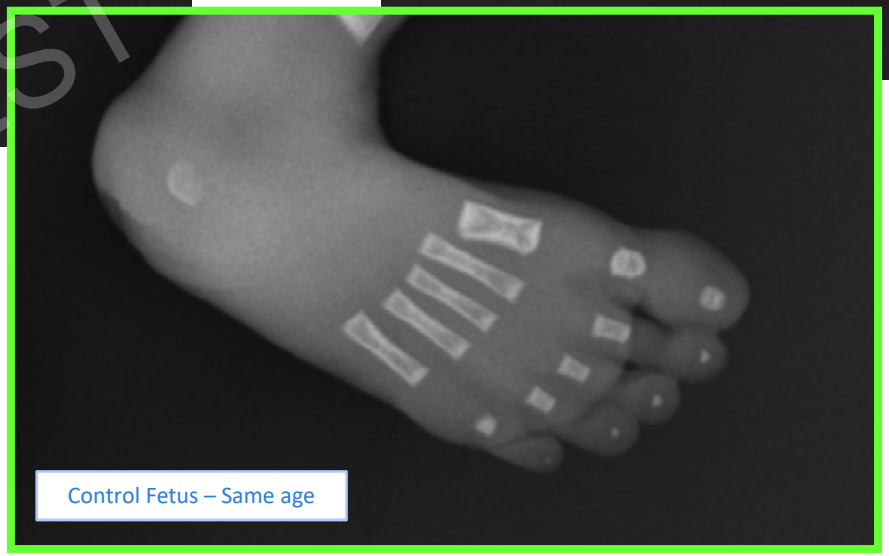




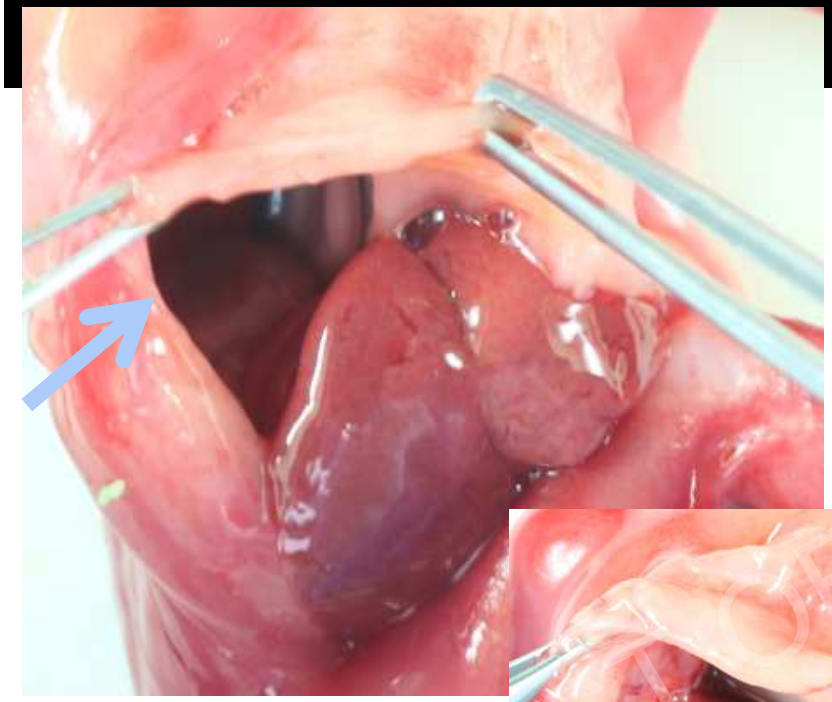
X-Rays

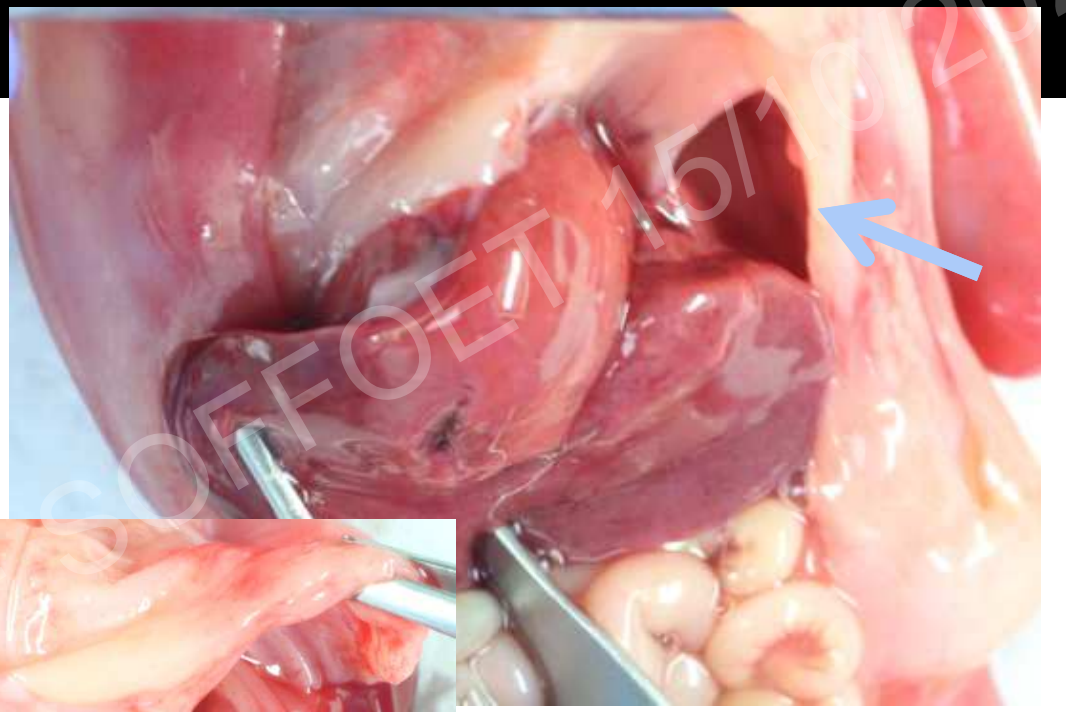


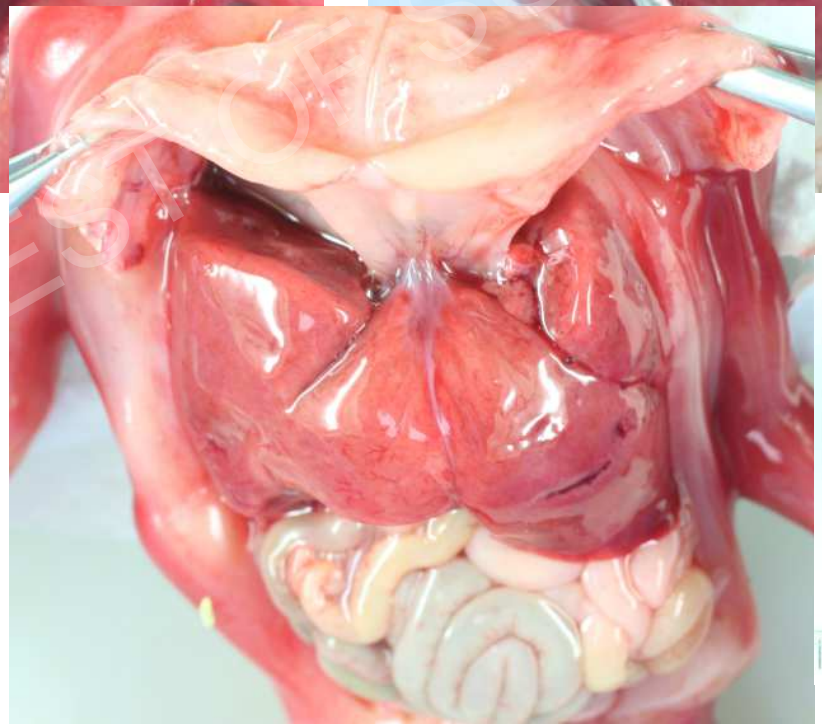


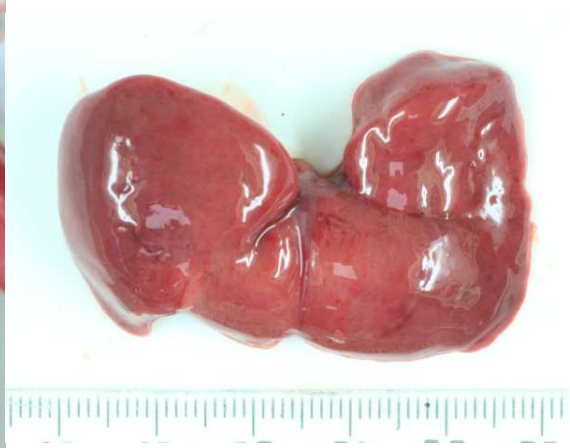


Congenital bilateral diaphragmatic hernia

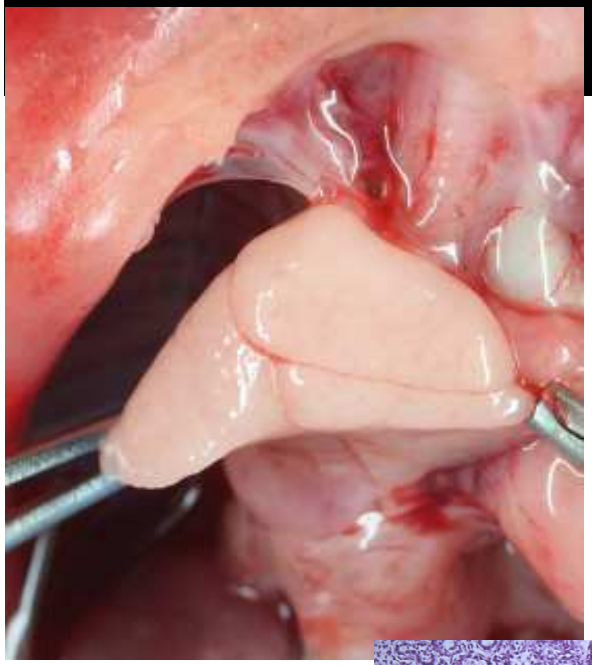


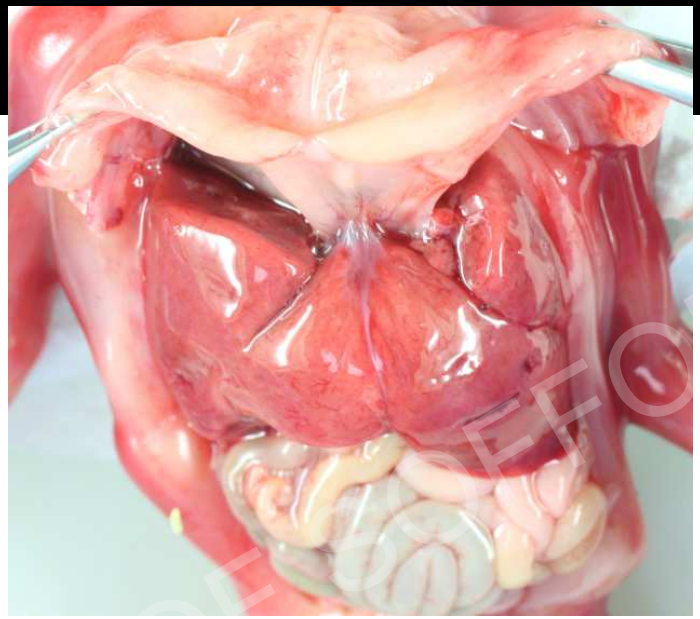


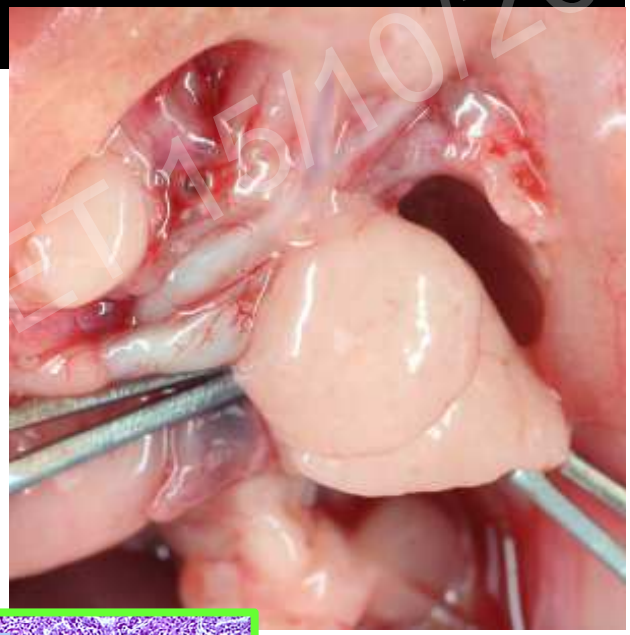


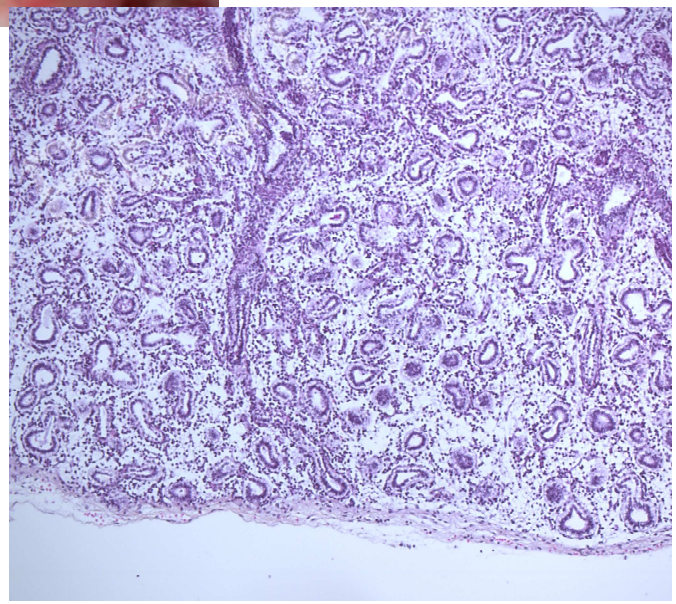


Lung hypoplasia : Fetal L/B ratio= 0,007<<0,015

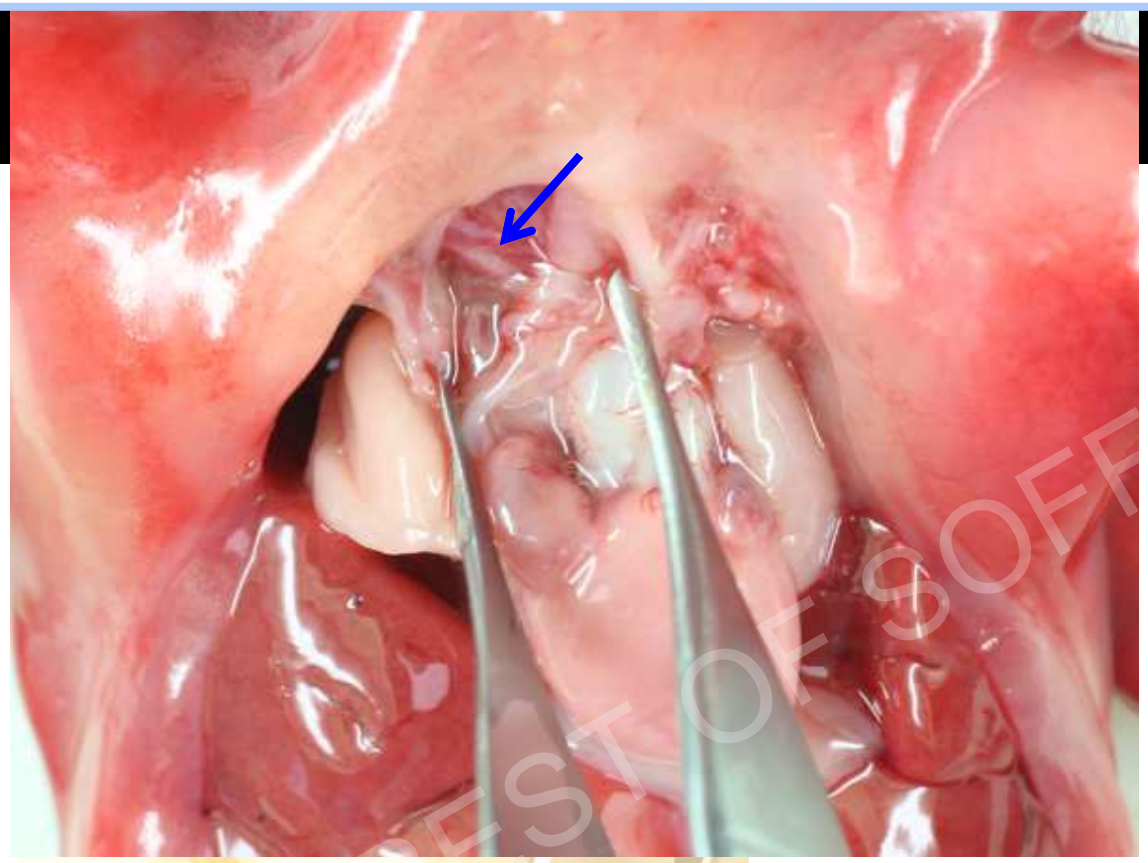


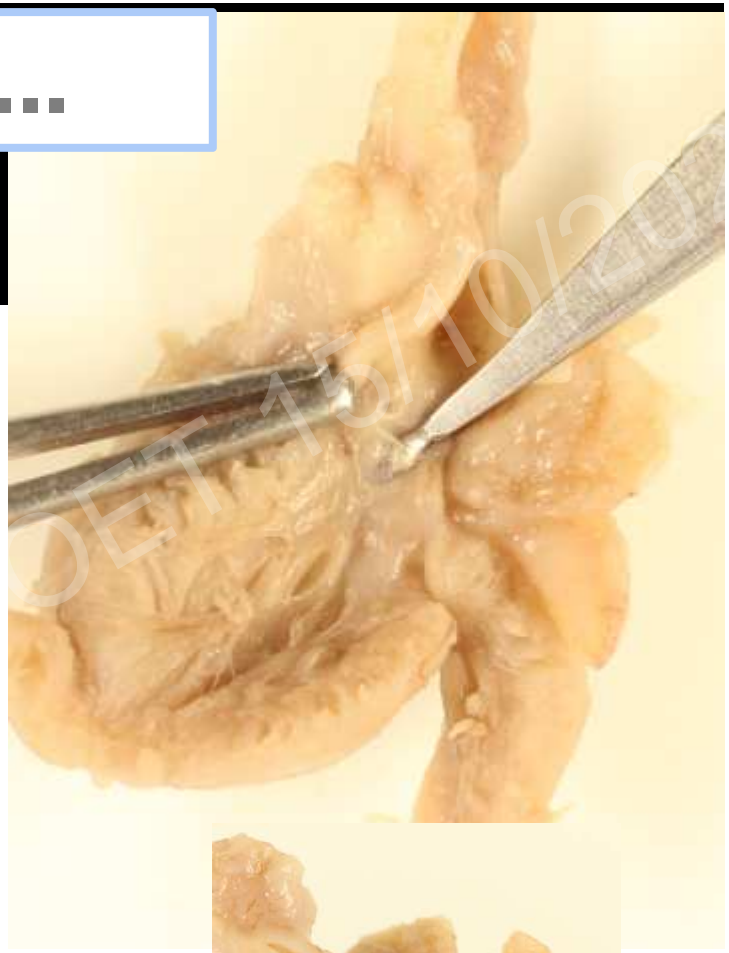


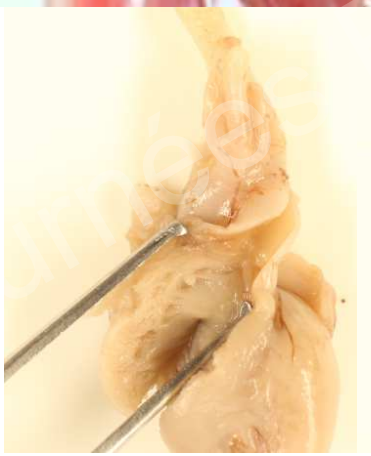


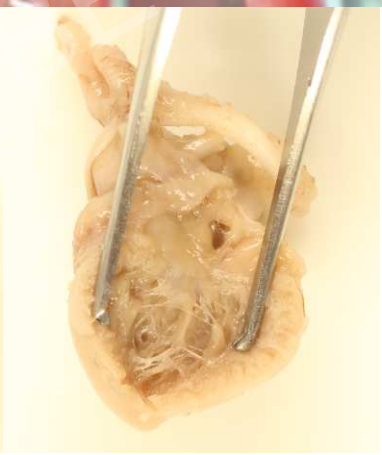


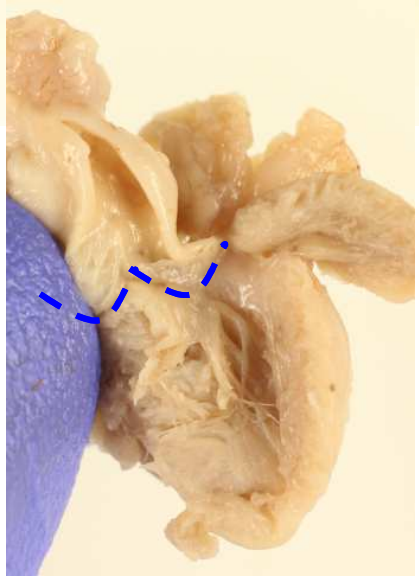
HEART : no septal defect but …



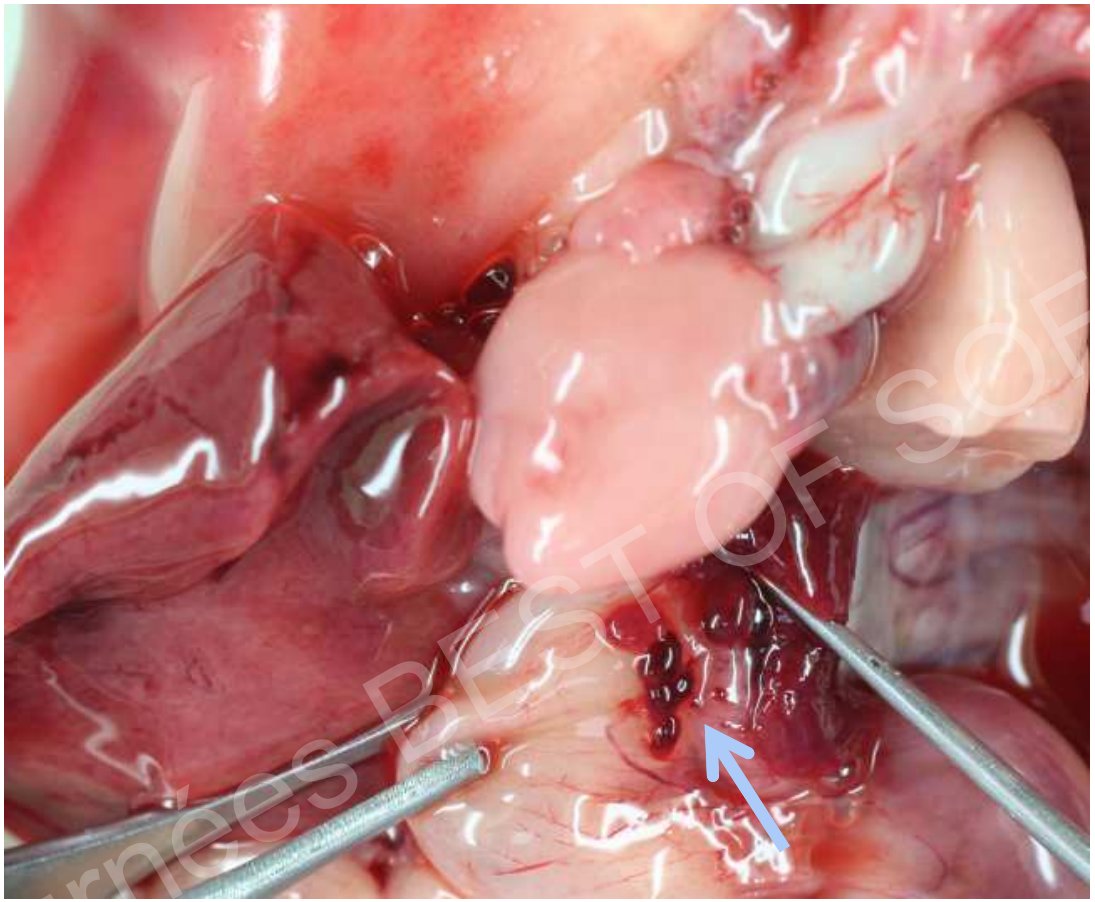


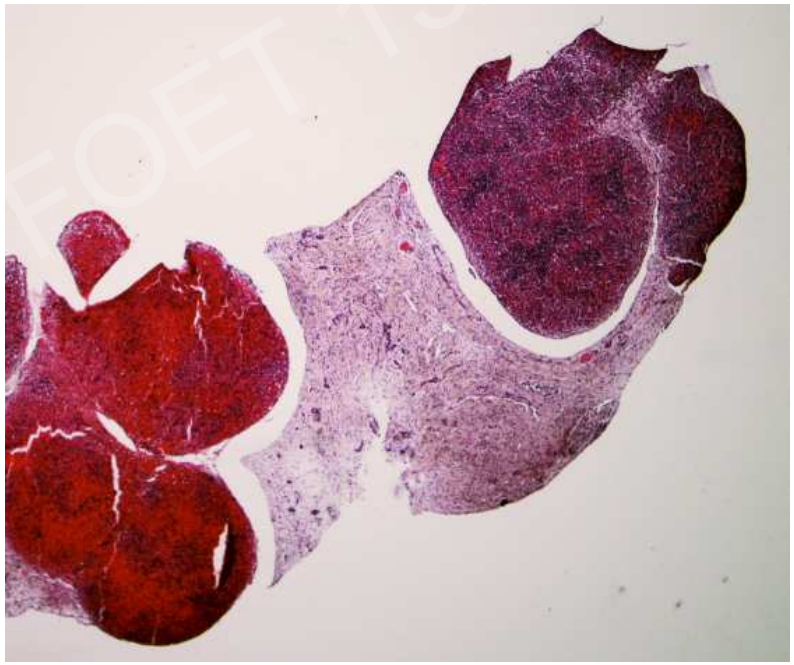






Polysplenia



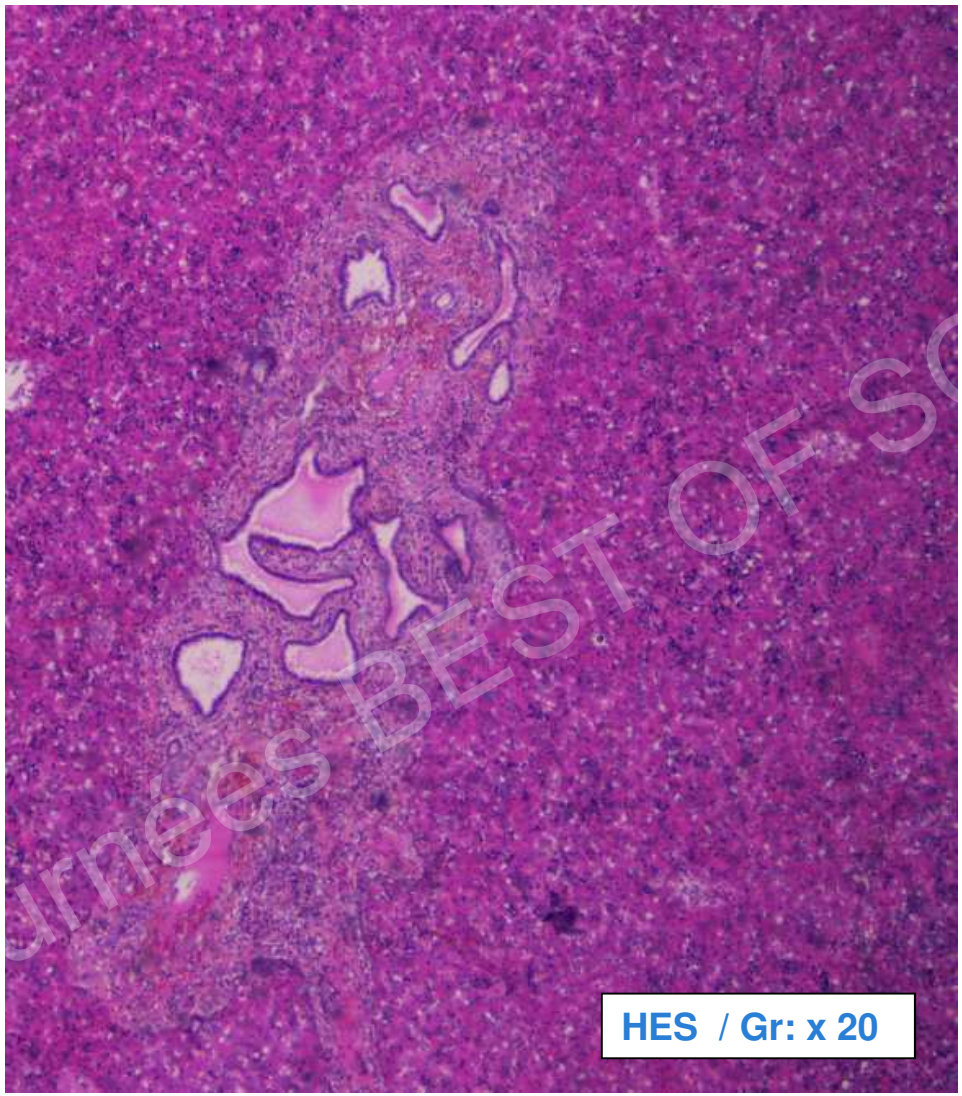


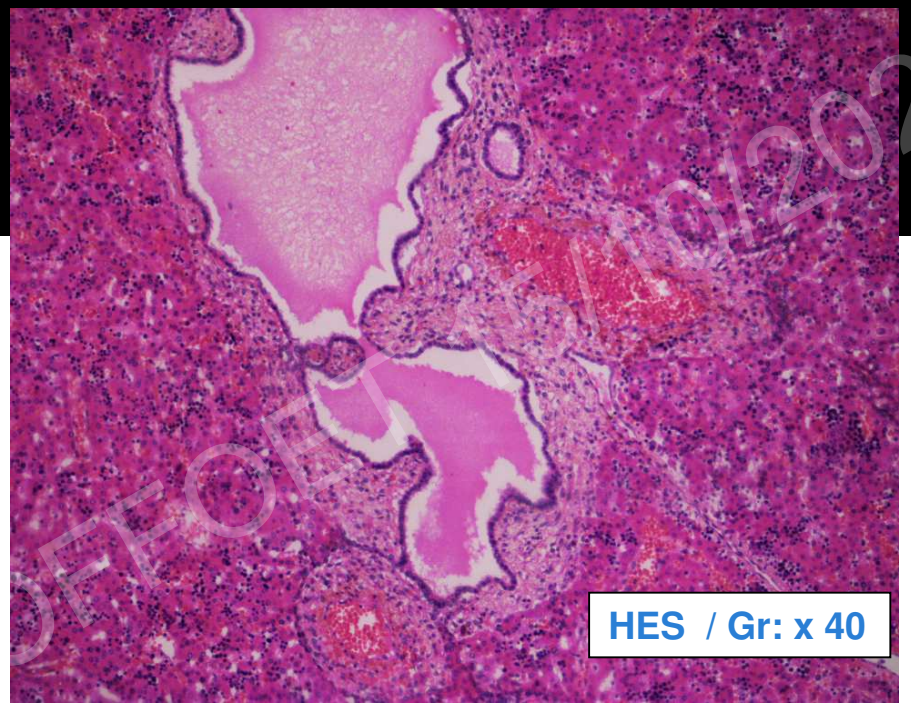
BRAIN

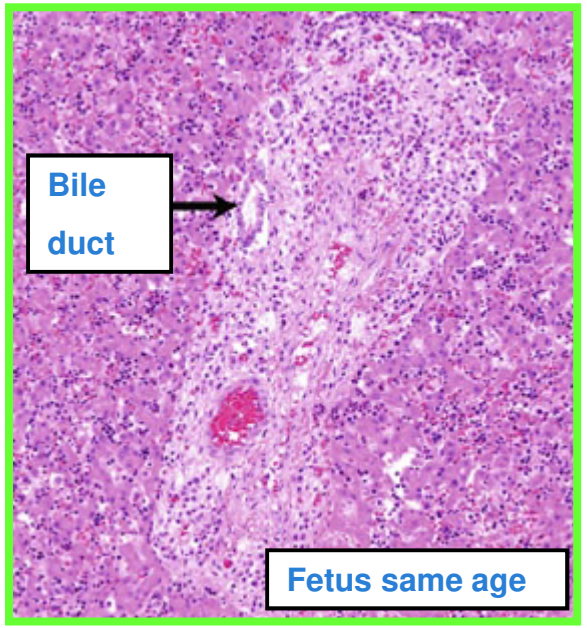
Small but NI

Fixed Brain Weight : (<5p 20GW – 50p 18 GW)
OF Right : 45 mm / Left : 45,5 mm (<5p 20GW – 50p 17,5 GW)
Cerebellar Weight : 1,62 g (<5p 20GW – 50p 18 GW)
Transversal Cerebellar size : 18,5 mm (10p 20GW)

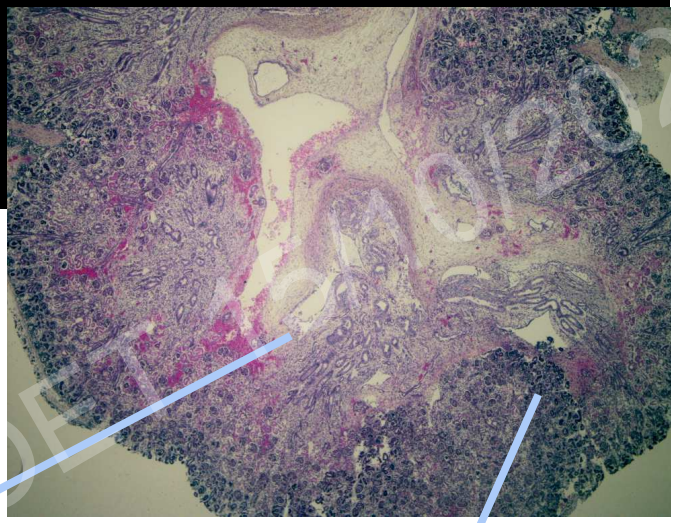
Liver : portal tracts

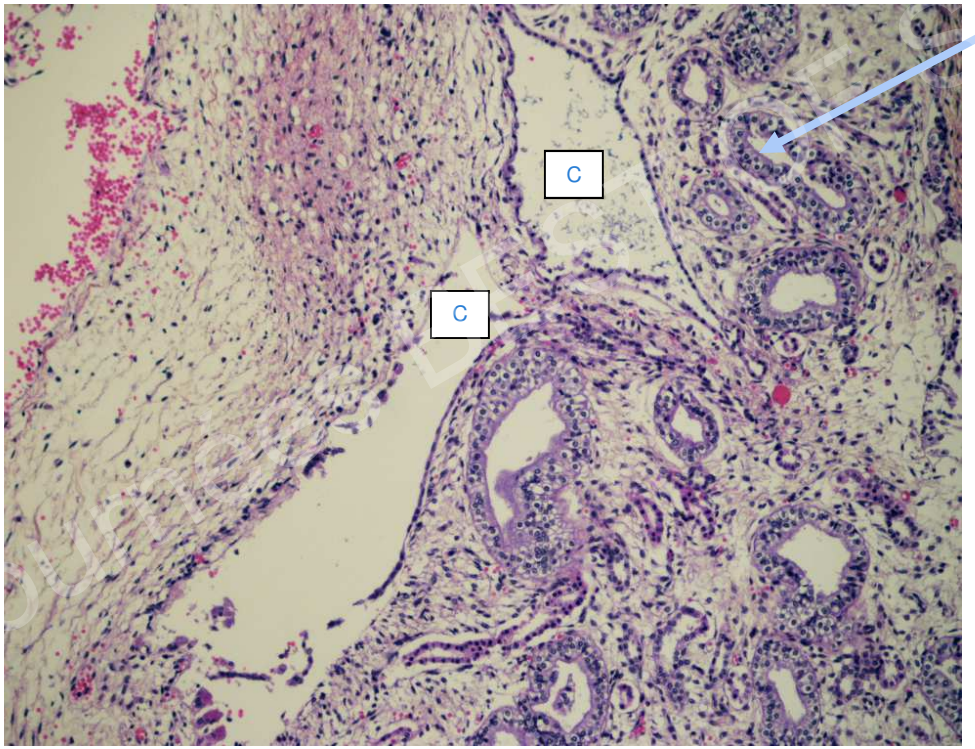


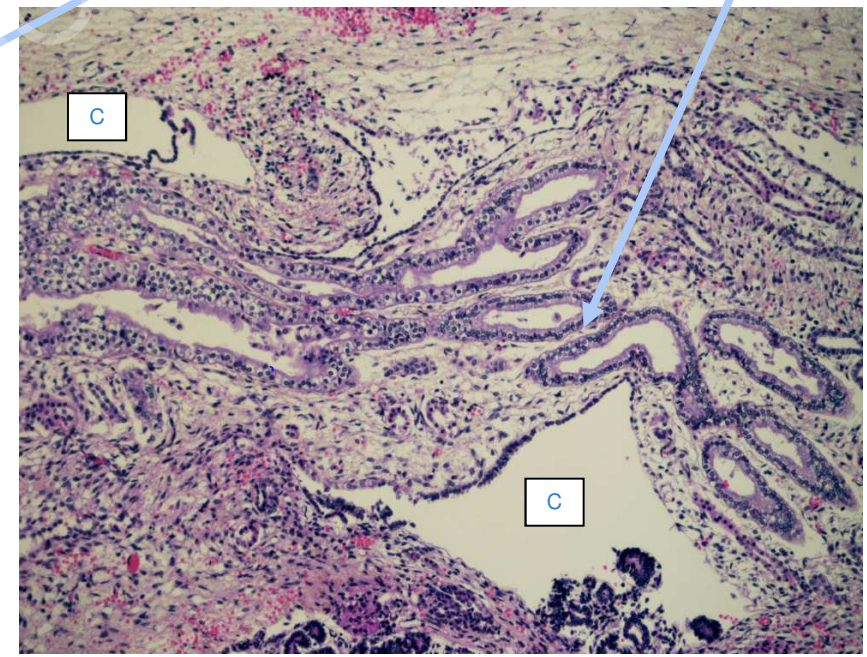




Kidneys

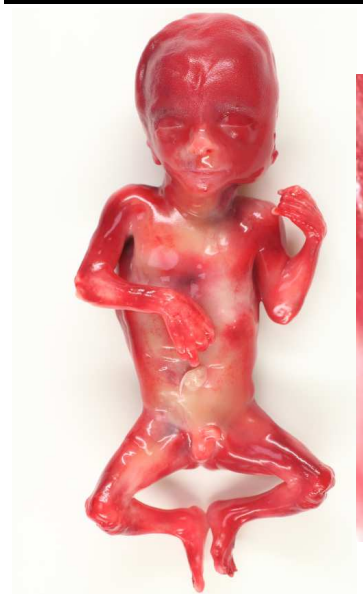


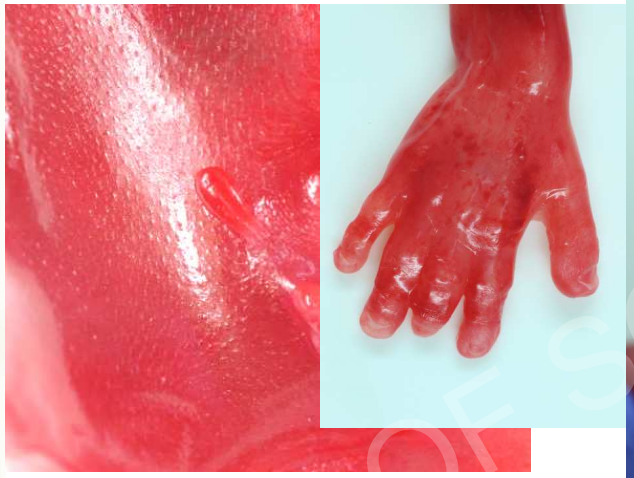


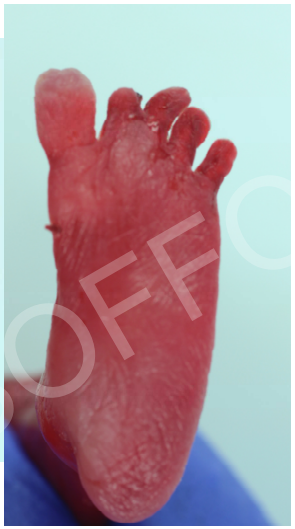


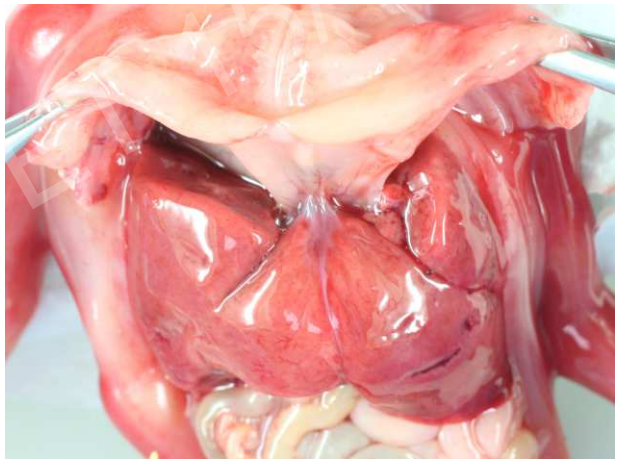
Molecular Genetics

→ Whole-exome sequencing

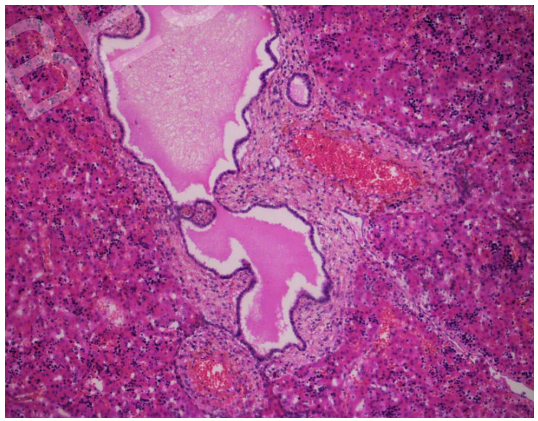


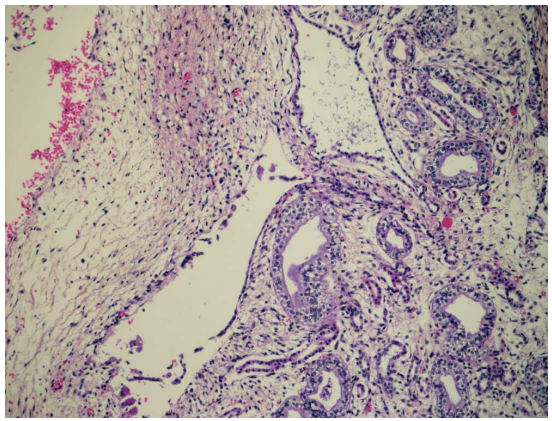






FRYNS ???





?

Molecular Genetics

WES : Missense mutation in the *RLIM* gene

NM_016120.4(RLIM):c.1831C>T (p.Arg611Cys)

ICD+

300978

TONNE-KALSCHEUER SYNDROME;
TOKAS

Alternative titles; symbols

INTELLECTUAL DEVELOPMENTAL DISORDER WITH OR WITHOUT HAND AND FOOT ANOMALIES, GENITAL ANOMALIES, OR CONGENITAL DIAPHRAGMATIC HERNIA
MENTAL RETARDATION, X-LINKED 61; MRX61

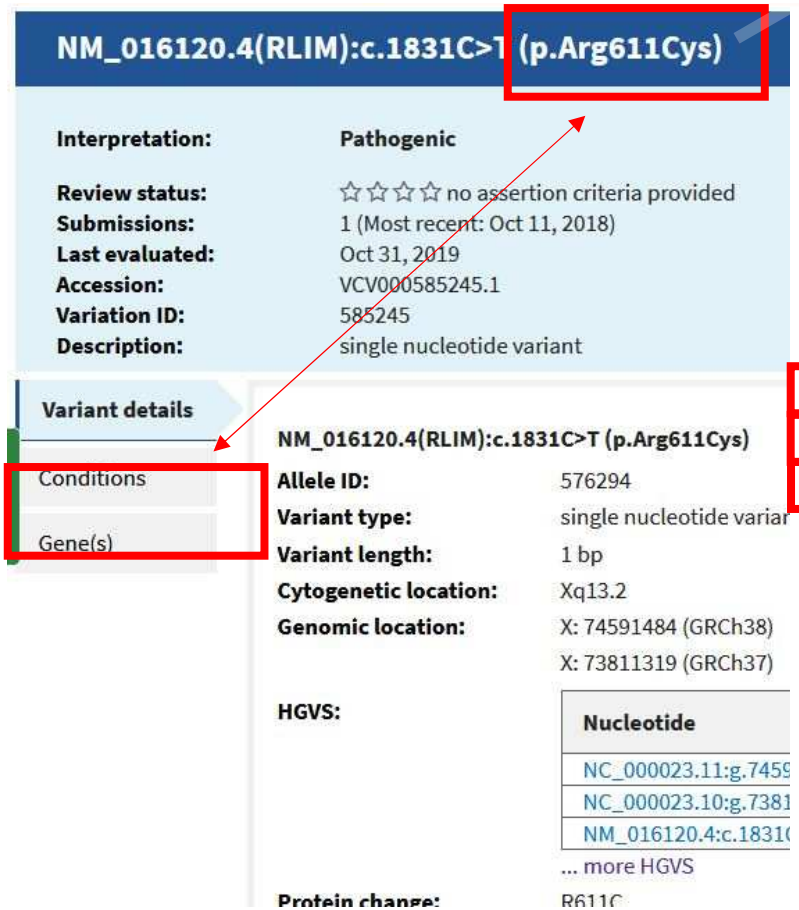
Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
Xq13.2	Tonne-Kalscheuer	300978	XL	3	RLIM	300379

TOKAS is caused by variants in the X-linked RLIM/RNF12 E3 ubiquitin ligase which controles processes including imprinted X-chromosome inactivation, stem cell maintenance and differentiation.

Missense mutation in the *RLIM* gene

TOKAS



Family I presented with lethal multiple congenital malformation (MCA) disorder in most affected individuals. The first genetic counselling in this large family was performed in a non-consanguineous couple (Figure 1. I.II:1 and I.II:2) after three of their sons died (Figure 1. I.III:1, I.III:2 and I.III:4). The first neonate was a reported stillbirth (>24th weeks of gestation, Figure 1. I:III.1) for unknown reasons and without further documentation or investigation in Kosovo/Albania. The second boy was born a preterm delivery (33+6/7 weeks of gestation, Figure 1. I.III:2) and died shortly after birth. He showed MCA such as mild growth retardation, urogenital abnormalities, syndactyly, nail hypoplasia, flat nose, retrognathia, dysmorphic ears (Supplementary Figure 2. I.III:2a-d). Cause of death was a diaphragmatic hernia with severe associated lung hypoplasia (LH). This second diseased male was clinically diagnosed with Fryns syndrome (*confirmed by Professor J.P. Fryns personally*) and the family received genetic counselling according to this autosomal-recessive syndrome with a phenotype only detectable in prenatal ultrasound since no genetic diagnoses for Fryns syndrome was available at that time. The next child of this family was a healthy girl (Figure 1 I.III:3) but the fourth pregnancy was again a boy with diaphragmatic hernia and lung hypoplasia (Figure 1. I.III:4, Supplementary Figure 1. I.III:4a-c). He, too, died shortly after birth due to extreme LH, but in contrast to his brother he showed no further malformations or dysmorphism. Several months after this event the mother reported that meanwhile, one of her sisters (Figure 1. I.II:10), had several pregnancies with similarly affected boys. Her first

Pathogenic variants in E3 ubiquitin ligase RLIM/RNF12 lead to a syndromic X-linked intellectual disability and behavior disorder

Suzanna G.M. Frints, Vera M. Kalscheuer, PhD[27**$]

Mol Psychiatry. 2019 *Nov;24(11):1748-1768.*

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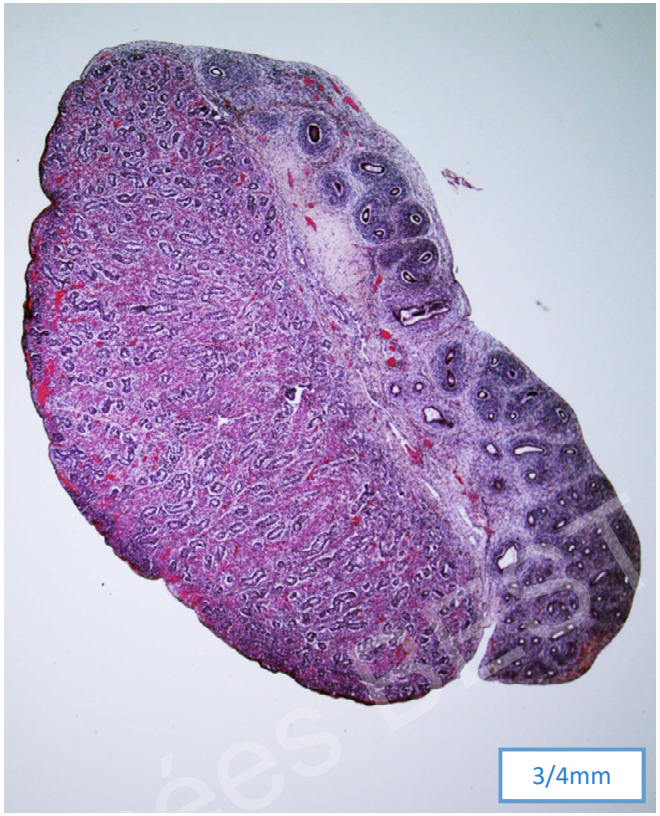
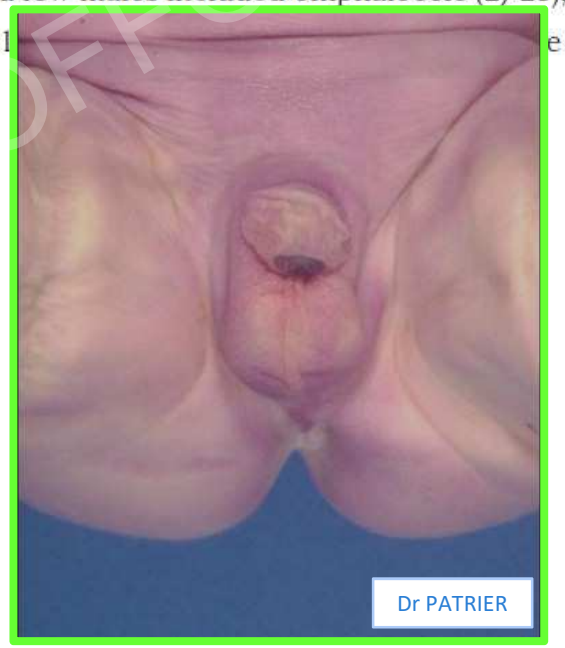


Urogenital abnormalities included micropenis (9/10), cryptorchidism (8/10), small or absent testis (9/11 by ultrasound investigation), and hypospadias (4/10). In one child (G.IV:5) and one deceased newborn (I.III:2) cysts of the renal collection ducts were present.
features reported in a few males included omphalocele [illegible] liver cysts (E.IV:1 multiple l[illegible]e liver



Our case : NO genitals or testes anomalies

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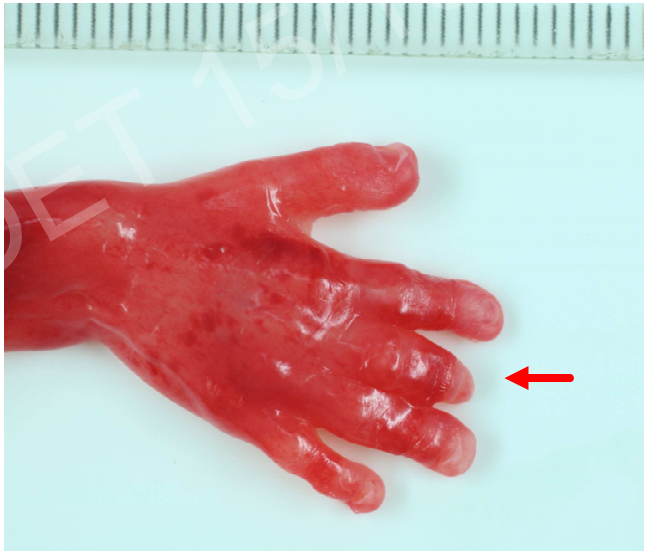
Hands showed short distal phalanges with broad stubby thumbs (14/16), camptodactyly (3/19), syndactyly (2/20), and nail hypoplasia or absent nails (5/17) (Supplementary Figures 2 and 4). Feet showed pes planus (6/8), preaxial polydactyly (3/20), and/or with (partial) cutaneous syndactyly (3/13) (Supplementary Figures 2 and 4).



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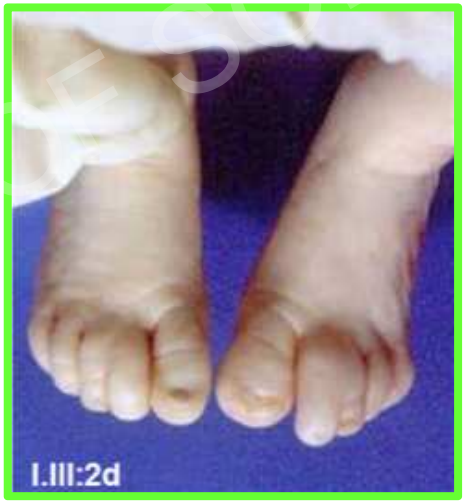

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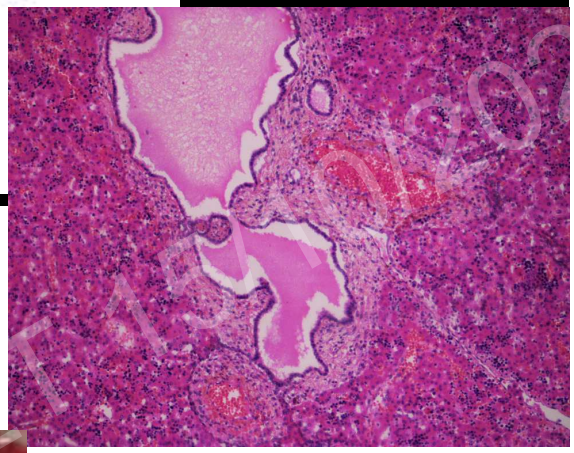
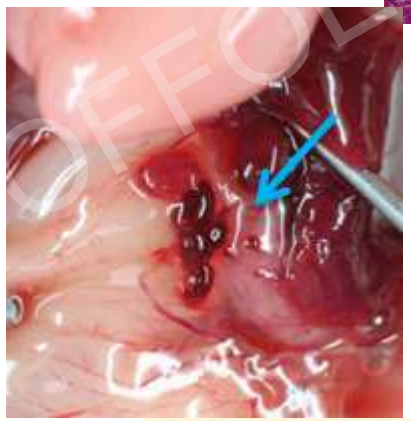
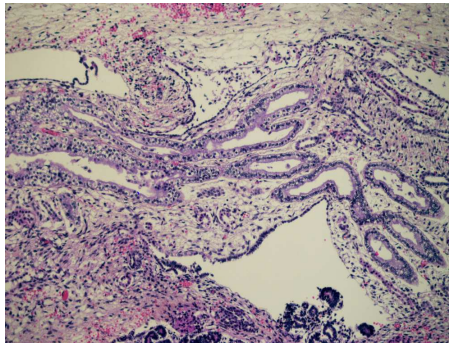
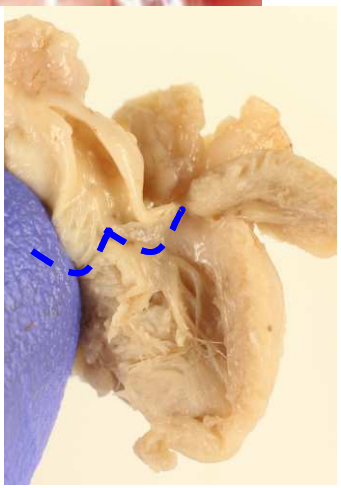




ent testis (9/11 by ultrasound investigation), and hypospadias (4/10). In one child (G.IV:5) and one deceased newborn (I.III:2) cysts of the renal collection ducts were present. Abdominal features reported in a few males included omphalocele (2/23), liver cysts (E.IV:1 multiple liver cysts in left lobe and G.VI:2 multiple liver cysts with ductal plate malformation), polysplenia (I.III:2), and malrotation of bowel (I.III:9).



Four affected males had congenital heart defects (CHD) (4/23), two with aortic stenosis (D.III:11, D.V:1), one with aortic isthmus stenosis with persistent foramen ovale and an atrial septal with persistent left upper vena cava, isolated separation of vertebral artery) (I.III:10) and one with Tetralogy of Fallot (D.IV:4).

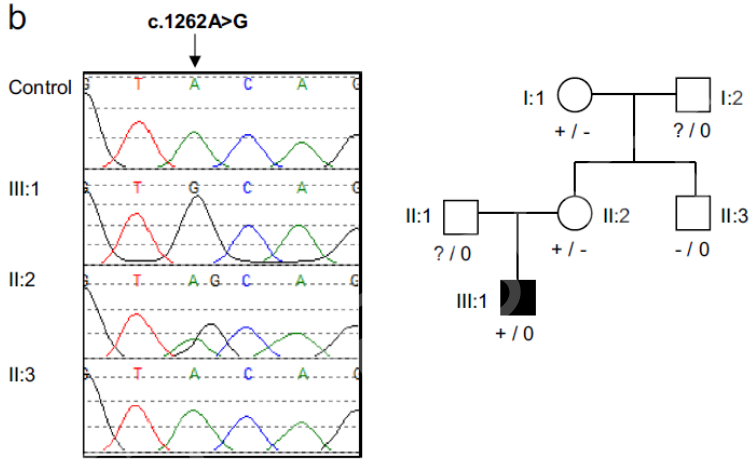


A novel RLIM/RNF12 variant disrupts protein stability and function to cause severe Tonne-Kalscheuer syndrome.

Bustos F, Espejo-Serrano C, Segarra-Fas A, Toth R, Eaton AJ, Kernohan KD, Wilson MJ, Riley LG, Findlay GM.

Sci Rep. 2021 *May 5;11(1):9560.*

Neonatal death *RLIM* missense variant,c.1262A>G p.(Tyr421Cys)



Postmortem examination revealed congenital diaphragmatic hernia with aplasia of the posterolateral left hemi-diaphragm, displacement of the mediastinum to the right, herniation of the small and large intestine, stomach, spleen, left lobe of liver, and pancreas into the left hemithorax, absent middle lobe right lung and severe bilateral pulmonary hypoplasia. There was an accessory spleen. The cardiovascular system showed aberrant aortic arch branching with the left subclavian, left common carotid and right common carotid arteries arising from a single brachiocephalic trunk. Urogenital abnormalities included cryptorchidism with pelvic testes, but kidneys were normal. A cavum septum pellucidum was present. The clinical features were considered to be most consistent with Fryns syndrome (MIM #229850). Pallister-Killian syndrome (tetrasomy 12p; MIM #601803) was considered, but fluorescence in-situ hybridisation for chromosome 12p on fetal lung imprints, standard karyotype on cultured fibroblasts and chromosome microarray on DNA extracted from stored fetal tissue (Agilent Sureprint G3 ISCA Targeted Microarray 8 × 60 K) were normal.

Tonne-Kalscheuer Syndrome
TOKAS

OMIM 300379
Hérédité XL
Gènes *RLIM*
Locus Xq13.2

THE HALLMARK FEATURES

- **IUGR** (80%) , short stature
- **Microcephaly** (86%)
- **Dysmorphie faciale** broad proeminent forehead, long narrow face, micrognathia, malar hypoplasia (asymetric 24%), hyper and then hypotelorism, straight lateral eyebrows, downslanting palpebral fissures,broad nasal bridge, small mouth with downturned corners
- **Hands and Feet** broad thumbs / hallux (double), hypoplasic distal phalanges/nails, pre/post axial campto-polydactyly
- **GenitoUrinary anomalies** small penis (90%), hypospadias (40%), small /ectopic testes (80%)
- **Diaphragmatic Hernia** (50%)

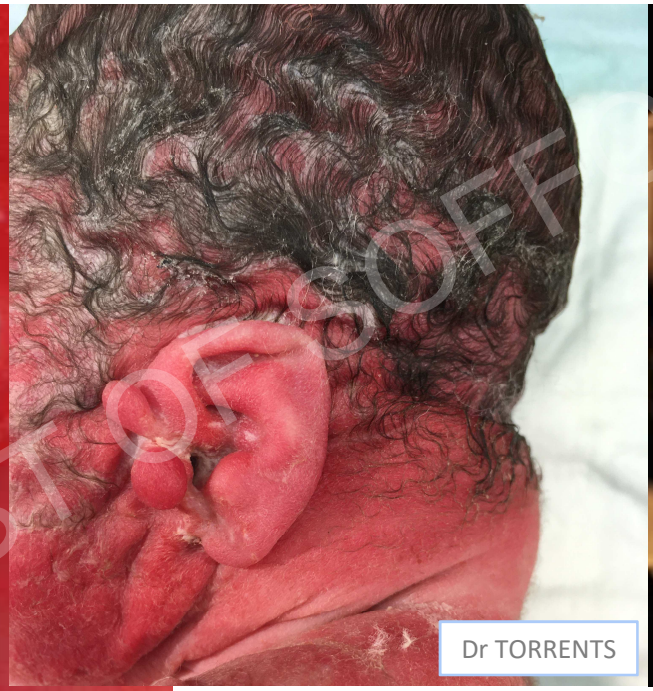
OTHERS

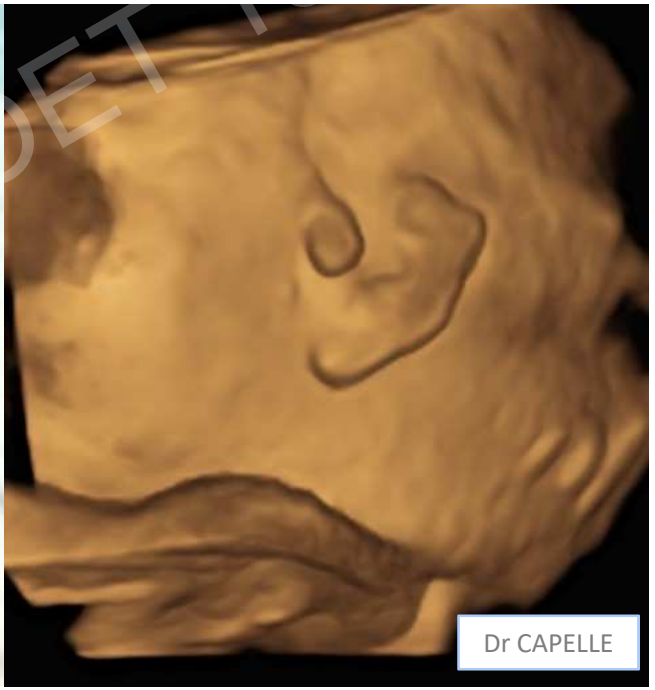
- Ductal plate anomalies, liver cysts (33%)
- Kidneys cysts (collecting ducts) (29%)
- Polysplenia (20%)
- Intestinal malrotation(20%)
- Congenital heart defects (17 %)
- Omphalocele (9%)
- Palate cleft SM (bifid uvula) (8%)
- Nipples (supernumerary, remote)(8%-12%)

And Impaired intelectual development, delayed psychomotor development etc…

syndromic X-linked intellectual disability and behavior disorder
Suzanna G.M. Frints, Vera M. Kalscheuer. *Molecular Psychiatry, 2019*

Preauricular skin TAGS





US 3D Surface Render view
showing preauricular skin tag

MERCI

TOKAS