An unusual case of VACTERL-H with holoprosencephaly spectrum

SOFFOET Meeting on line
Best Of English version
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SoFFœt
Société Française de Fœtopathologie

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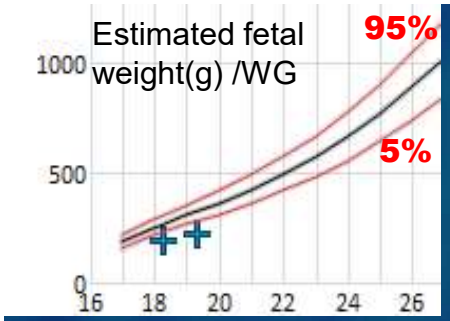
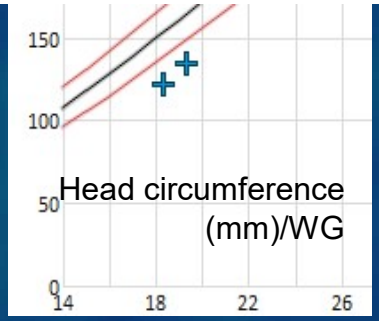
Centre Pluridisciplinaire de Diagnostic Prénatal LEONARD DE VINCI

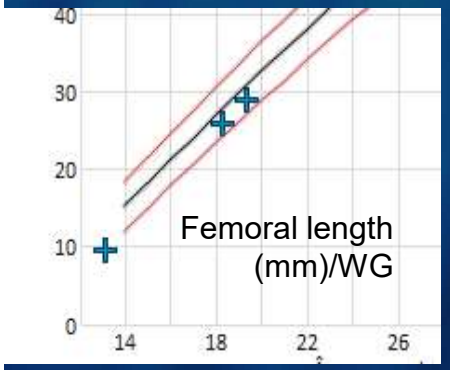
Clinical history

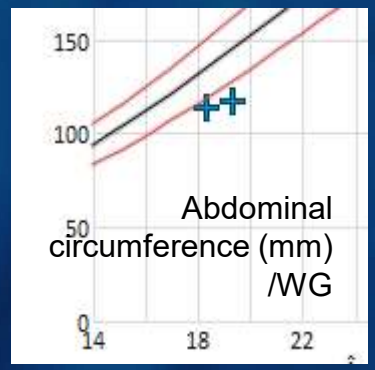
- Mother : 39 yo. Hashimoto's thyroiditis.
- Father : mutation of BRCA2 gene (ovarian cancer in his mother)
- non consanguineous
- G2P1 : healthy girl (2700g).

- US 11w+3d : NT=1.3mm / CRL=49.5 mm, intra-abdominal anechogenic image 2x8 mm
- NIPT (17WG) : negative for T 21, 18, 13



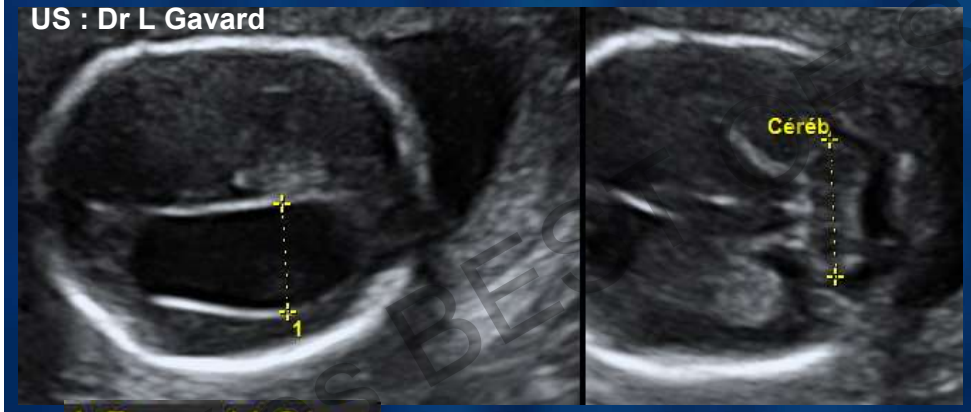


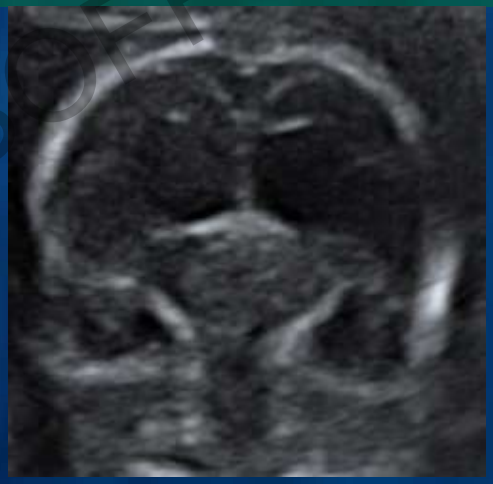


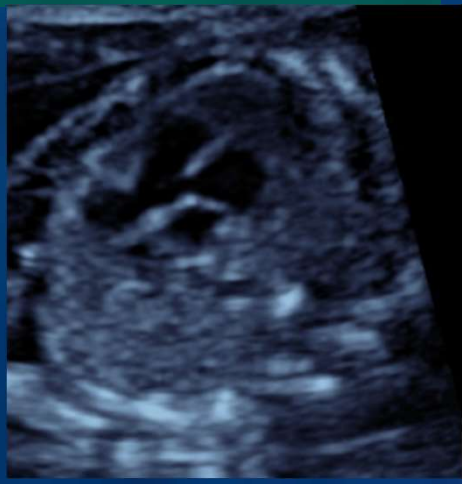


US 18+2 :

- severe IUGR
- cerebral ventriculomegaly
- absent septum pellucidum
- cerebellar hypoplasia
- common arterial trunk

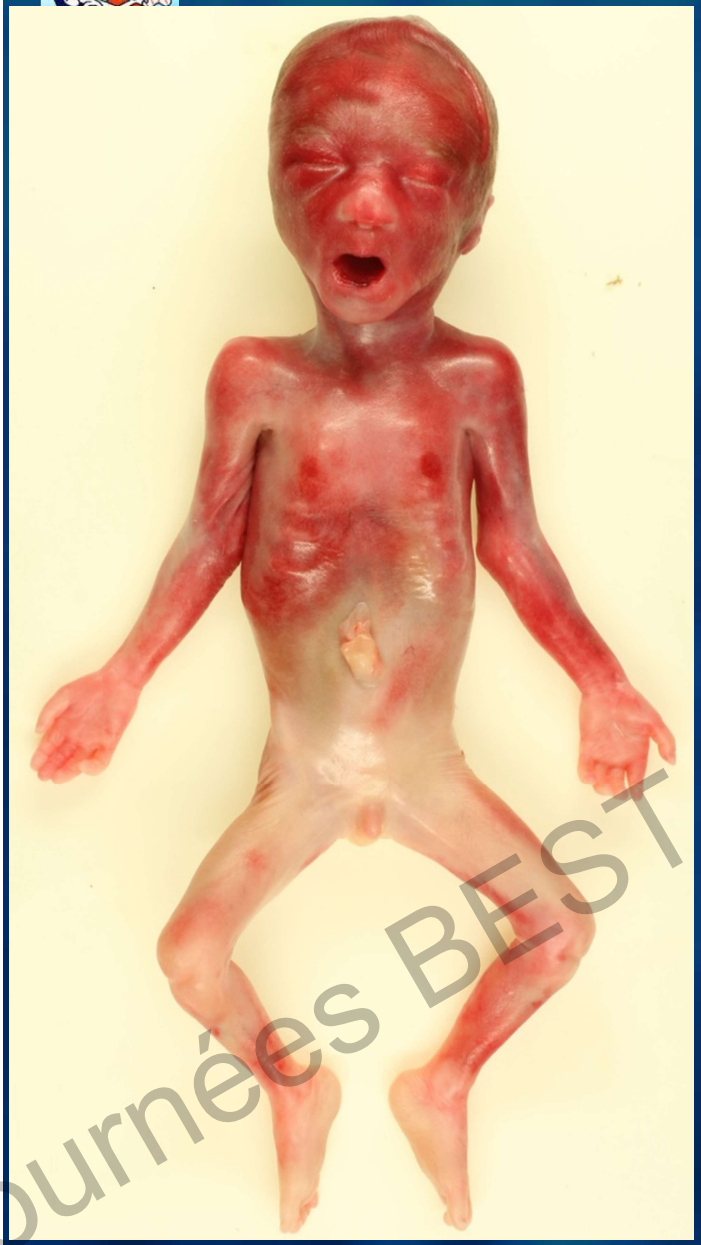


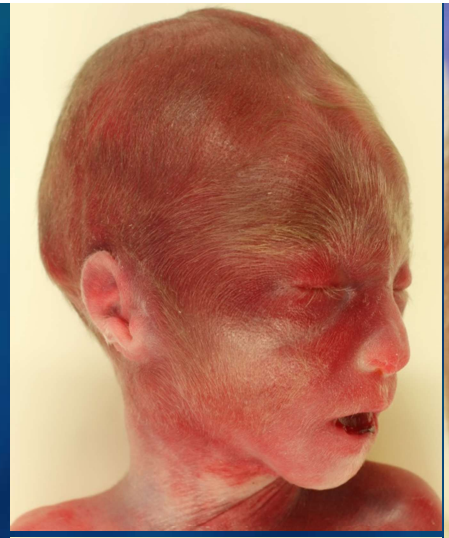


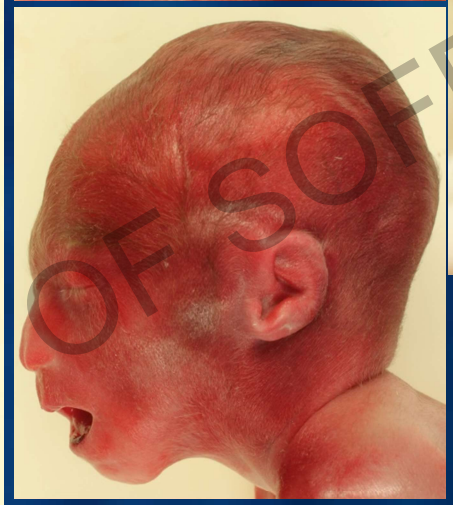


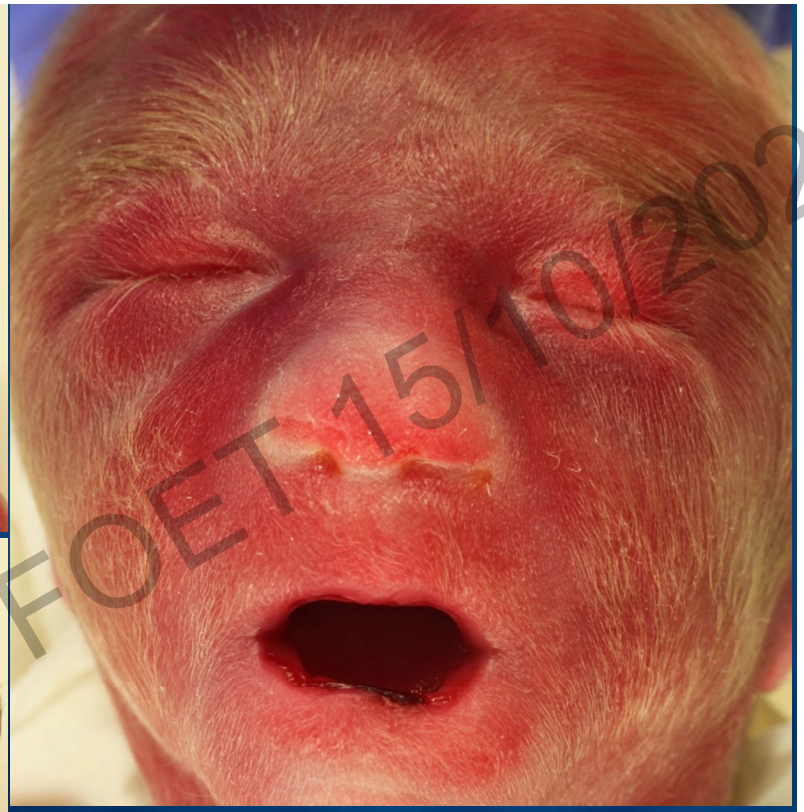
- Amniocentesis : normal array CGH
- TOP : 24+1.

TOP 24WG





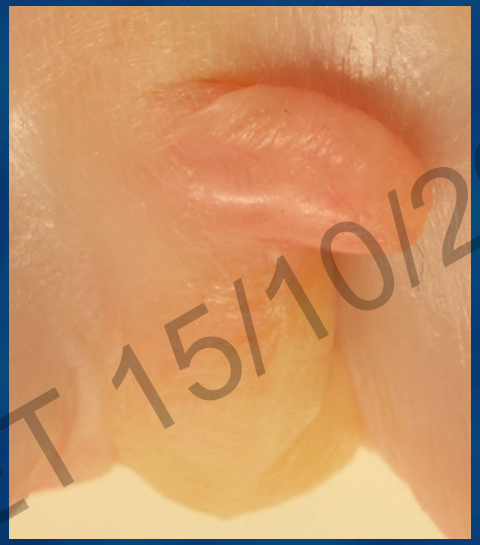


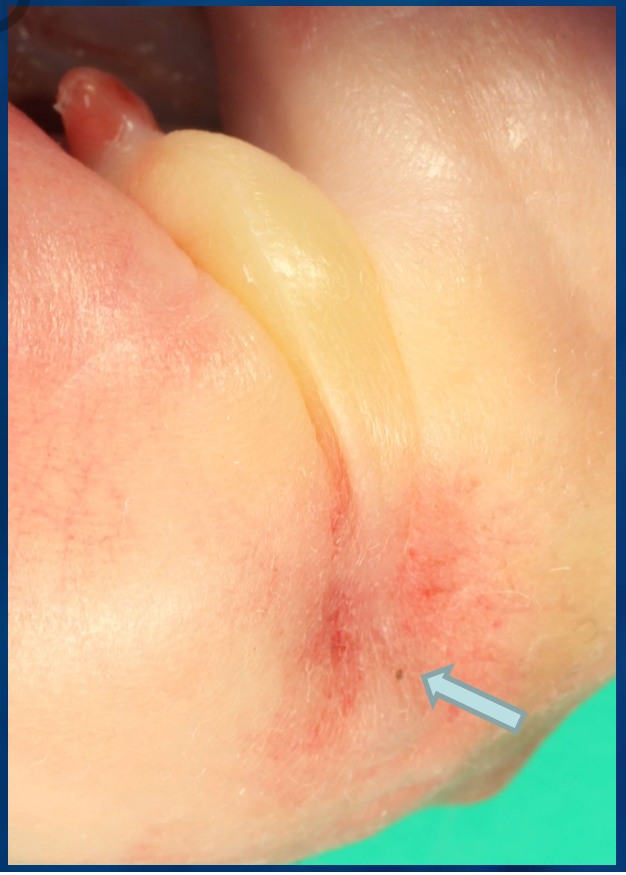


Weight = 21 WG
CRL = 22 WG
CHL = 23 WG
Foot L = 22 WG

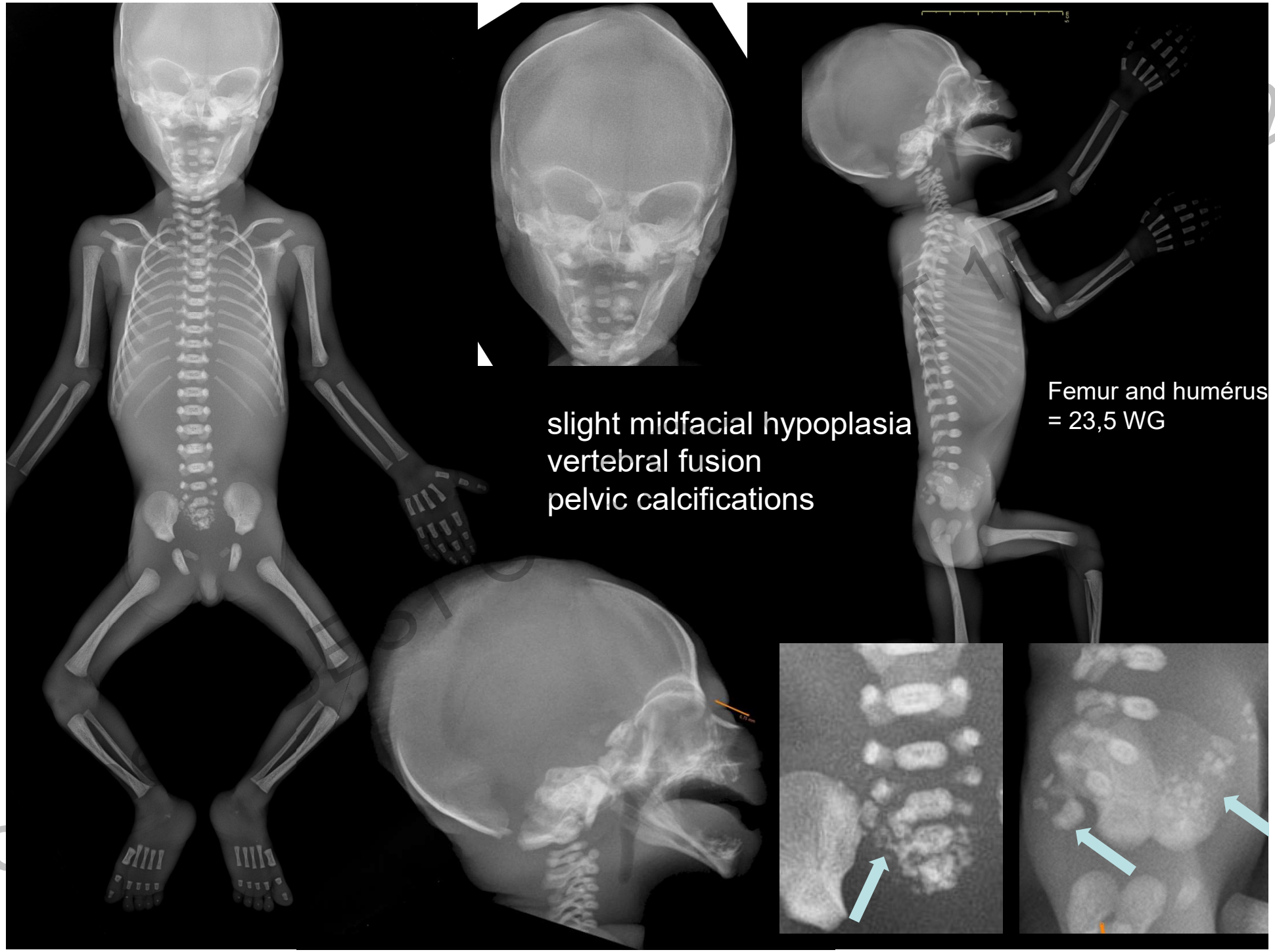
HC <p5, = 20 WG
BIP <p5, = 20 WG

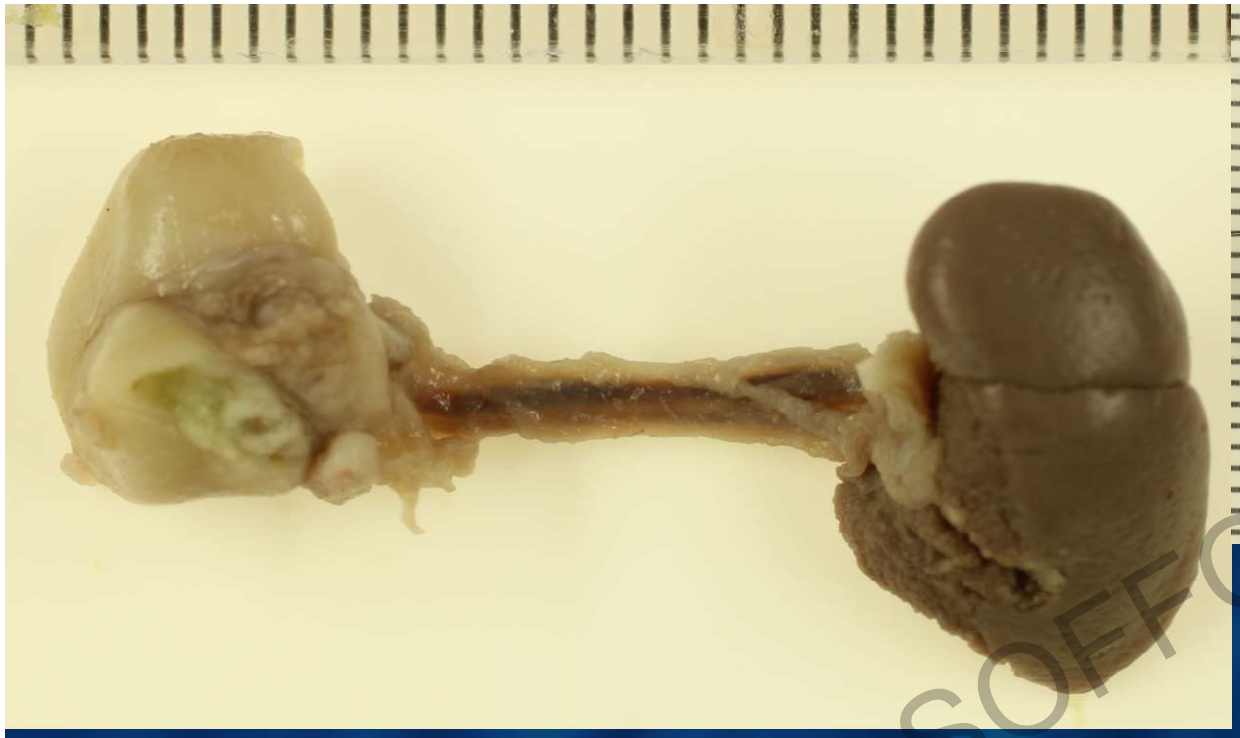
- enophtalmos
- short palpebral fissures
- wide nose
- small nostrils
- narrow philtrum

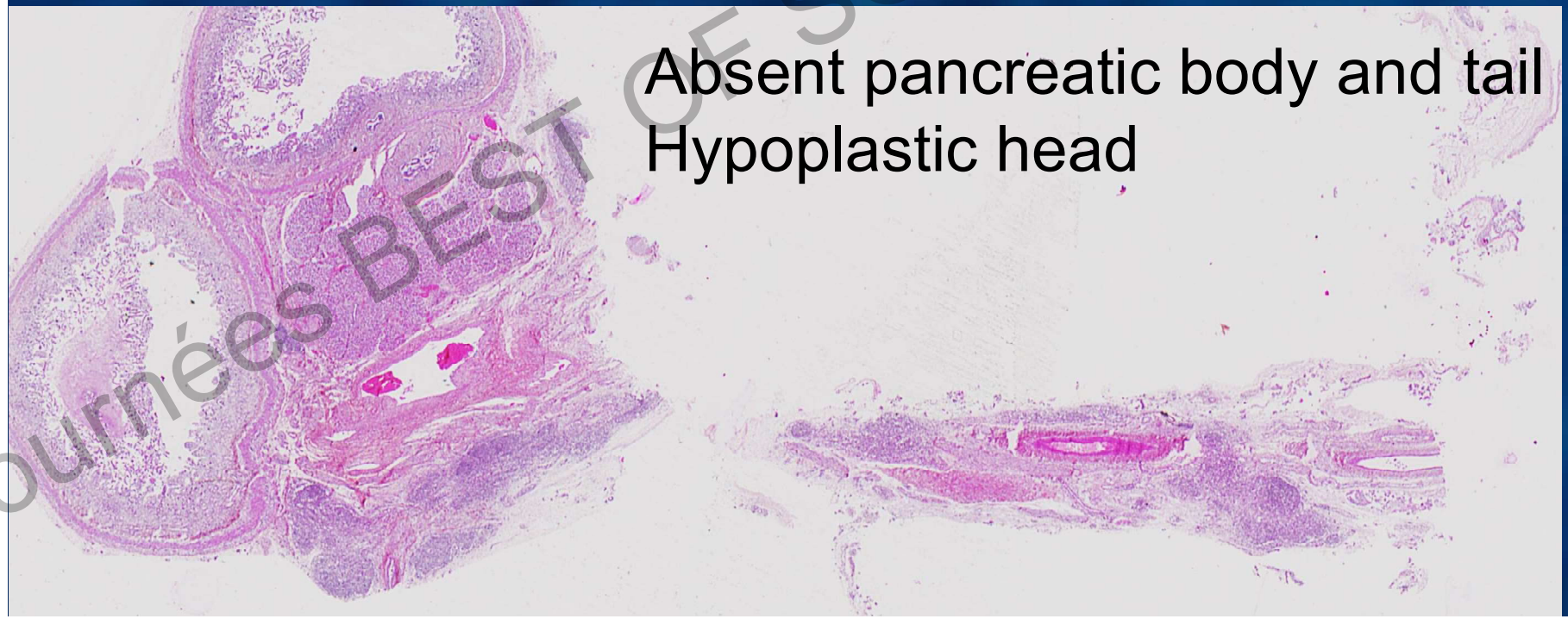




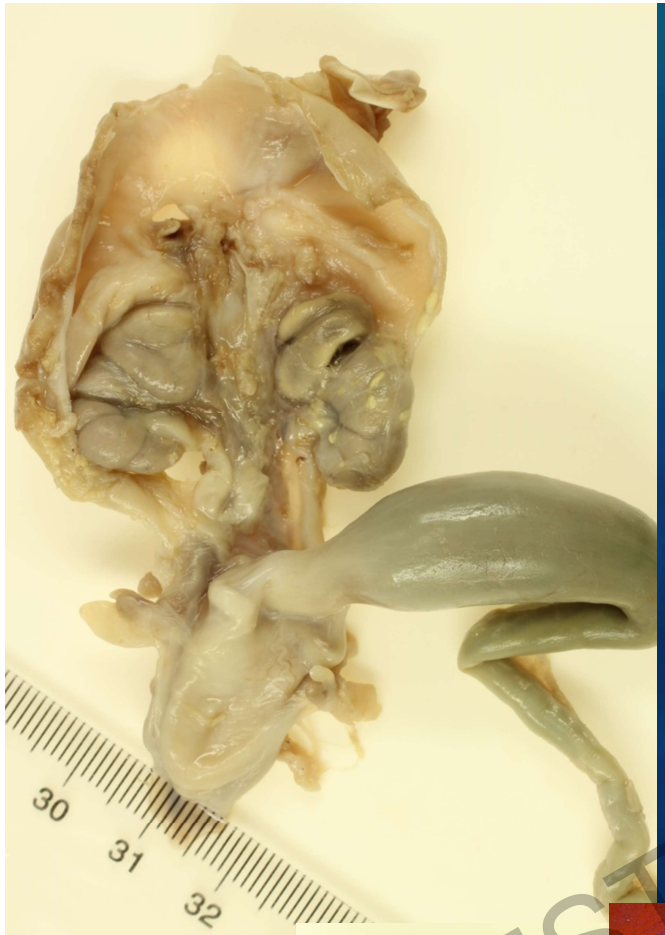
- Bilateral single transverse palmar crease
- Imperforate anus

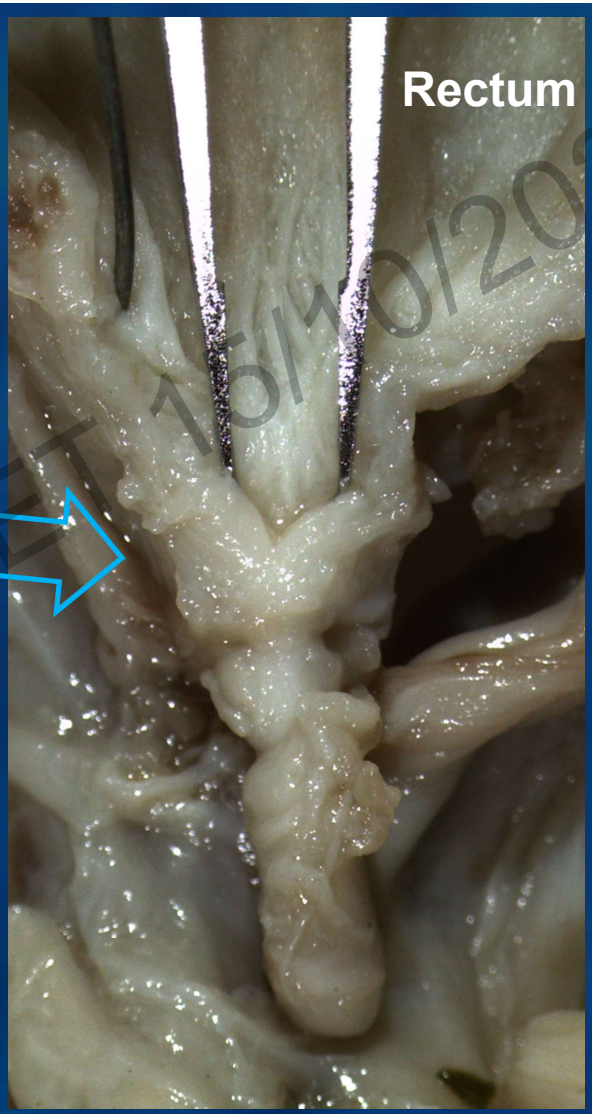

slight midfacial hypoplasia
vertebral fusion
pelvic calcifications
Femur and humérus
= 23,5 WG

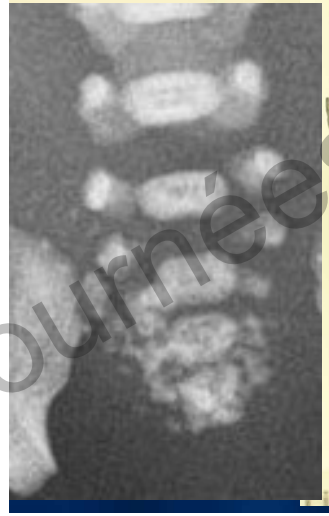




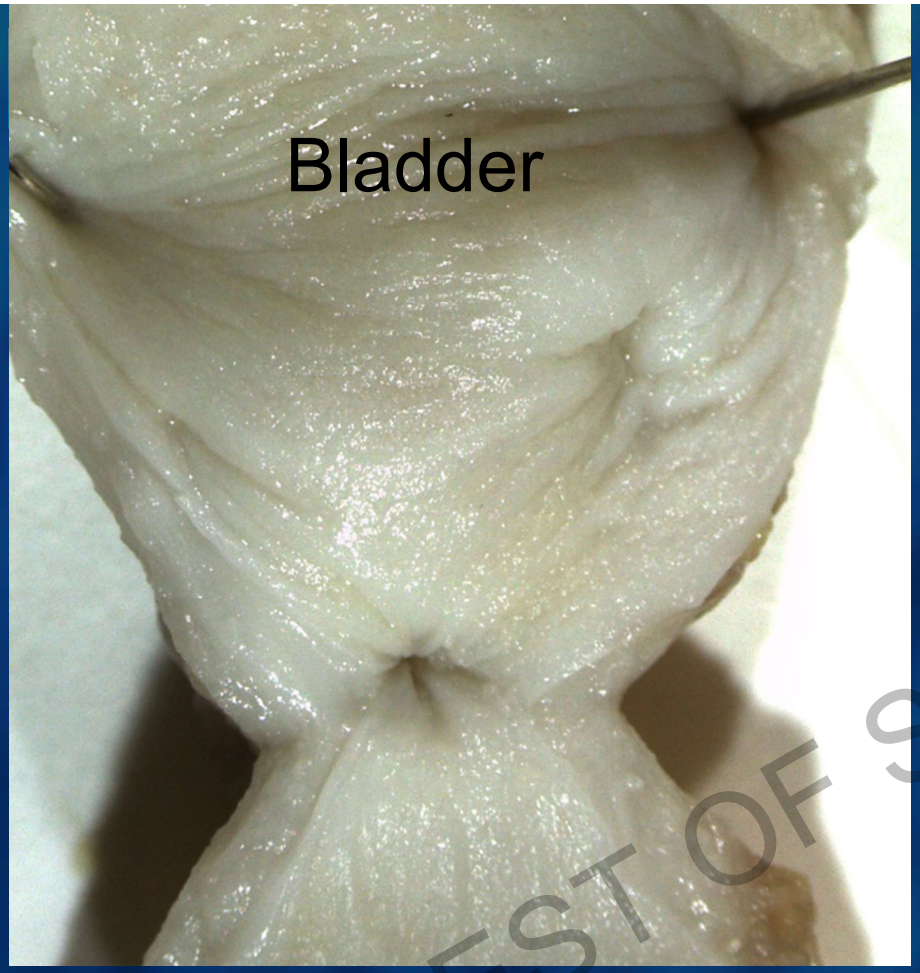
Absent pancreatic body and tail
Hypoplastic head



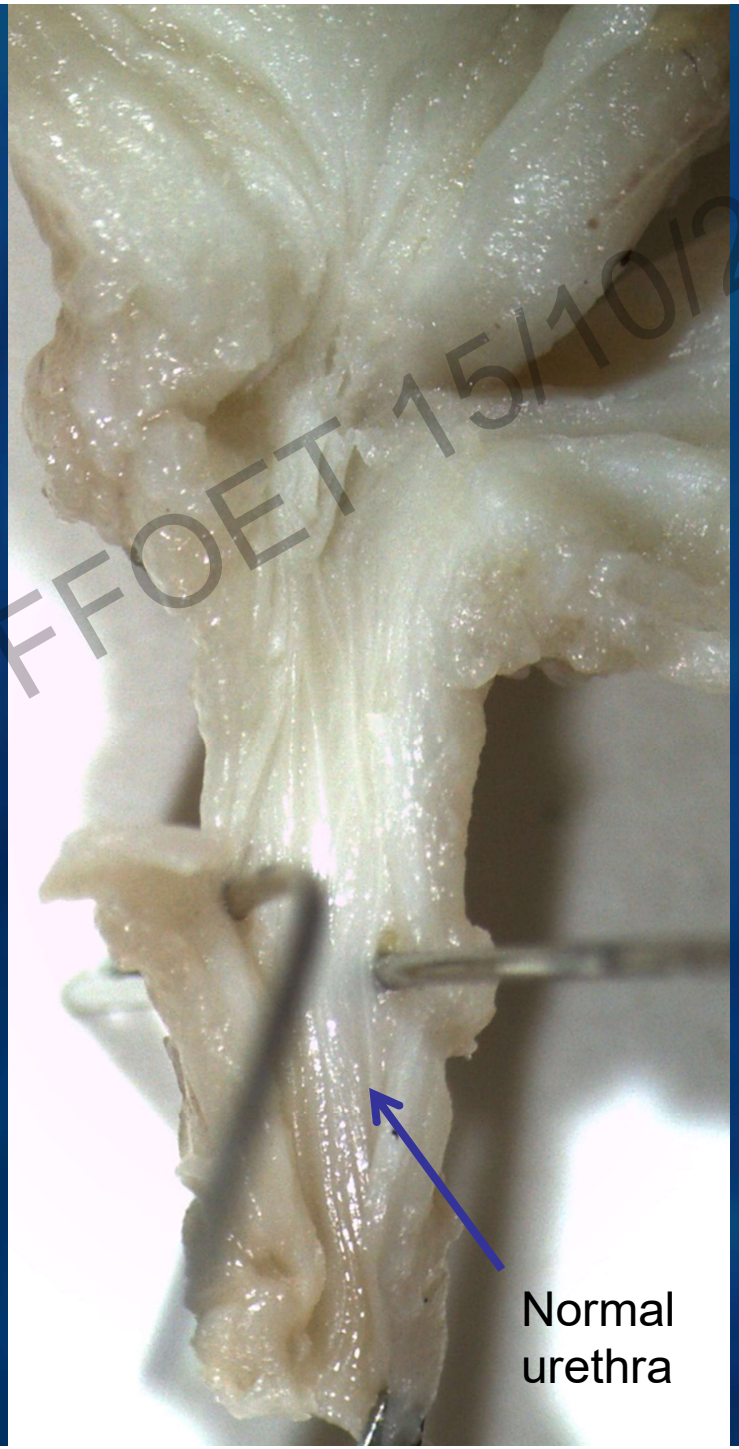


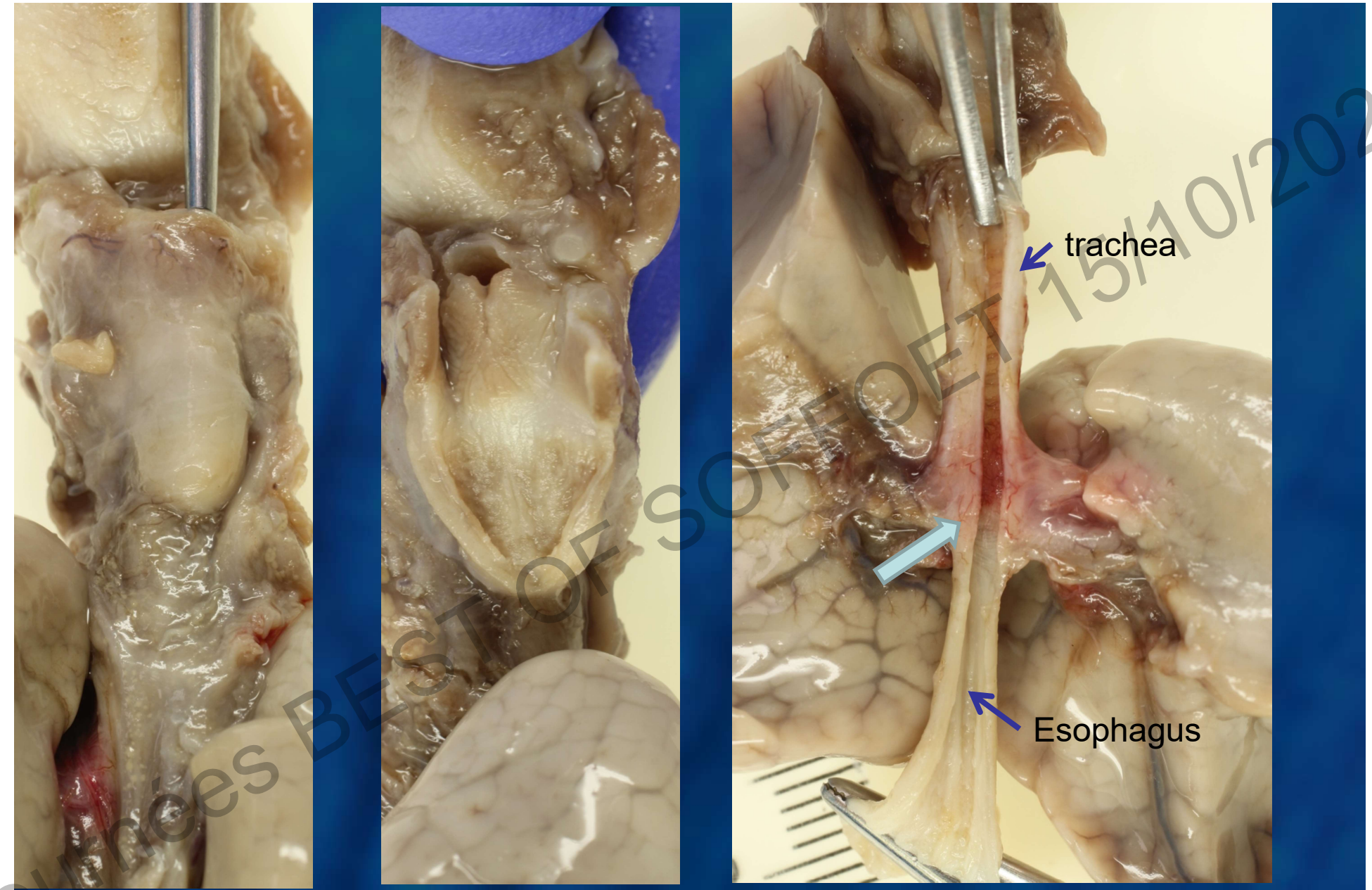


- dilated sigmoid colon
- rectal atresia
- stercoliths

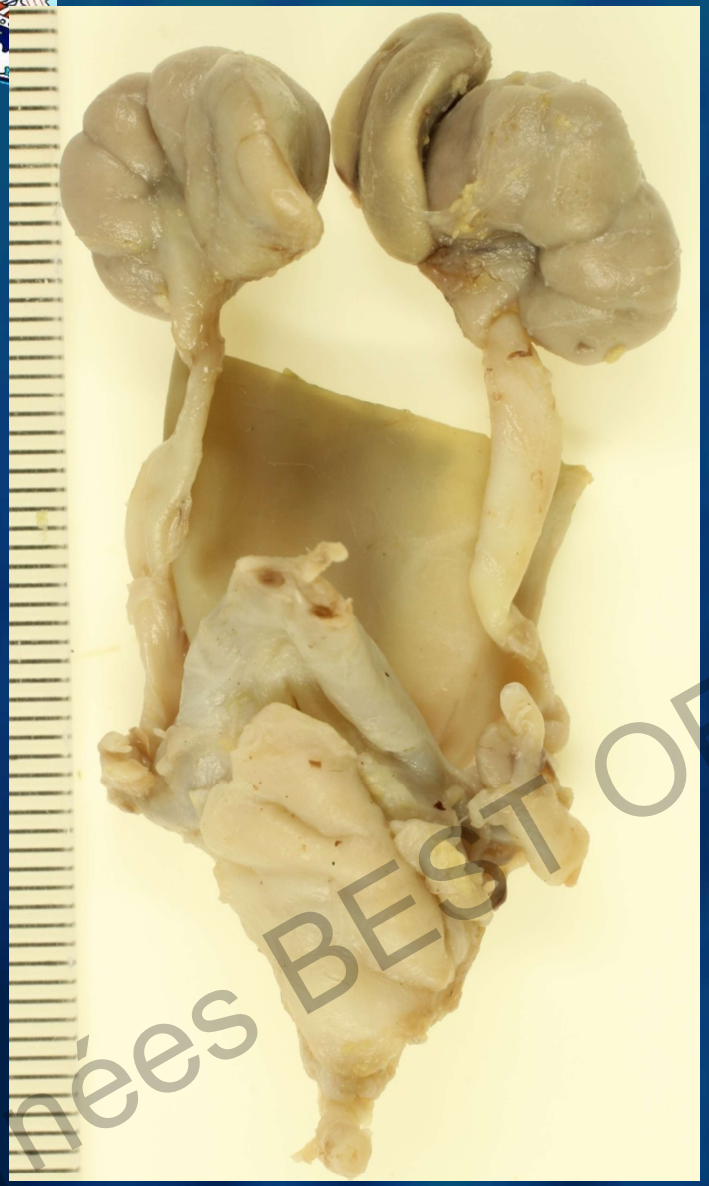


no urinary-digestive fistula
!!!

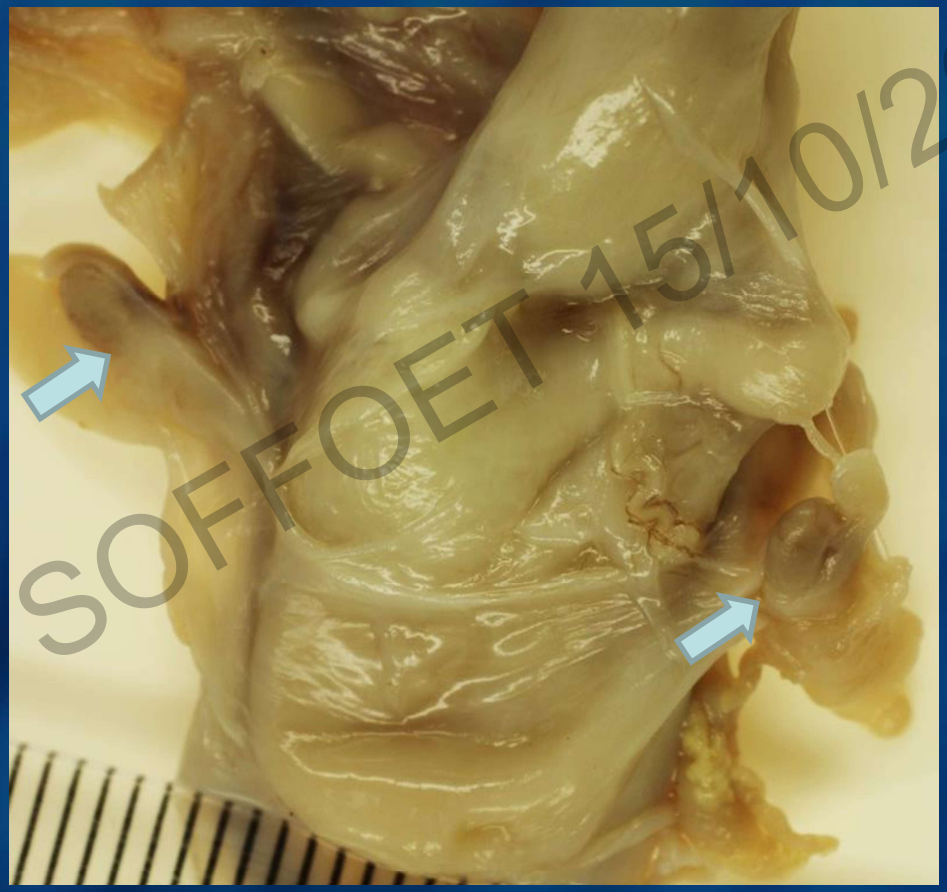




Oesophageal atresia with distal oesophageal fistula to the tracheal carina

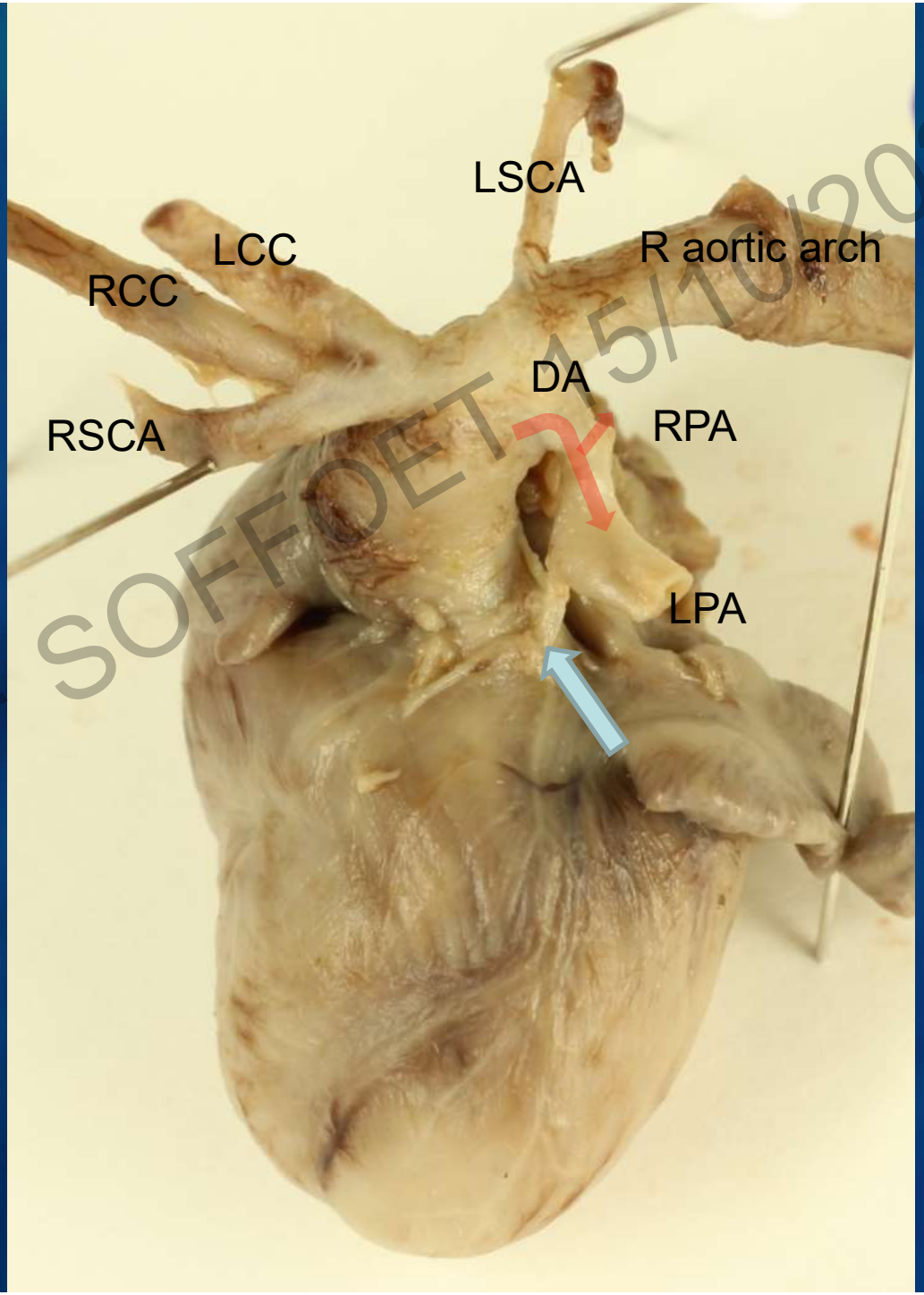


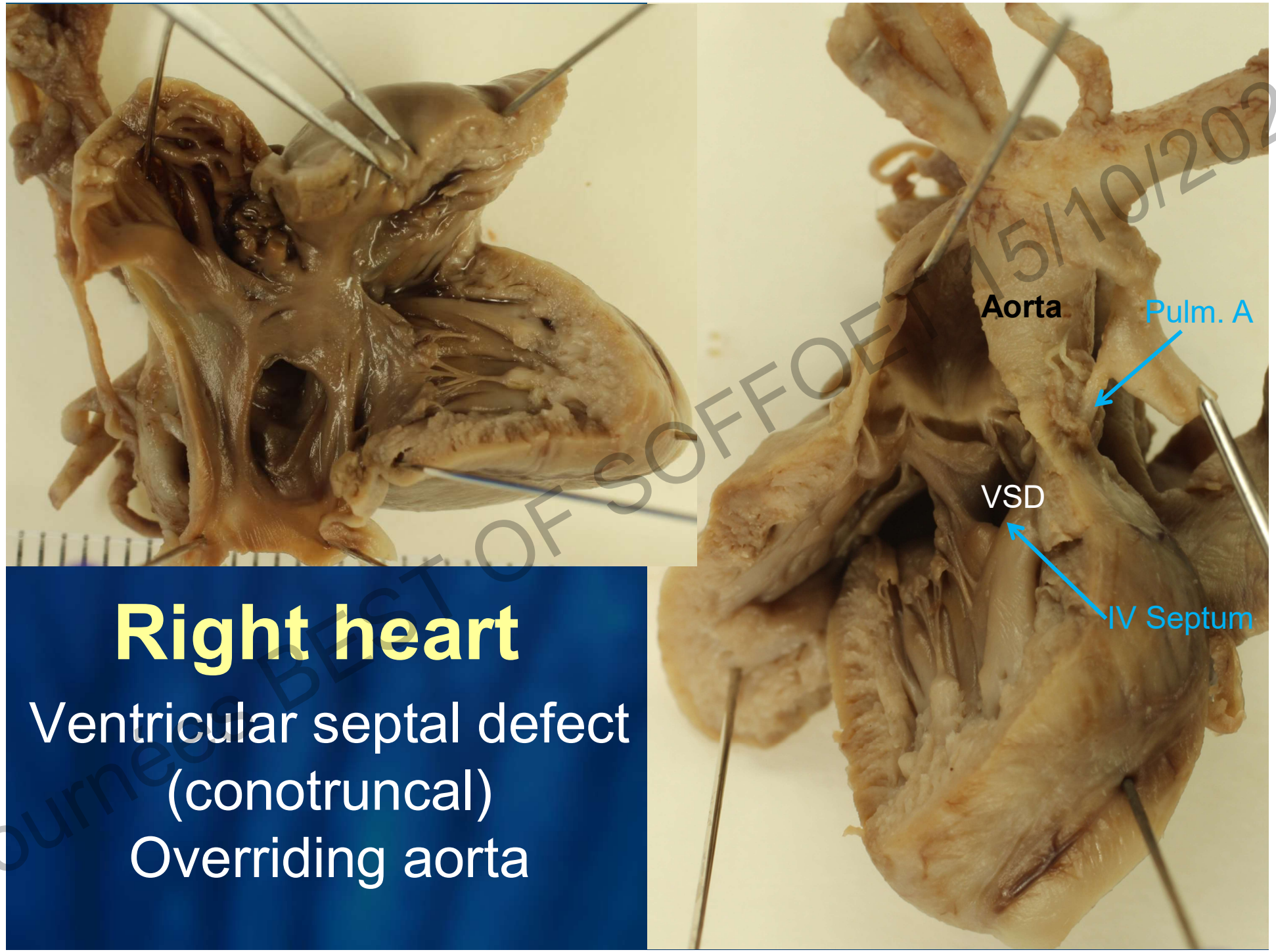
Kidneys = 1.7g, N = 3.5 g
Adrenals = 0.5 g, N = 1.6 g



Hypoplastic testes

- pulmonary atresia
- right aortic arch





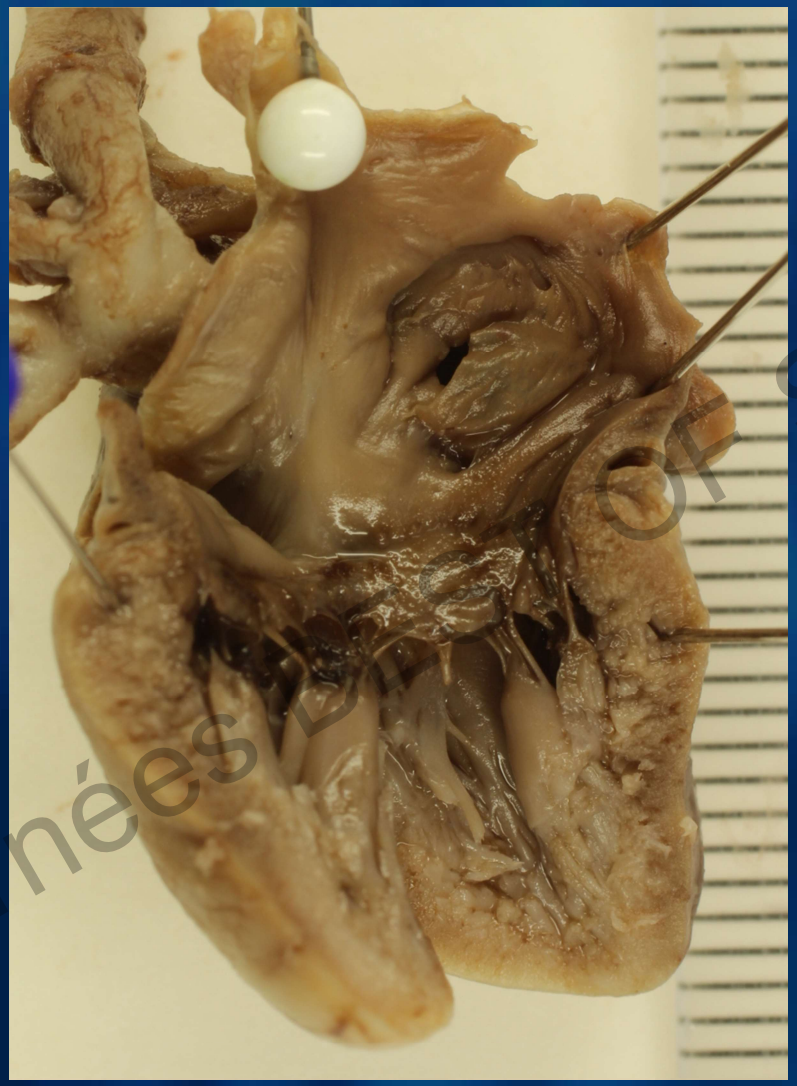
Right heart

Ventricular septal defect (conotruncal)

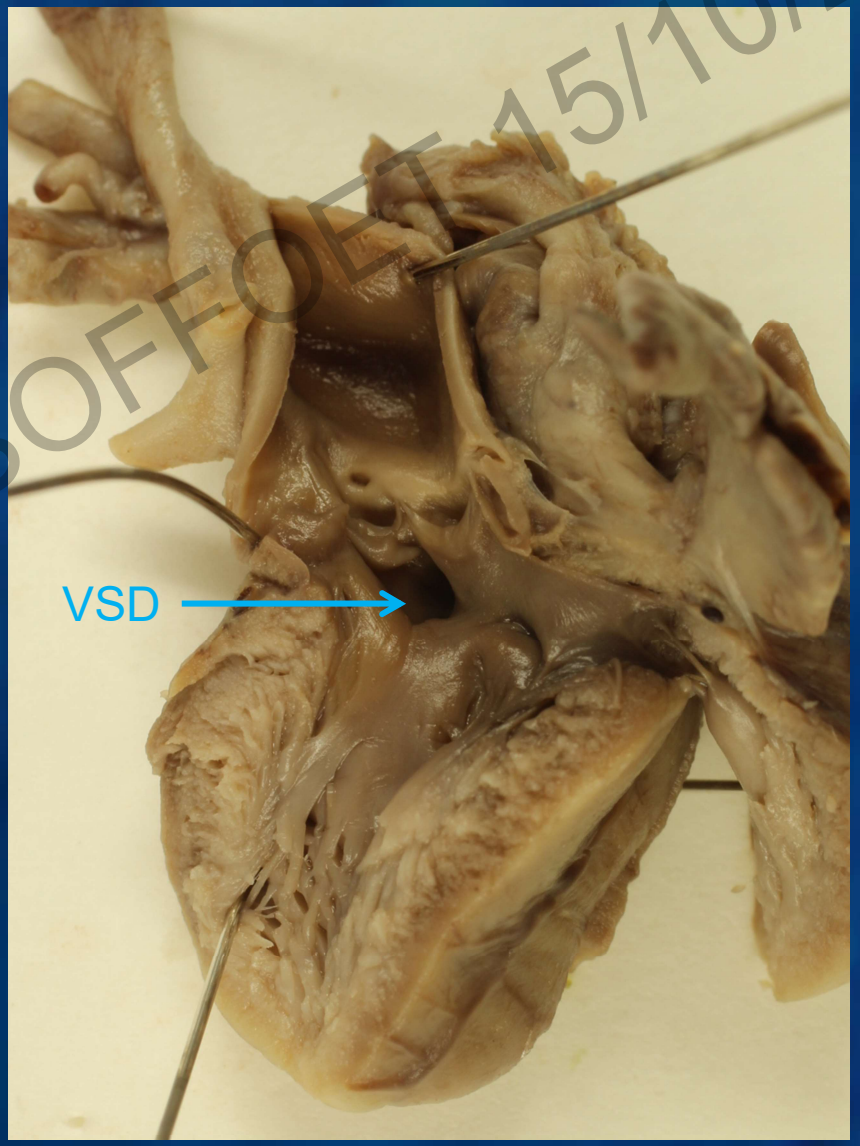
Overriding aorta

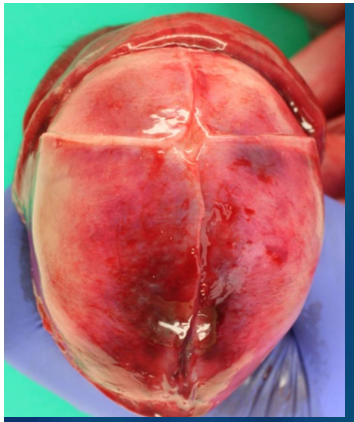
Left heart

Inlet

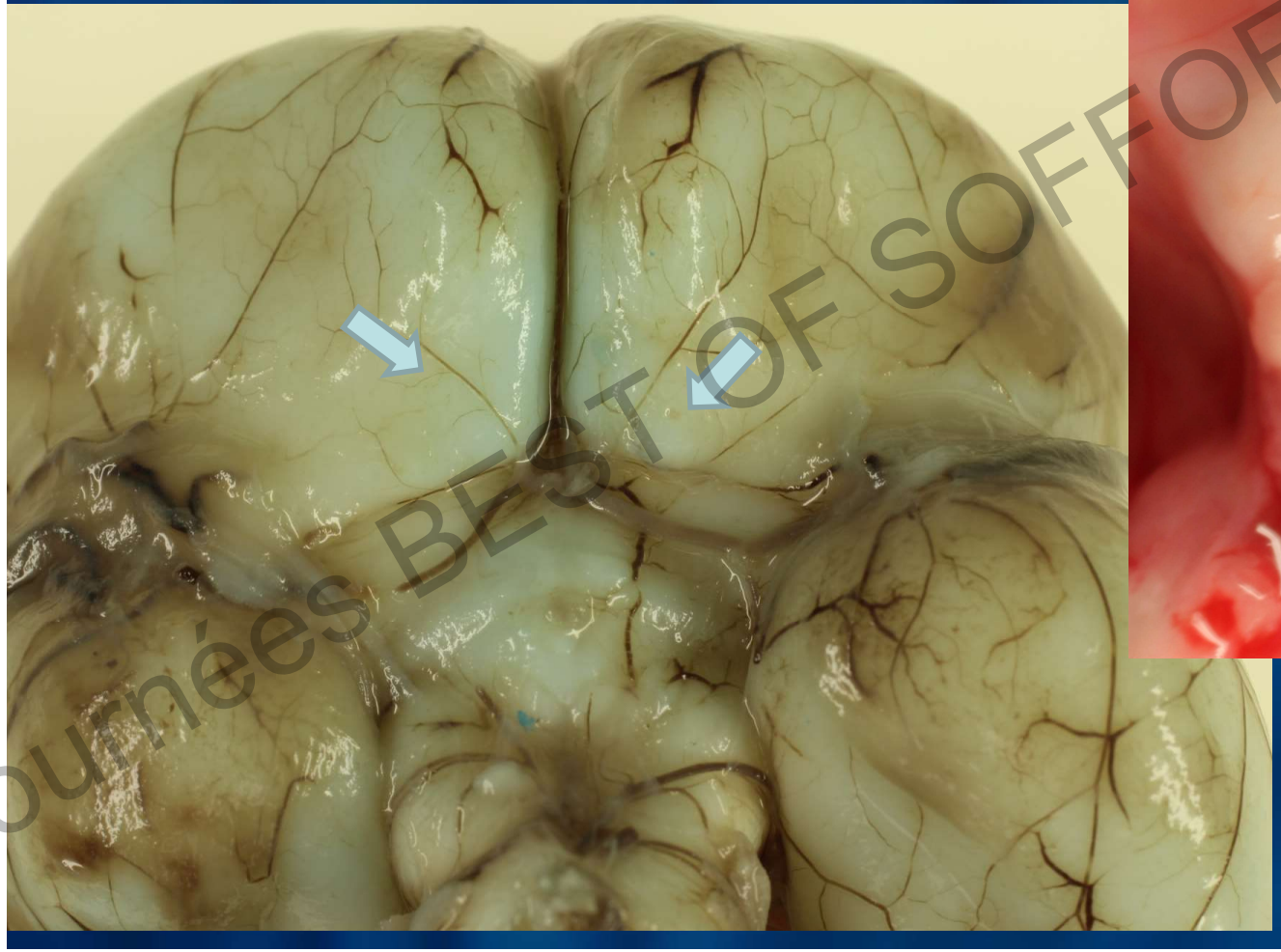


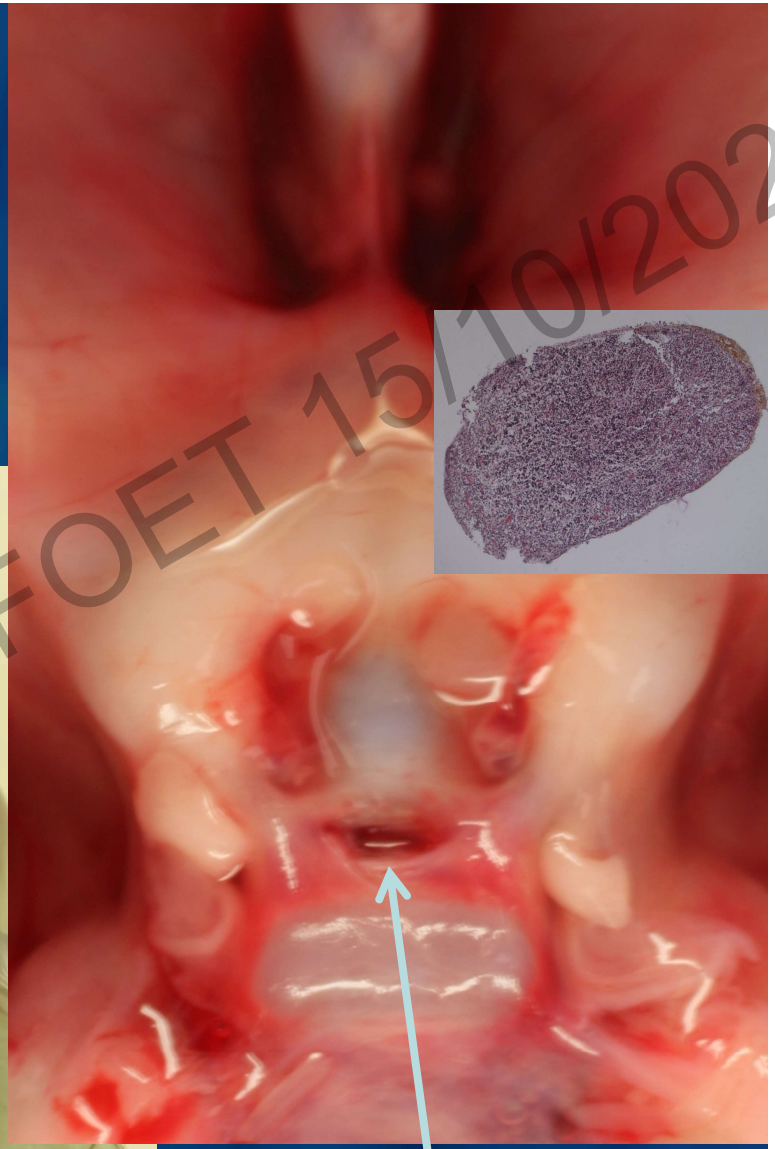
Oulet



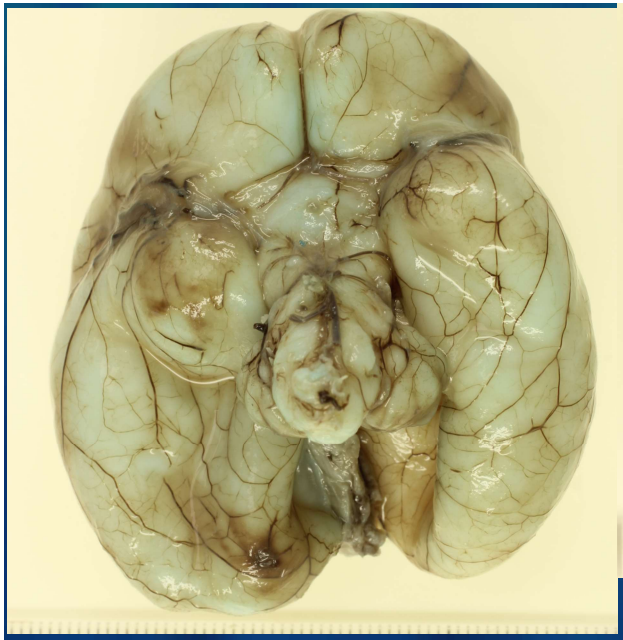


Agenesis of olfactory bulbs
Hypoplastic pipuitary
Hypoplastic optic chiasm





Small sella turcica

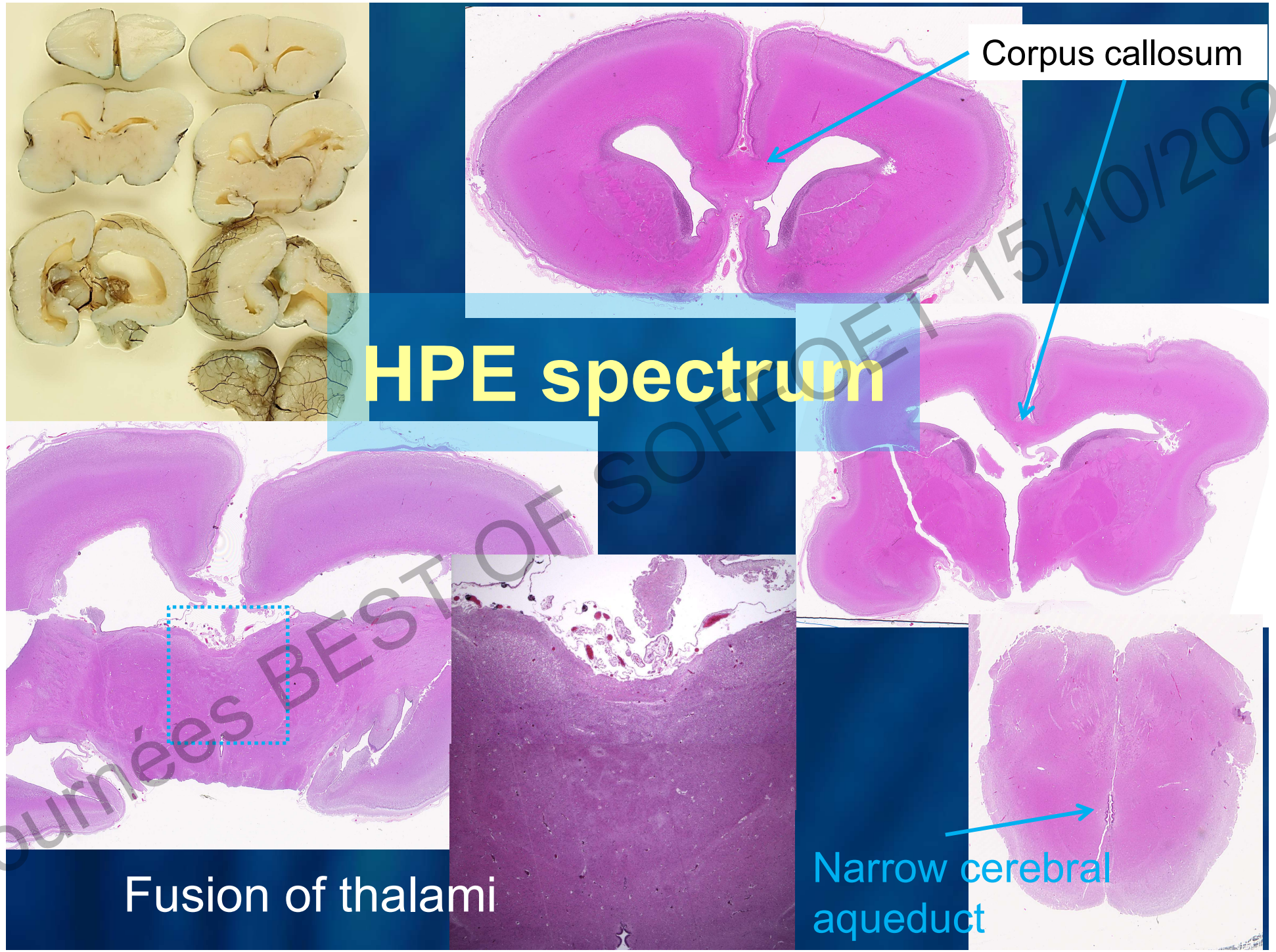


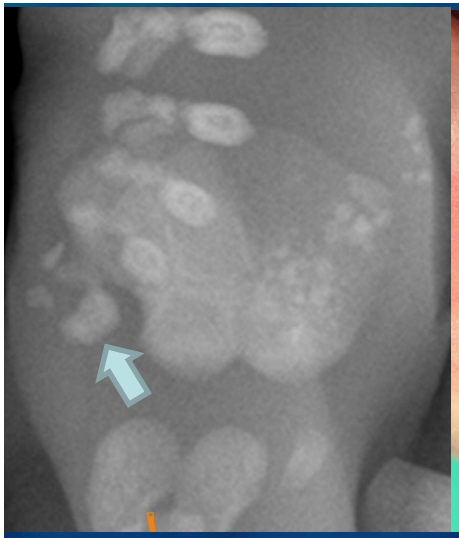
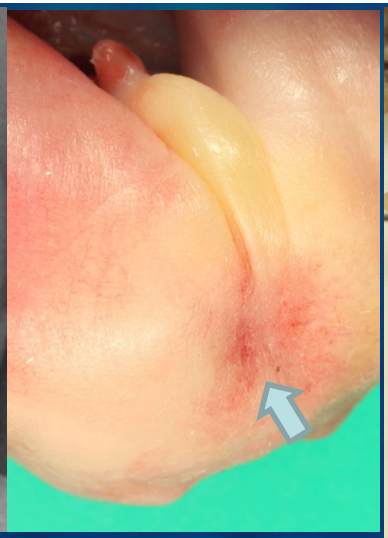
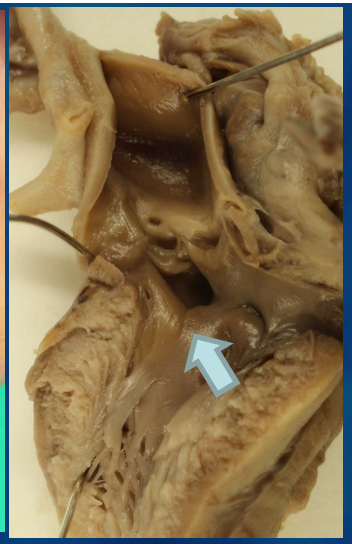
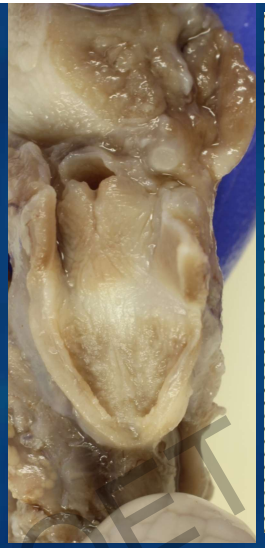
TOP = 24 WG

Brain weight <p5, = **19** WG
RFOD <p5, = **20** WG
LFOD <p5, = **20** WG
BIP = 41,5 mm

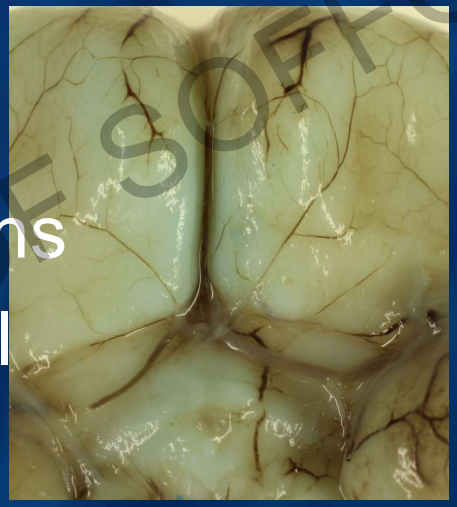
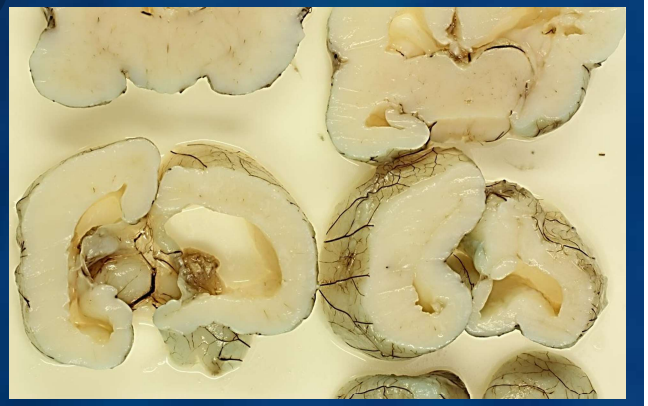
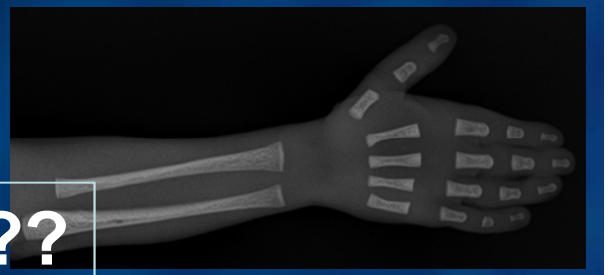
CTD <p5, = **19** WG
Cerebellar W <p5, = **18,5** WG

Microphthalmia




- **V**ertebral anomalies
- **A**nal atresia
- **C**ardiac malformations
- **T**racheo-**E**sophageal fistula
- **R**enal anomalies
- ~~**L**imb abnormalities~~
- + **H**ydrocephalus

VACTERL-H ??

Holoprosencephaly spectrum

Genetic testings:

- Prenatal : **Normal** FISH and array CGH arr(1-22)x2,(X,Y)x1
- Genetic testing for holoprosencephaly : negative
- Trio exome sequencing :

two compound heterozygous variants in the *BRCA2* gene inherited from the parents:

  - Mother : frameshift (NM_000059.3:c.5213_5216del, p.(Thr1738Ilefs*2))
  - Father : splice (NM_000059.3:c.7007G>C, p.?).
  - Two variants classified as pathogenic (ClinVar database) and responsible for the polymalformative syndrome in the fetus.

* 600185

BRCA2 DNA REPAIR-ASSOCIATED PROTEIN; BRCA2

Alternative titles; symbols

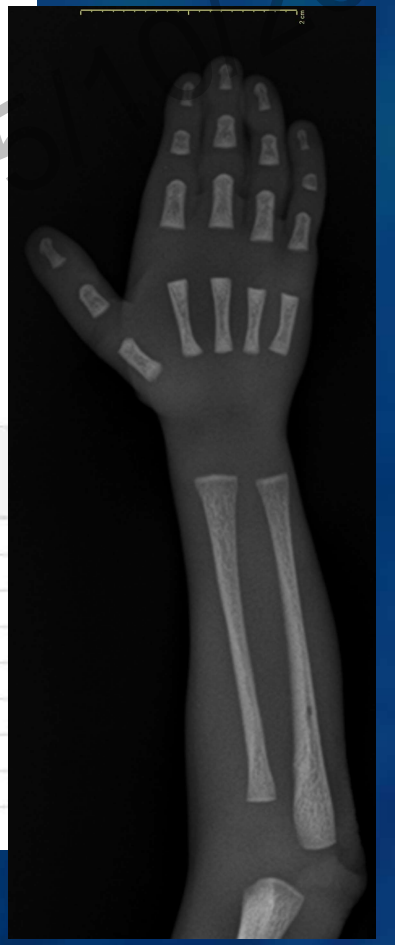
BRCA2 GENE
FANCD1 GENE; FANCD1

HGNC Approved Gene Symbol: BRCA2

Cytogenetic location: 13q13.1 *Genomic coordinates (GRCh38): 13:32,315,507-32,400,267* (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
13q13.1	Fanconi anemia, complementation group D1	605724	AR	3
	Wilms tumor	194070	AD, SMu	3
	{Breast cancer, male, susceptibility to}	114480	AD, SMu	3
	{Breast-ovarian cancer, familial, 2}	612555	AD	3
	{Glioblastoma 3}	613029	AR	3
	{Medulloblastoma}	155255	AD, AR, SMu	3
	{Pancreatic cancer 2}	613347		3
	{Prostate cancer}	176807	AD, SMu	3



VACTERL ⟺ Fanconi anemia

?HPE?

VACTERL with hydrocephalus: one end of the Fanconi anemia spectrum of anomalies?

Porteous ME, Cross I, Burn J.

Am J Med Genet. 1992 Aug 1;43(6):1032-4. doi: 10.1002/ajmg.1320430624.

PMID: 1415330

BRCA2 VACTERLH

BRCA2 VACTERL-H

BRCA2 VACTERL H

BRCA2 VACTERL

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3-4 results

1 Clinical and molecular features associated with biallelic mutations in FANCD1/**BRCA2**.

Cite Share

Alter BP, Rosenberg PS, Brody LC.

J Med Genet. 2007 Jan;44(1):1-9. doi: 10.1136/jmg.2006.043257. Epub 2006 Jul 6.

PMID: 16825431 Free PMC article.

Patients with biallelic mutations in **BRCA2** are in Fanconi anaemia group D1. We analysed the severity of the mutations in 27 cases, classified according to their association with breast cancer in heterozygotes, and their predicted functional effect. ...Missense mutations fo ...

FANCD1 = BRCA2

2 VACTERL-H Association and Fanconi Anemia.

Cite Share

Alter BP, Rosenberg PS.

Mol Syndromol. 2013 Feb;4(1-2):87-93. doi: 10.1159/000346035.

PMID: 23653579 Free PMC article.

The relative frequencies of the genotypes of the patients with FA VATER were strikingly different from those expected from the general FA population; only 19% were FANCA, while 21% were FANCB, 14% FANCD1/**BRCA2**, and 12% FANCD2. Consistent with their genotypes, those with th ...

3 Hepatoblastoma in a 4-year-old girl with Fanconi anaemia.

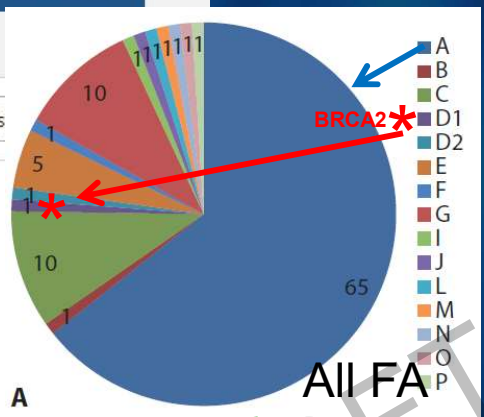
Cite Share

Kopic S, Eirich K, Schuster B, Hanenberg H, Varon-Mateeva R, Rittinger O, Schimpl G, Schindler D, Jones N.

Acta Paediatr. 2011 May;100(5):780-3. doi: 10.1111/j

PMID: 21138478

Subsequent genotyping revealed biallelic mutations describe the first case of hepatoblastoma in a patien the close clinical observation of early cancer-prone



Conclusion: We describe the first case of hepatoblastoma in a patient with FA to raise awareness of this tumour type in the close clinical observation of early cancer-prone forms of th condition, particularly in the presence of *FANCD1/BRCA2* mutations. The present case also underscores the importance of FA testing in patients with VACTERL(-H)

microcephaly and microphthalmia
Cranial MRI demonstrated an ectopic posterior pituary gland

4 Case report: Antenatal diagnostic of a polymalformative syndrome due to biallelic **BRCA2** mutations.

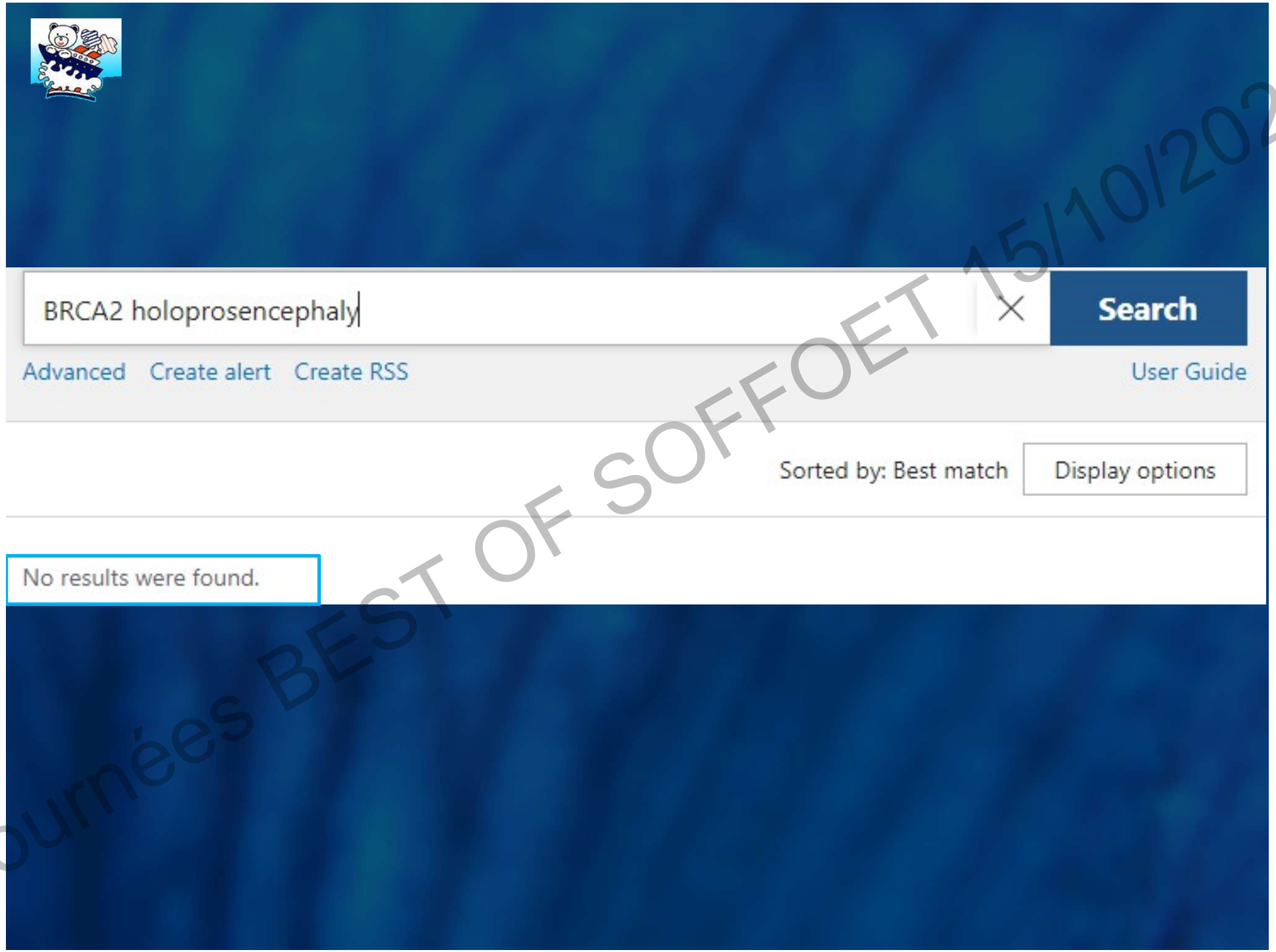
Cite Share

Anquetil A, Khung Savatovsky S, Gavard L, Bazin A, Guimiot F, Dubourg C, Mandelbrot L, Picone O.

Clin Case Rep. 2021 Sep 22;9(9):e04838. doi: 10.1002/ccr3.4838. eCollection 2021 Sep.

PMID: 34584710 Free PMC article.

Testing the partner of a **BRCA2** carrier must always be discussed. If both members of the couple are **BRCA2** carriers, they should be informed about the high risks of polymalformative syndromes....



VACTERL H holoprosencephaly

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2 results

1

Rhombencephalosynapsis and related anomalies: a neuropathological study of 40 fetal cases.

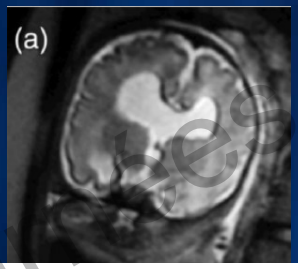
Pasquier L, Marcorelles P, Loget P, Pelluard F, Carles D, Perez MJ, Bendavid C, de La Rochebrochard C, Ferry M, David V, Odent S, Laquerrière A.

Acta Neuropathol. 2009 Feb;117(2):185-200. doi: 10.1007/s00401-008-0469-9. Epub 2008 Dec 5.

PMID: 19057916

Morphological analysis of 40 fetuses after medical termination of pregnancy allowed us to confirm that rhombencephalosynapsis was always associated with other brain abnormalities or malformations: Purkinje cell heterotopias, fusion of colliculi, forking and/or atresia of the aque ...

Rhombencephalosynapsis
VACTERL-H syndrome
(= 6 cases)



1 case of VACTERL H
+ HPE
No gene

2

Cite

Share

Vesico-amniotic shunting for lower urinary tract obstruction in a fetus with **VACTERL association**.

Kanasugi T, Kikuchi A, Haba G, Sasaki Y, Isurugi C, Oyama R, Sugiyama T.

Congenit Anom (Kyoto). 2016 Sep;56(5):237-9. doi: 10.1111/cga.12166.

PMID: 27061706

Newborn cases of **VACTERL association** with lower urinary tract obstruction (LUTO) are rare and there have been no reports on those patients undergoing fetal therapy in English literature. ...Although fetal karyotype was normal 46XY, follow-up fetal ultrasound examina ...

fanconi anemia AND holoprosencephaly

Search

4 results

1 Cite Share

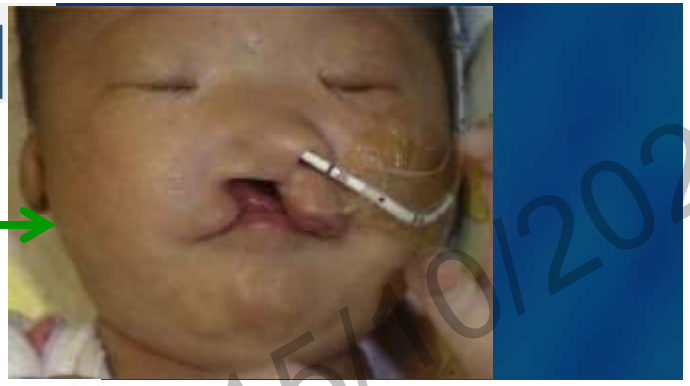
Expanding the FANCQ/RAD51C associated phenotype: Cleft lip and palate and lobar **holoprosencephaly**, two rare findings in **Fanconi anemia**.

Jacquinet A, Brown L, Sawkins J, Liu P, Pugash D, Van Allen MI, Patel MS.

Eur J Med Genet. 2018 May;61(5):257-261. doi: 10.1016/j.ejmg.2017.12.011. Epub 2017 Dec 24.

PMID: 29278735

Fanconi anemia is a rare chromosome instability disorder with a highly variable phenotype. In the antenatal and neonatal periods, the diagnosis is usually suggested by the presence of typical congen abnormalities such as intrauterine growth retardation, microcep ...



Neuropathology reports

Patient	*Age*	*Comments*
1	22 yrs	Migrational defects, hippocampus
2	1 yr	Hydrocephalus, aqueductal stenosis, VP shun
3	8 yrs	Dilated posterior ventricles
4	2 days	Dilated ventricles, aqueductal stenosis, holoprosencephaly, fused thalami, polymicrog absent septum pellucidum
5	3 mths	Dilated left ventricle, atrophic corpus callosu
6	11 yrs	Hydrocephalus, aqueductal stenosis, atrophic

2 Cite Share

Fanconi anemia: a model for genetic causes of abnormal brain development.

Pavlakis SG, Frissora CL, Giampietro PF, Davis JG, Gould RJ, Adler-Brecher B, Auerbach AD.

Dev Med Child Neurol. 1992 Dec;34(12):1081-4. doi: 10.1111/j.1469-8749.1992.tb11420.x.

PMID: 1451937

Aqueductal stenosis, agenesis of the corpus callosum and septum pellucidum, and **holoprosenceph** were found. The authors conclude that **Fanconi anemia** than previously recogr

3 Cite Share

CDK5RAP2 primary microcephaly is associated with hypothalamic, retinal and cochlear developmental defects.

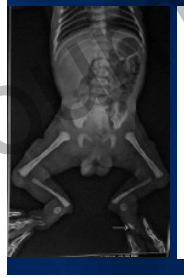
Nasser H, Vera L, Elmaleh-Bergès M, Steindl K, Letard P, Teissier N, Ernault A, Guimiot F, Afenjar A, Moutard ML, Héron D, Alembik Y, Momtchilova M, Milani P, Kubis N, Pouvreau N, Zollino M, Guilmin Crepon S, Kaguelidou F, Gressens P, Verloes A, Rauch A, El Ghouzzi V, Drunat S, Passemard S.

J Med Genet. 2020 Jun;57(6):389-399. doi: 10.1136/jmedgenet-2019-106474. Epub 2020 Feb 3.

PMID: 32015000 Clinical Trial.

Finally, hypothalamic anomalies consisting of interhypothalamic adhesions, a congenital midline defect usually associated with **holoprosencephaly**, was detected in 5 cases. CONCLUSION: This is the first report indicating that CDK5RAP2 not only governs brain size but also pla ...

??No FA in the texte???

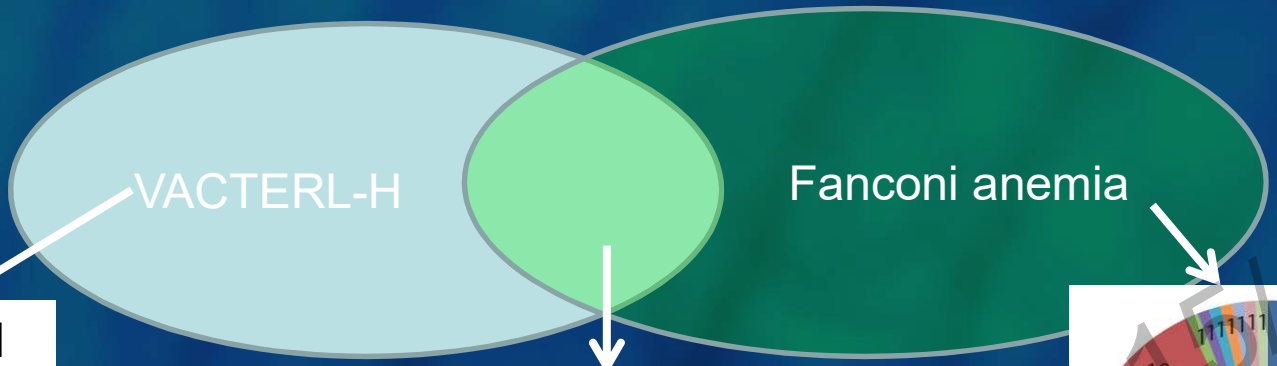


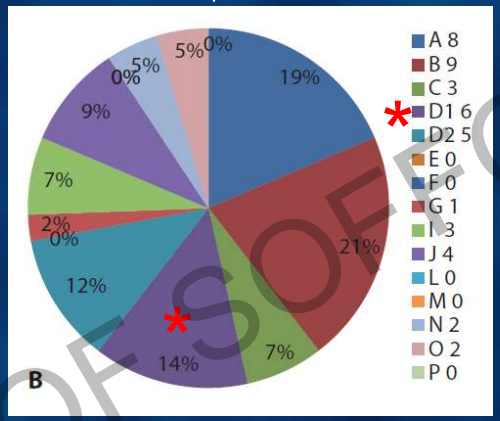
« telomeropathy »
4 patients limb anom.
-1 w HPE
-1 w FA

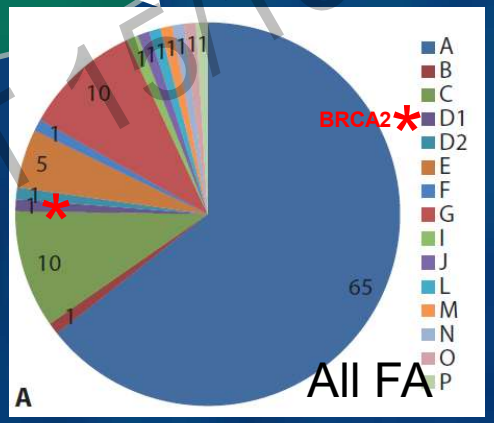
4 te

Patients with Congenital Limb Anomaly Show Short Telomere, Shutdown of Telomerase and Deregulated Expression of Various Telomere-Associated Proteins in Peripheral Blood Mononuclear Cells-A Case Series.

Mazumdar J, Chowdhury P, Bhattacharya T, Mondal BC, Ghosh U.







- BRAC2 → Cancer
- BRAC2 → FANCD1 / VACTERL-H
- H could be Holoprosencephaly

(other : agenesis of corpus callosum and septum pellucidum, aqueductal stenosis)

VACTERL