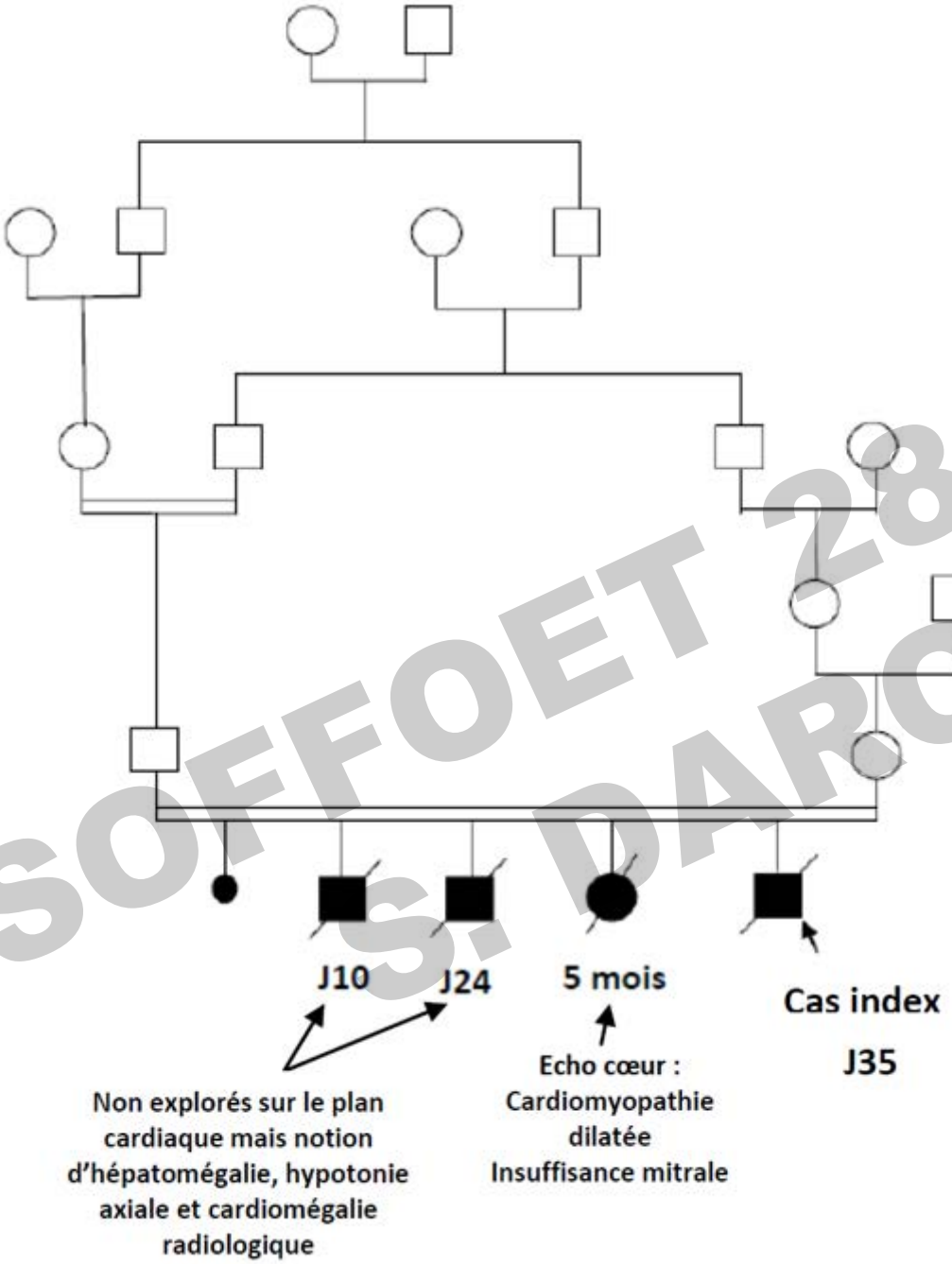
Novel Myl2 Variant Identified Through Exome Sequencing Of An Autosomal Recessive Form Of Hypertrophic Cardiomyopathy

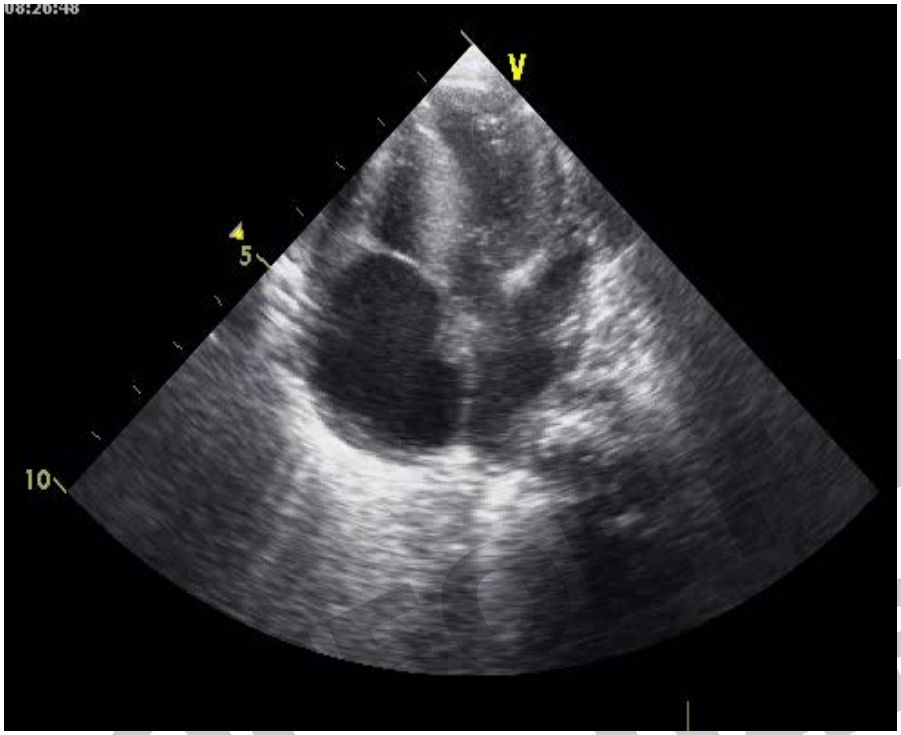
Manivannan S*, Darouich S**, Masmoudi A**, Gordon D*, Zender G*, Fitzgerald-Butt S*, Lariani I**; McBride K*, White P*, Kharrat M**, Garg V*.
*Nationwide Children's Hosp, Columbus, OH, USA
**Univ of Tunis El Manar, Tunis, Tunisia



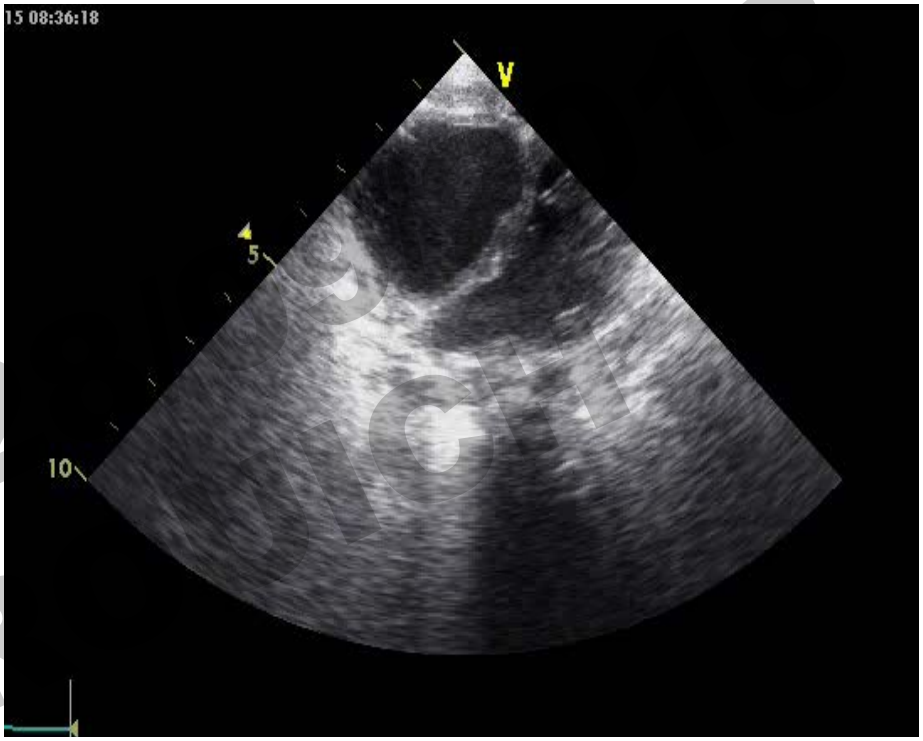
- Echo cœur des parents : strictement normale
- Pas d'antécédents familiaux de cardiopathie

Biologie
- TP bas, hypoprotidémie
-Anémie
- Insuffisance rénale
(Bas débit)

Cas index



Coupe 4 cavités montrant une hypertrophie bi ventriculaire avec dilatation bi atriale



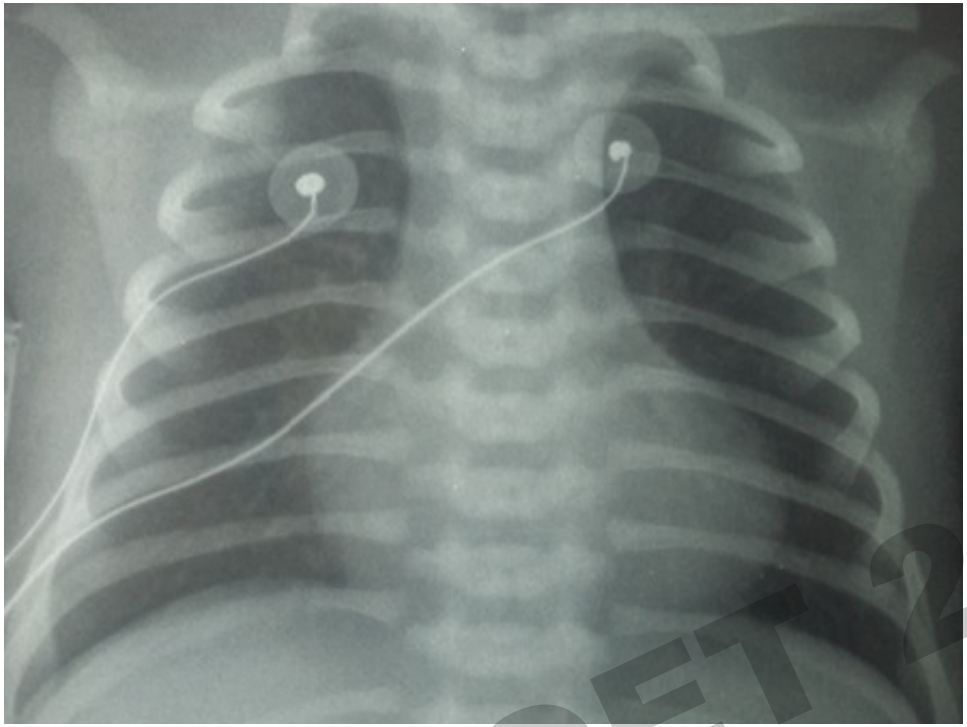
Coupe échographique montrant une importante dilatation bi atriale avec un septum inter auriculaire bombant

Echographie postnatale (J4 de vie) :

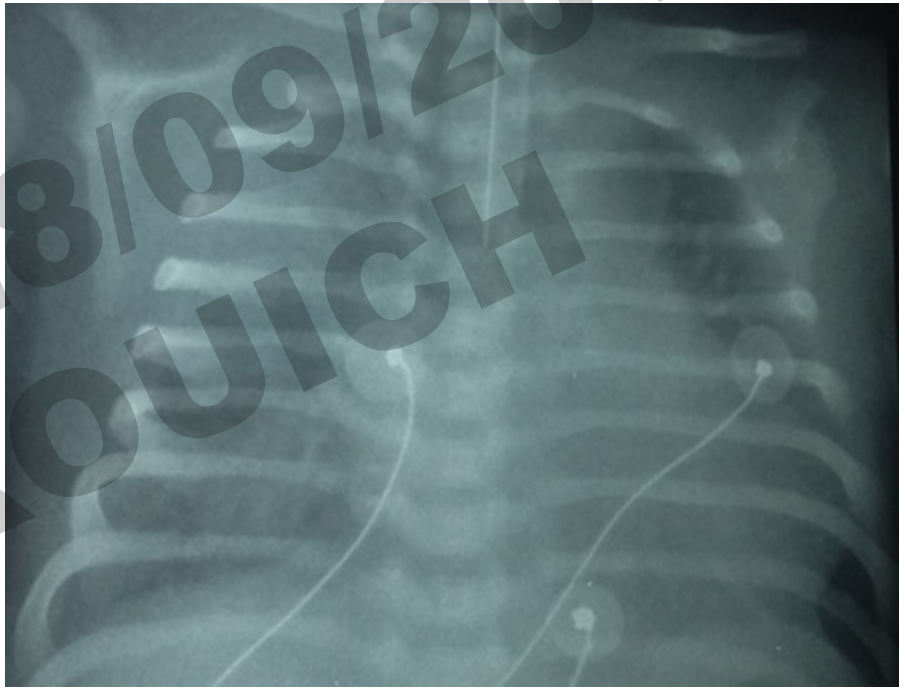
CMH avec dilatation biatriale

Insuffisance mitrale importante avec VM épaissie

HTAP



RX thorax J4 de vie

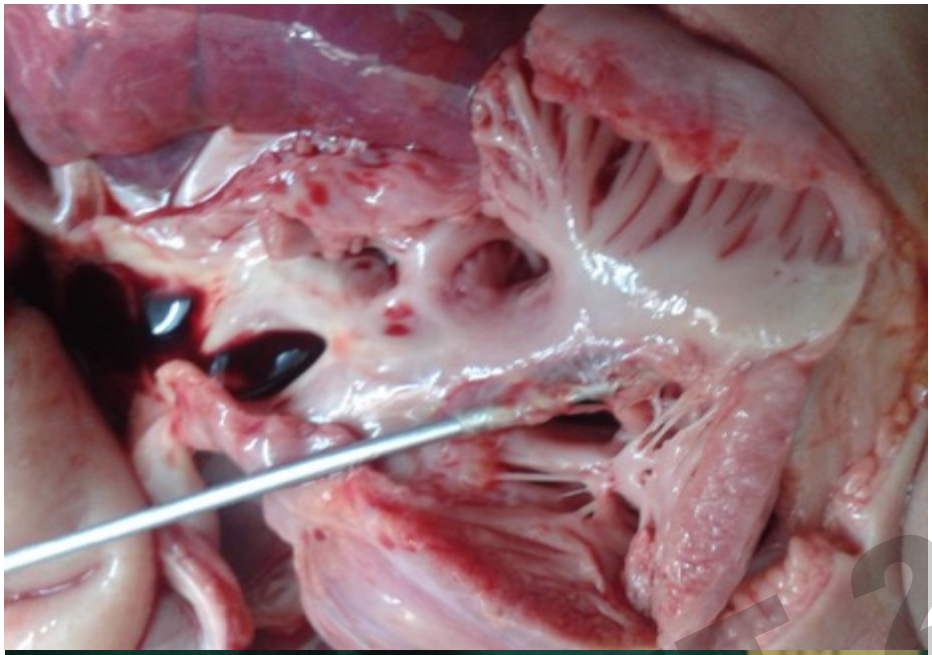


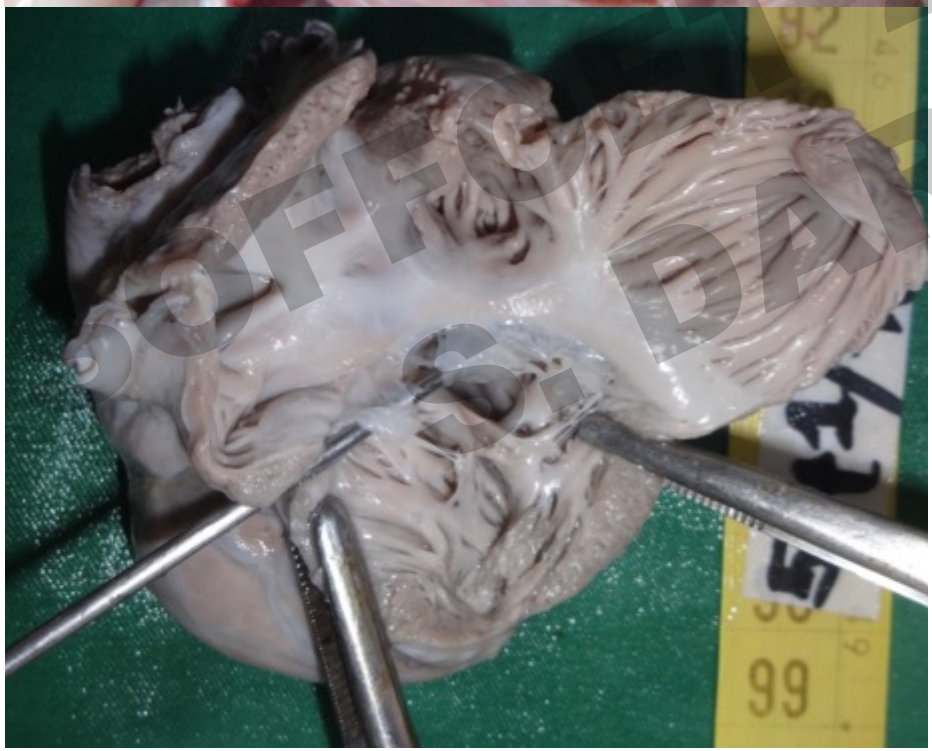
RX thorax J34 (OAP)

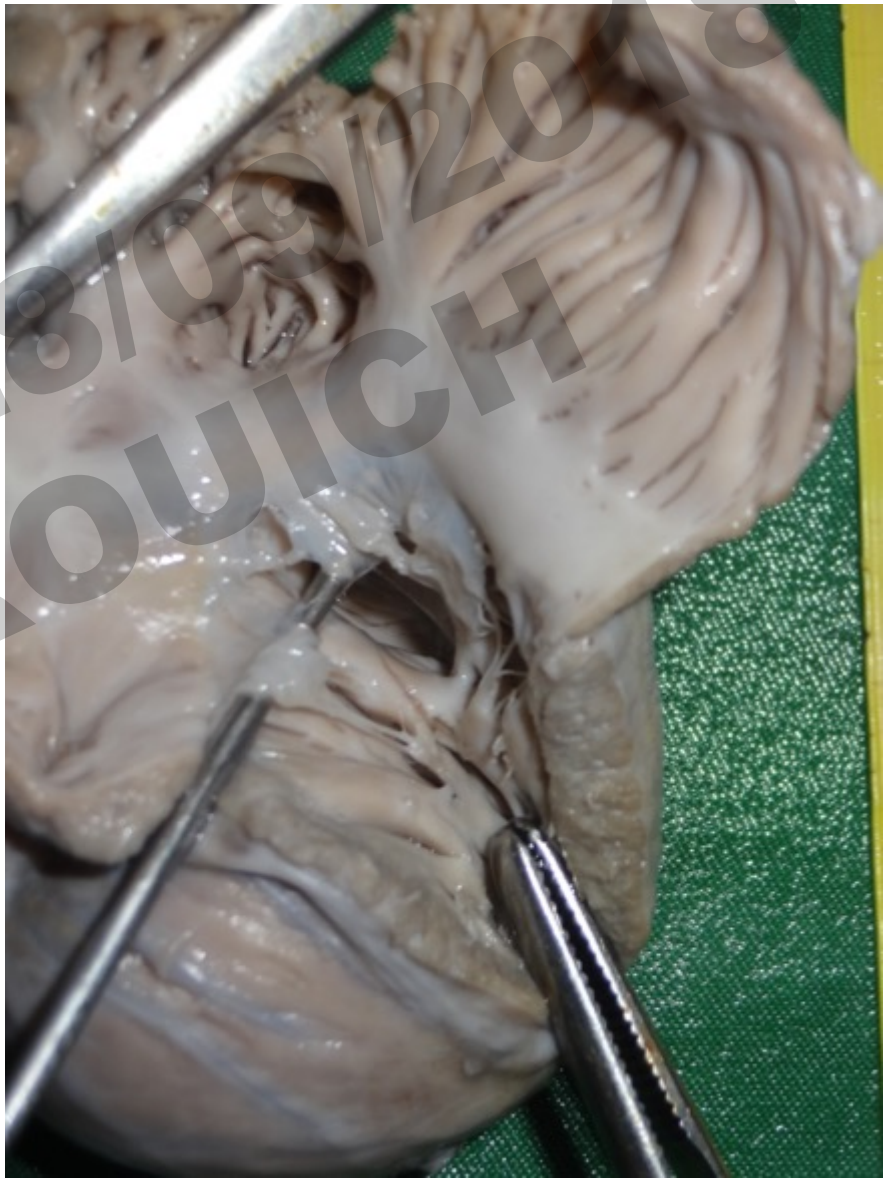
Examen foetopathologique

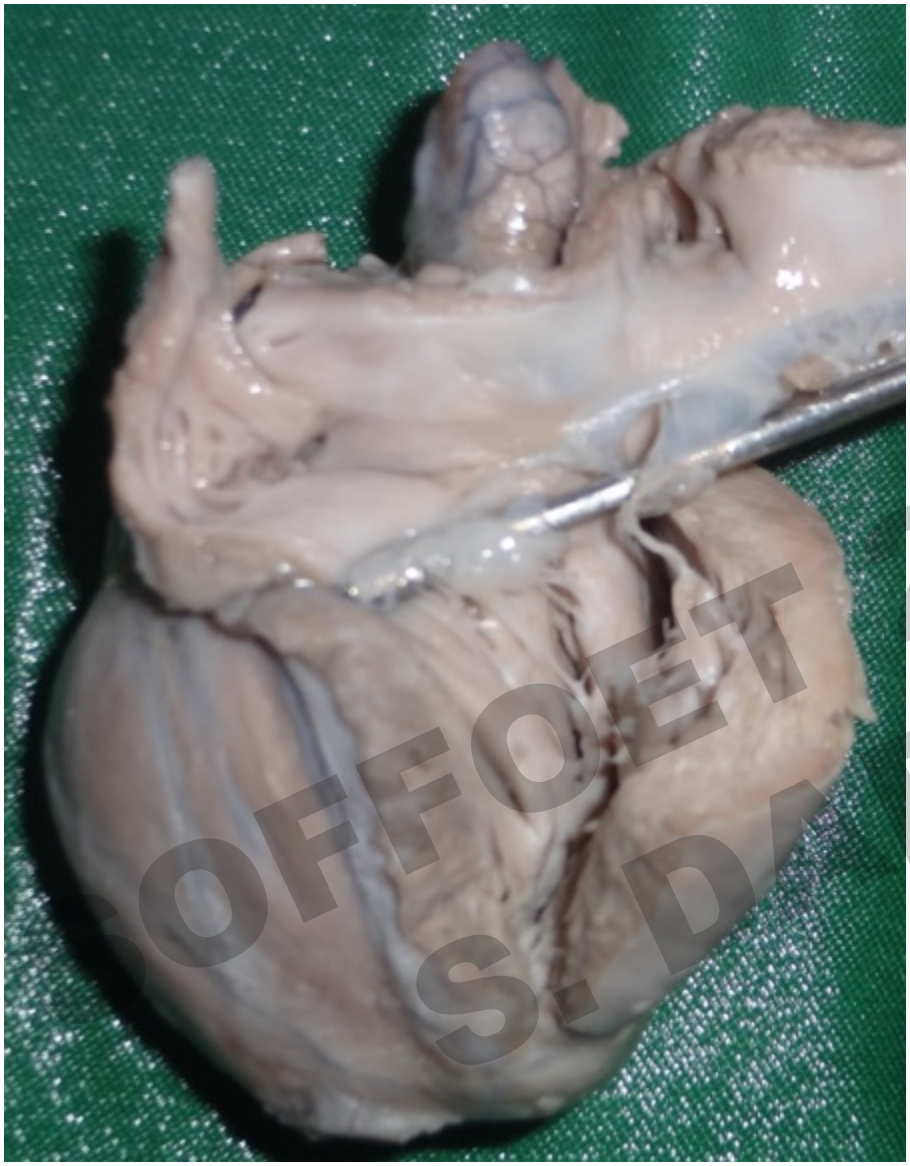
- **Hypertrophie concentrique importante de deux ventricules**,
- **Dilatation bi-atriale importante**
- **Dysplasie polyvalvulaire** (atteinte plus sévère de la valve mitrale)
- **Hépatomégalie** homogène sans anomalies macroscopiques

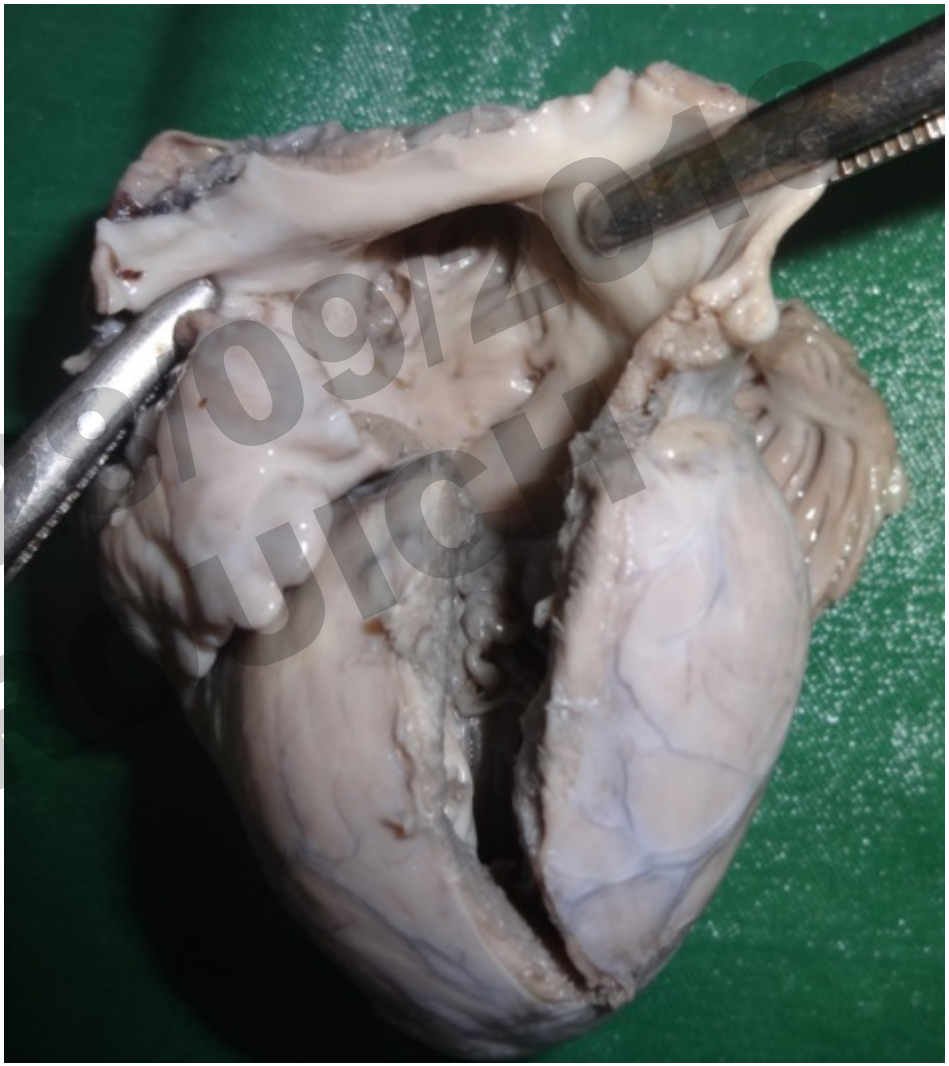
Valve tricuspide

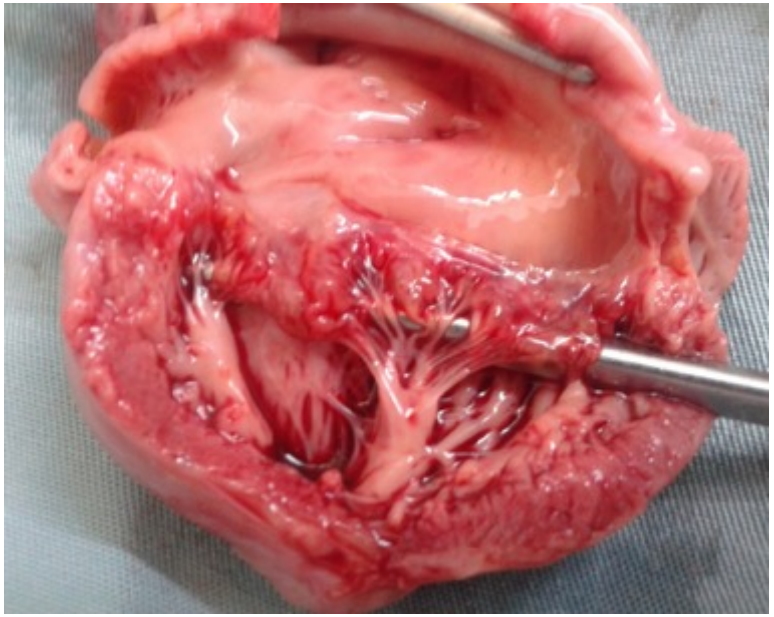




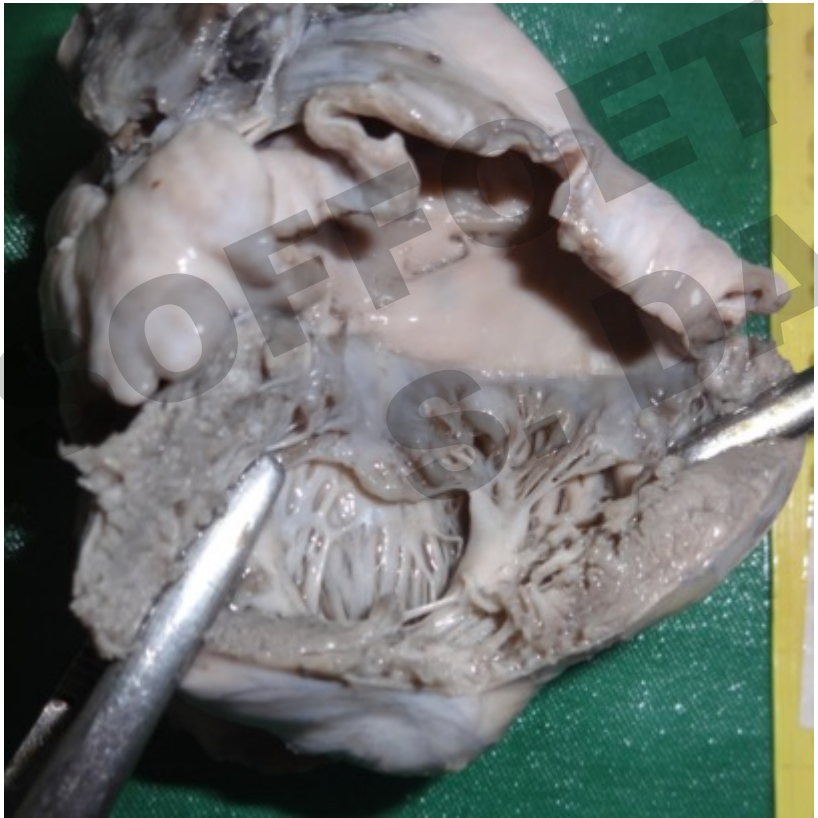


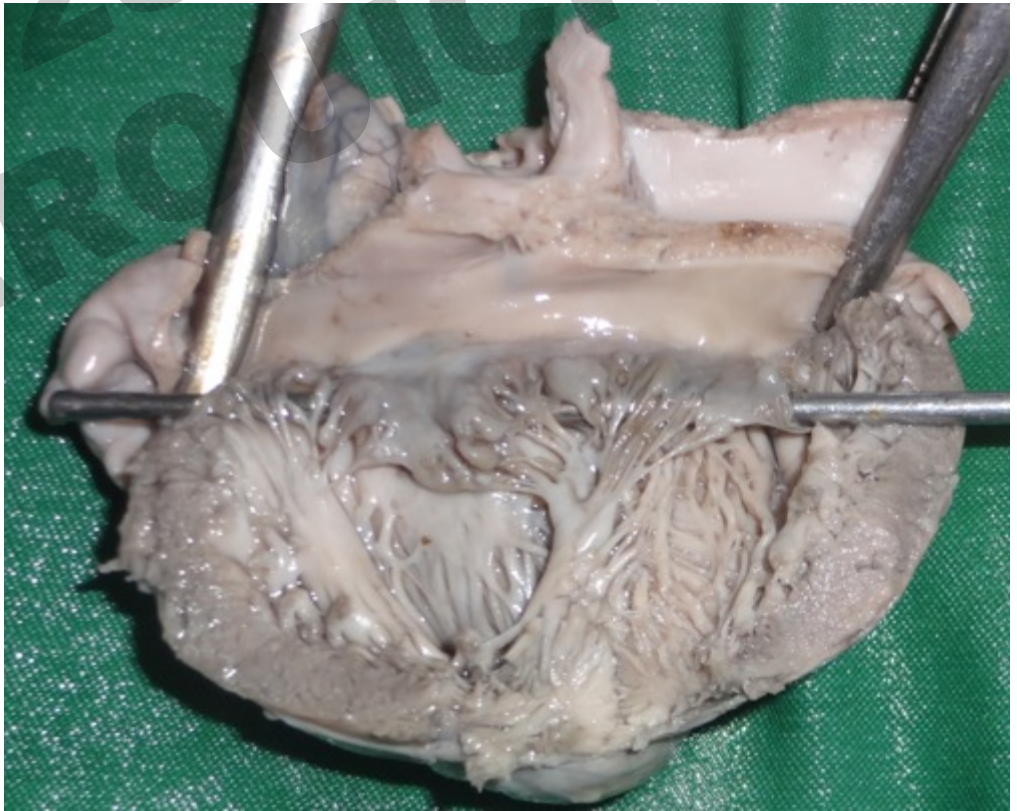


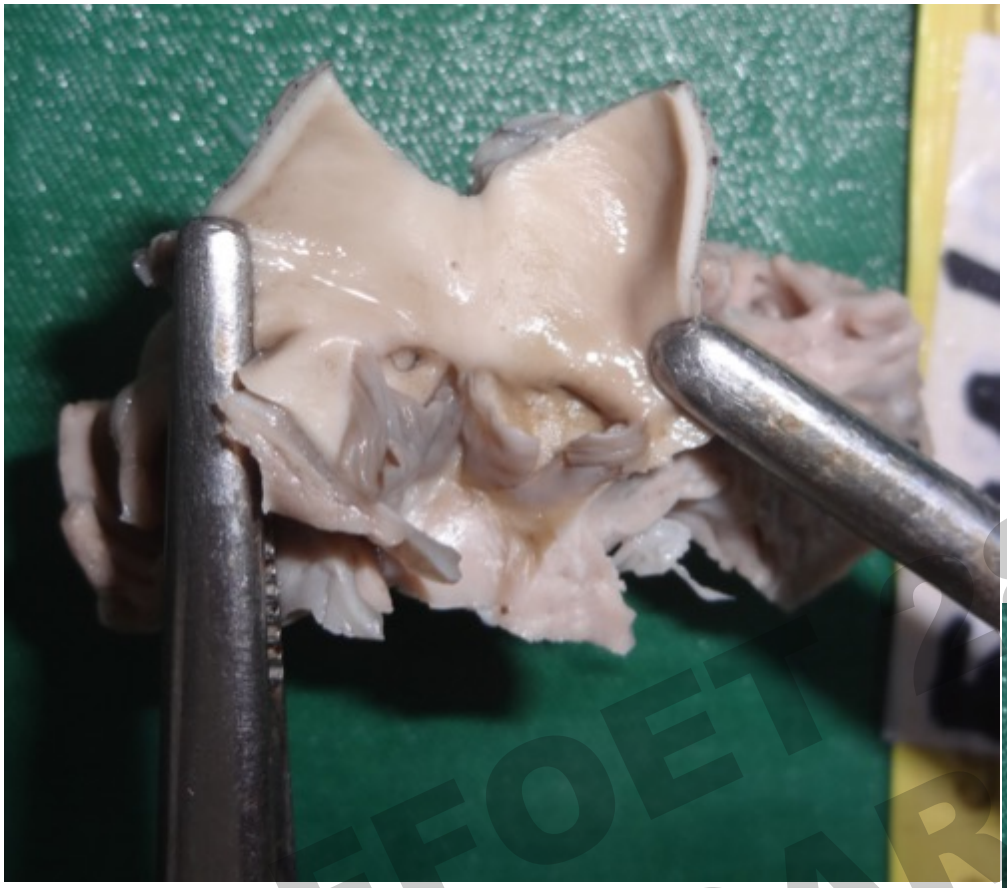


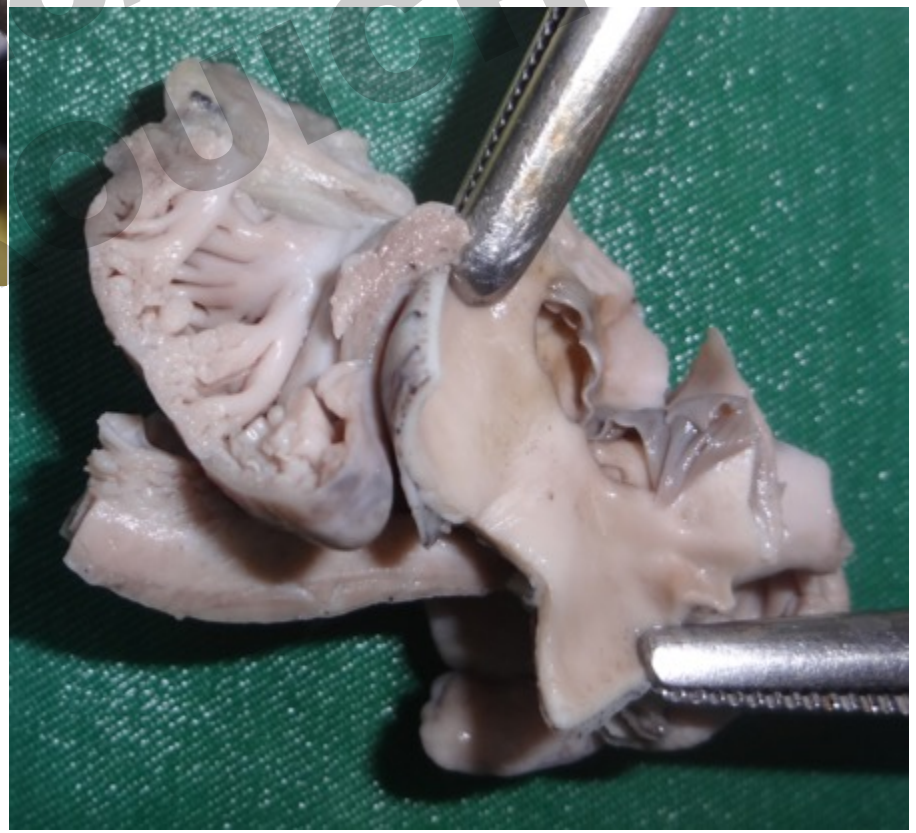


Valve mitrale

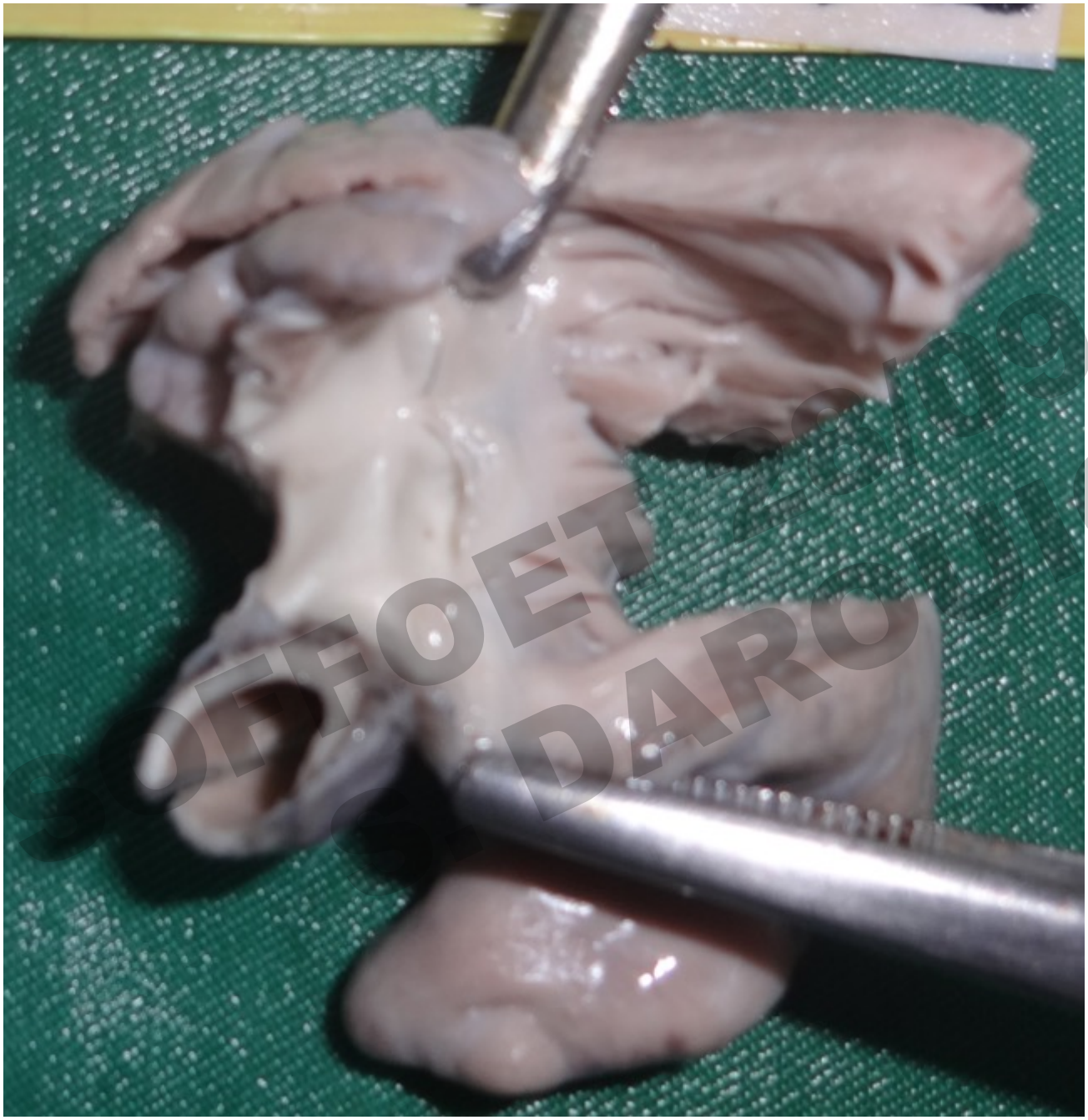




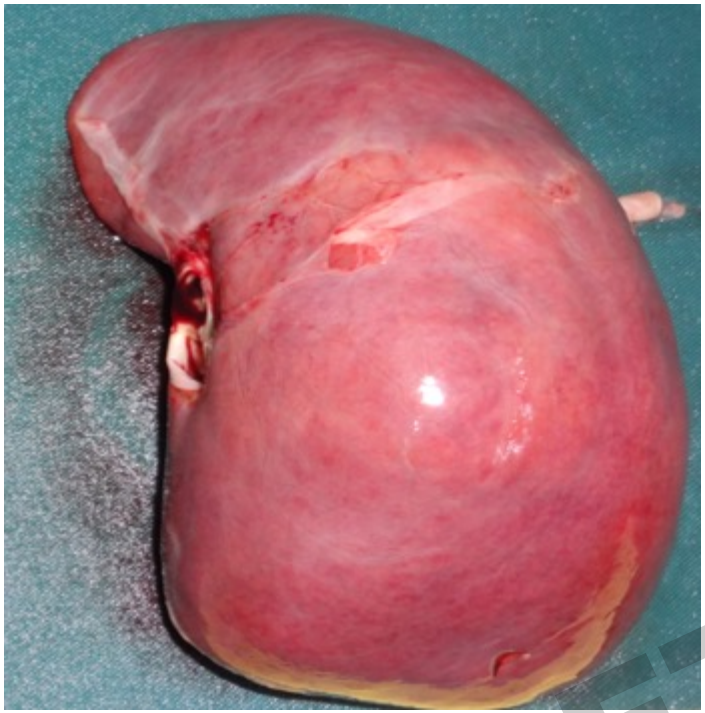




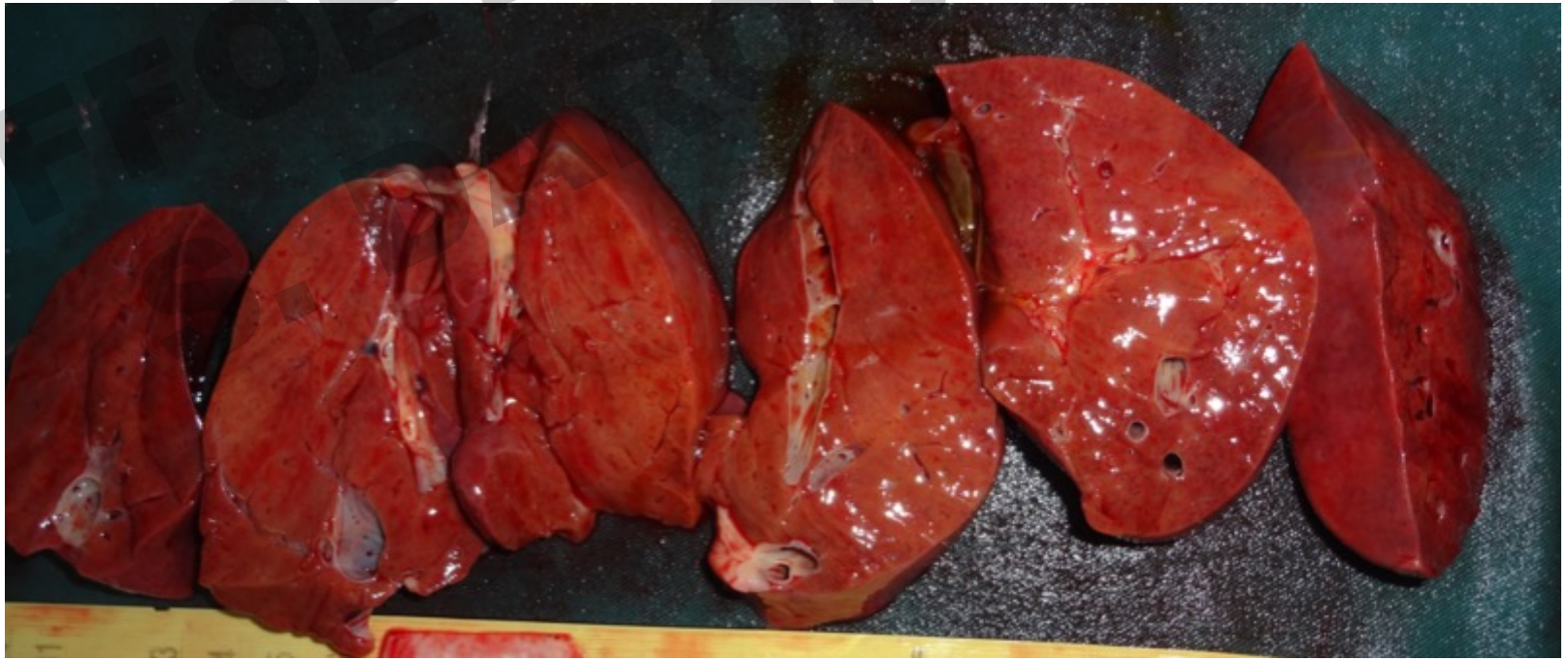
Sigmoïdes pulmonaires



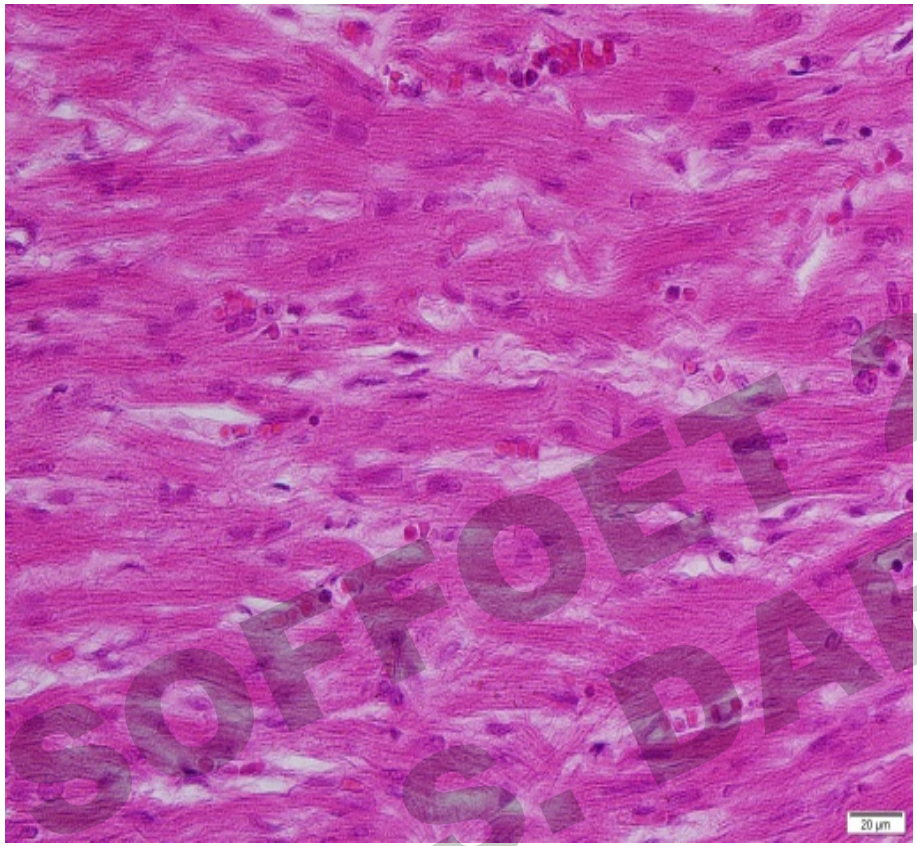
Sigmoïdes aortiques



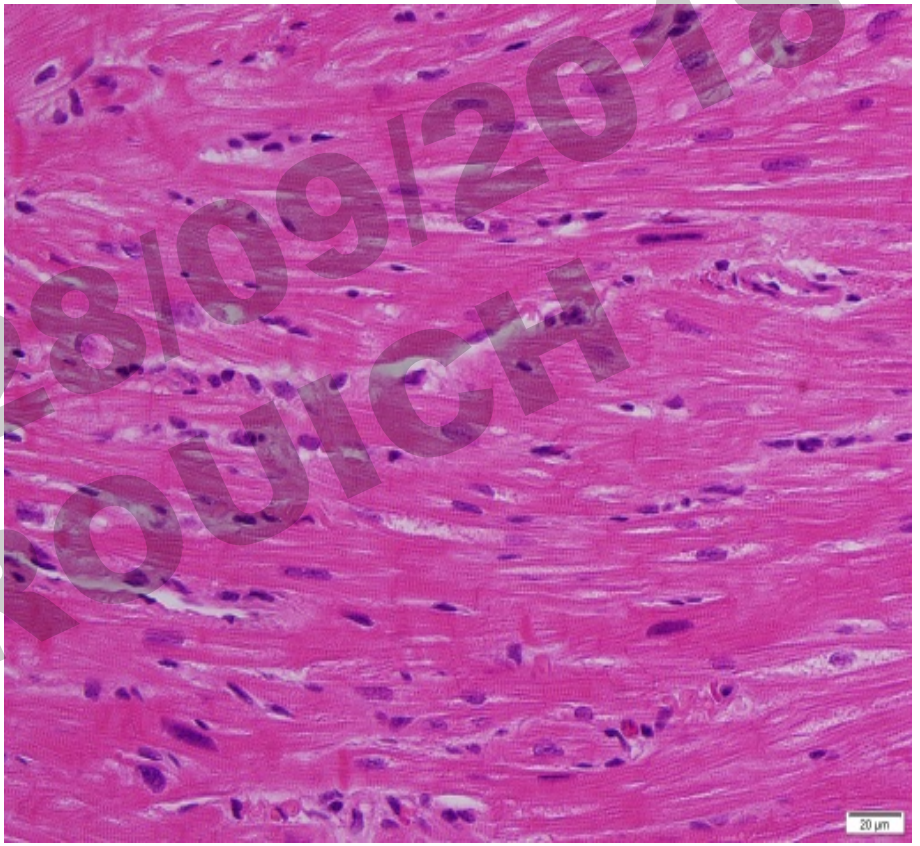
Foie 162,44g (nl 68-70)



Proband ventricular muscle



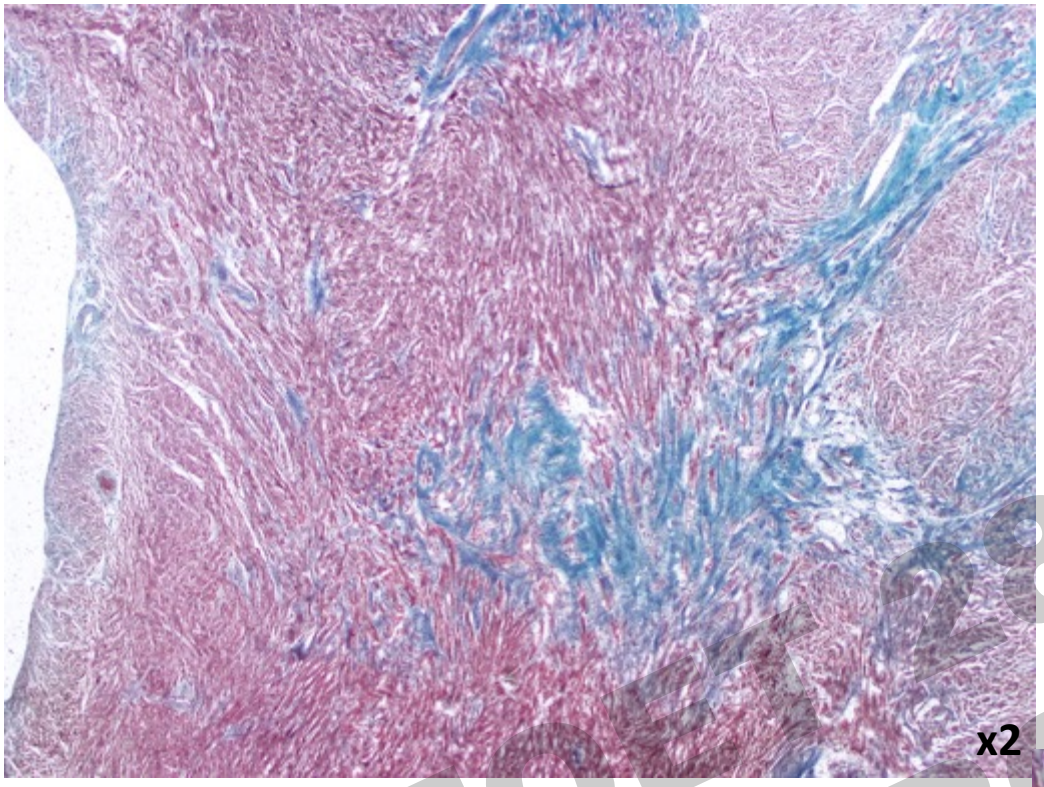
Control ventricular muscle

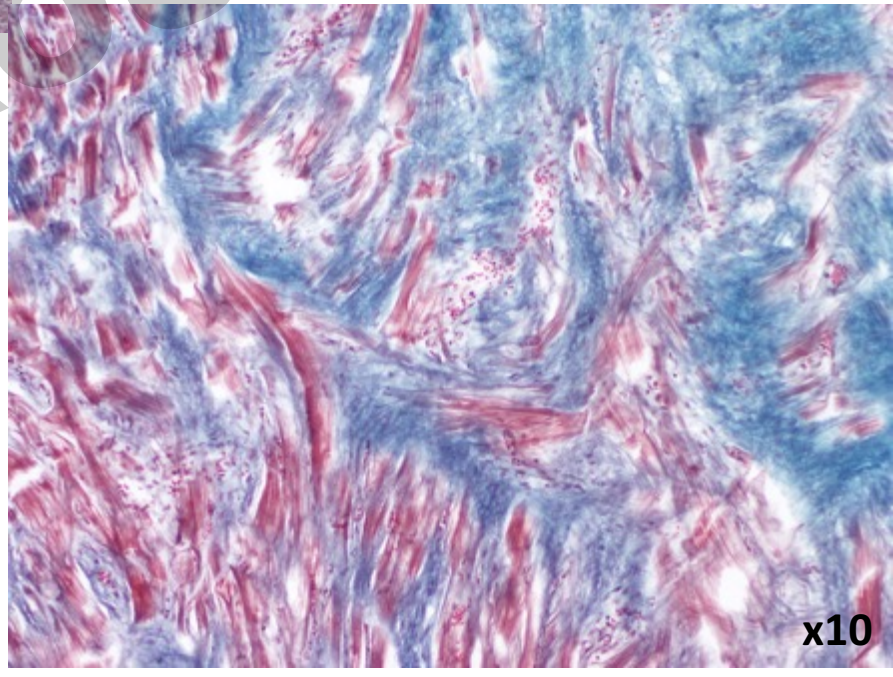


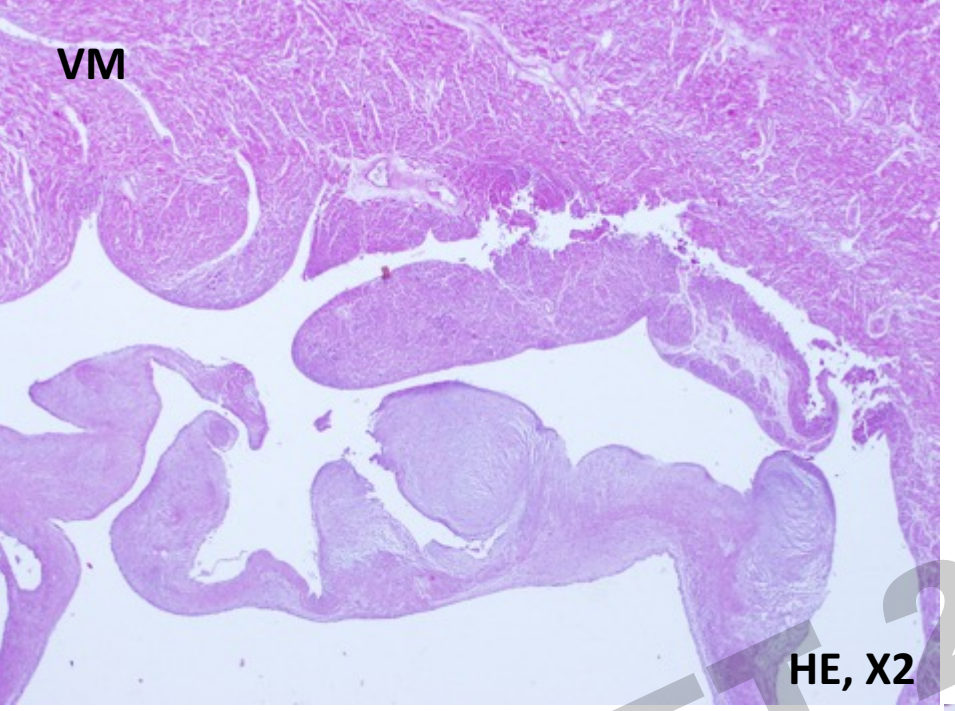
H&E

Hypertrophie significative des cardiomyocytes avec Disorganisation de l'architecture

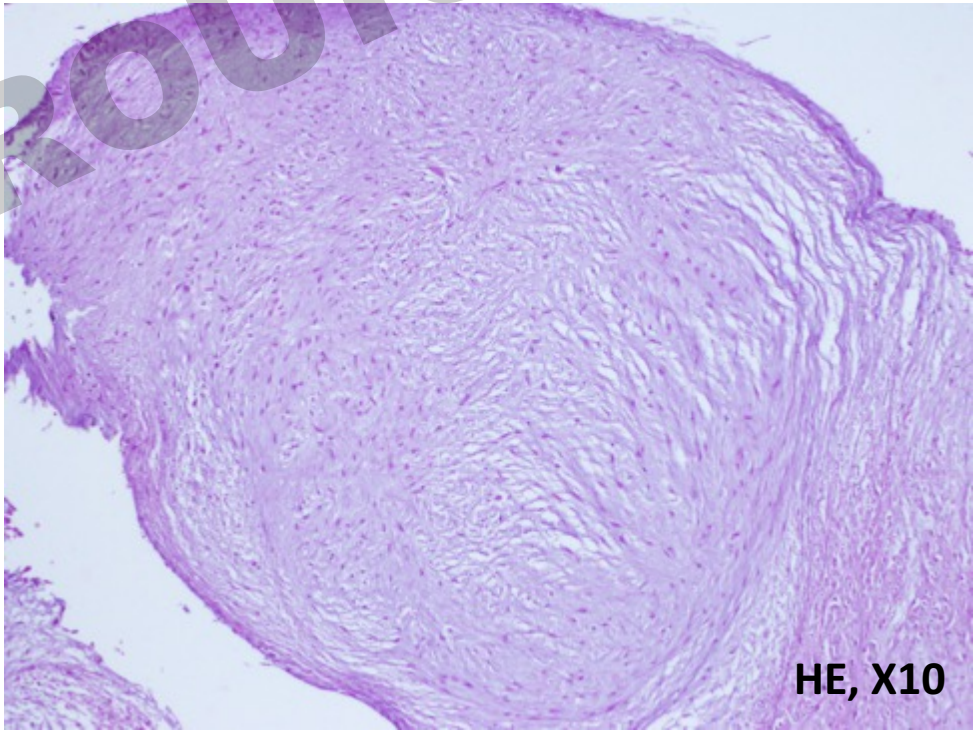
Fibrose interstitielle myocardique (Trichrome)



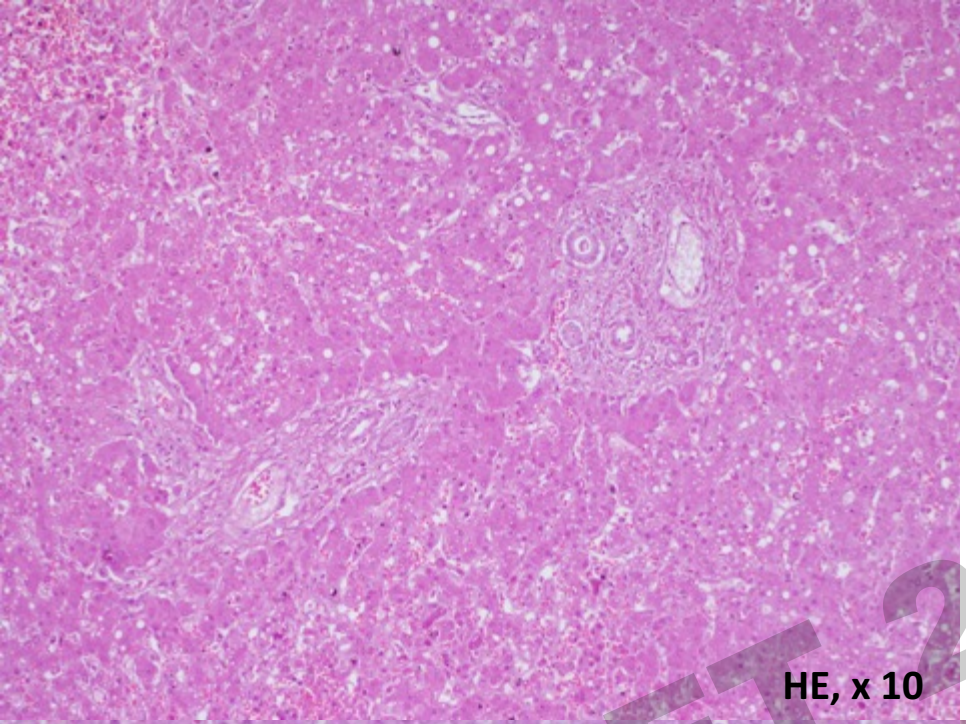




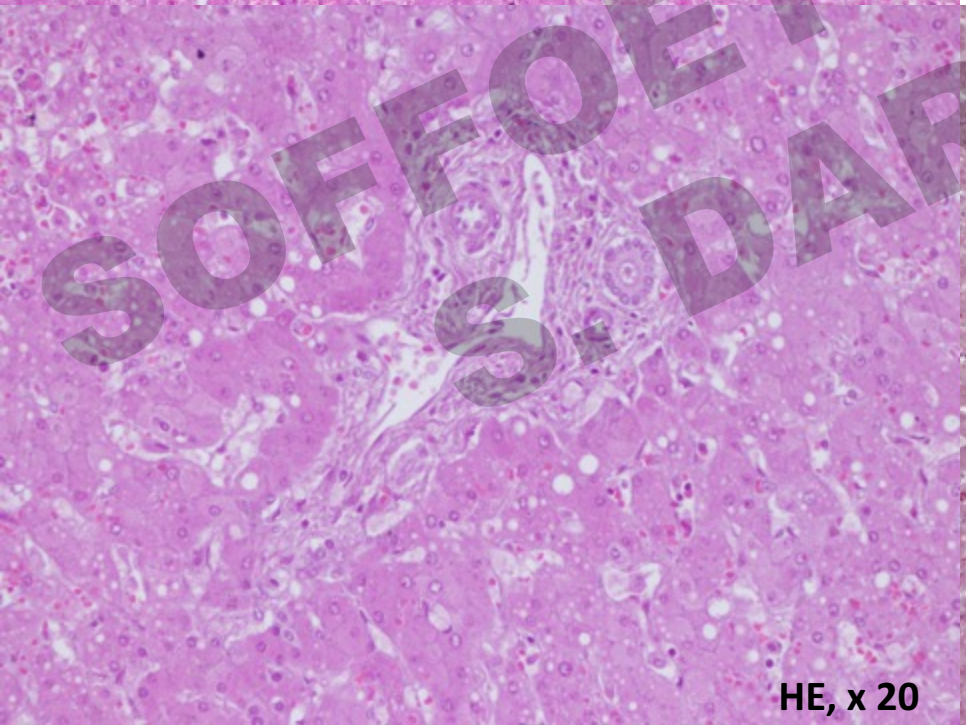
Dysplasie valvulaire



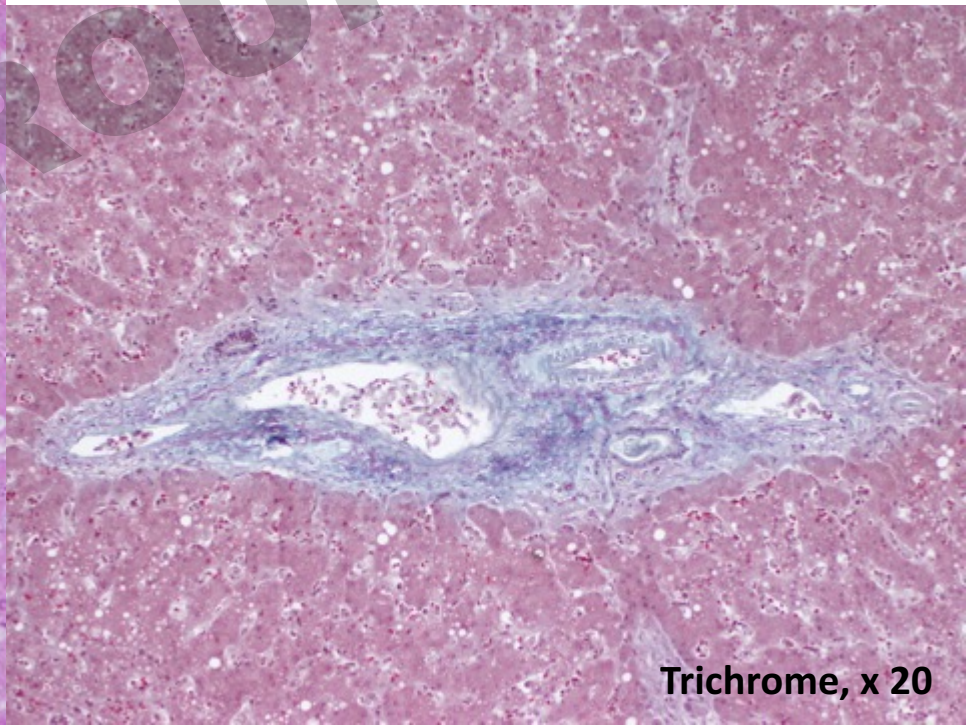
Fibrose portale



HE, x 10



HE, x 20



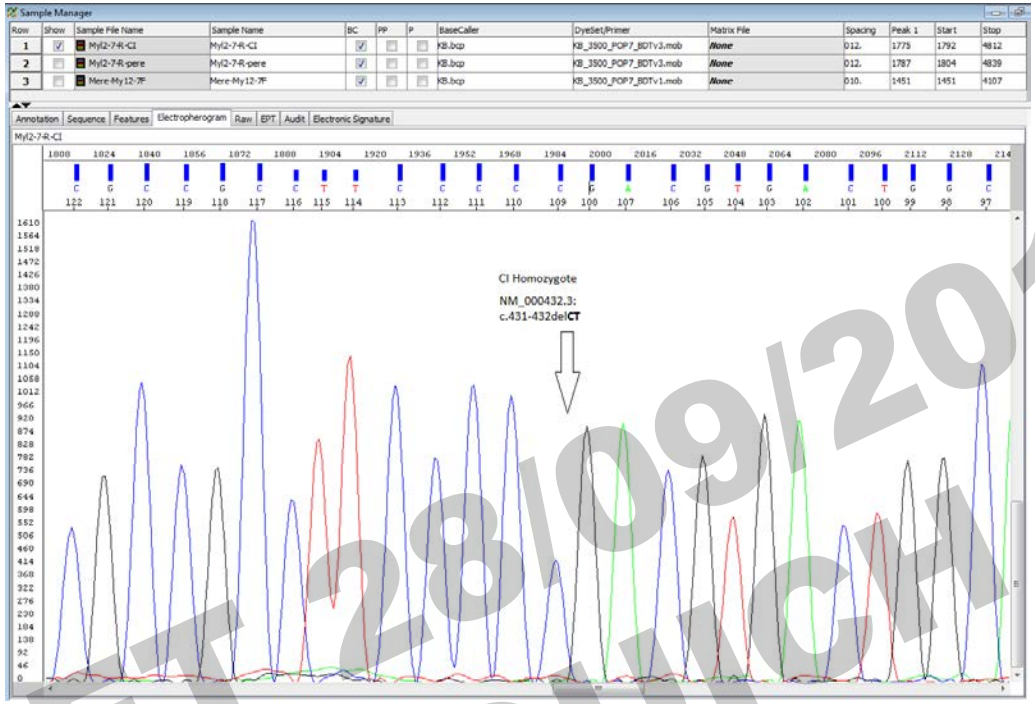
Trichrome, x 20

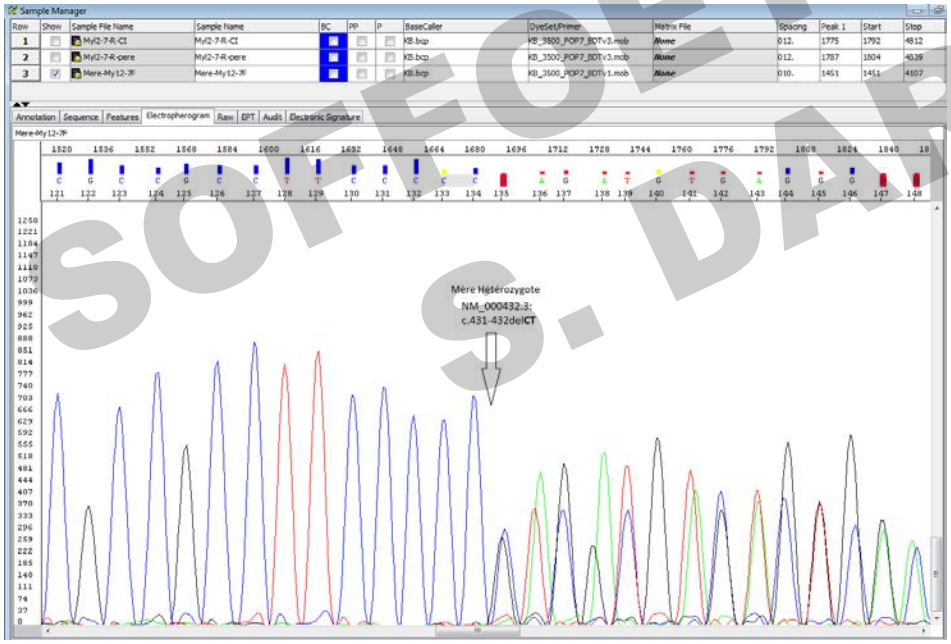
Etude génétique (exome)

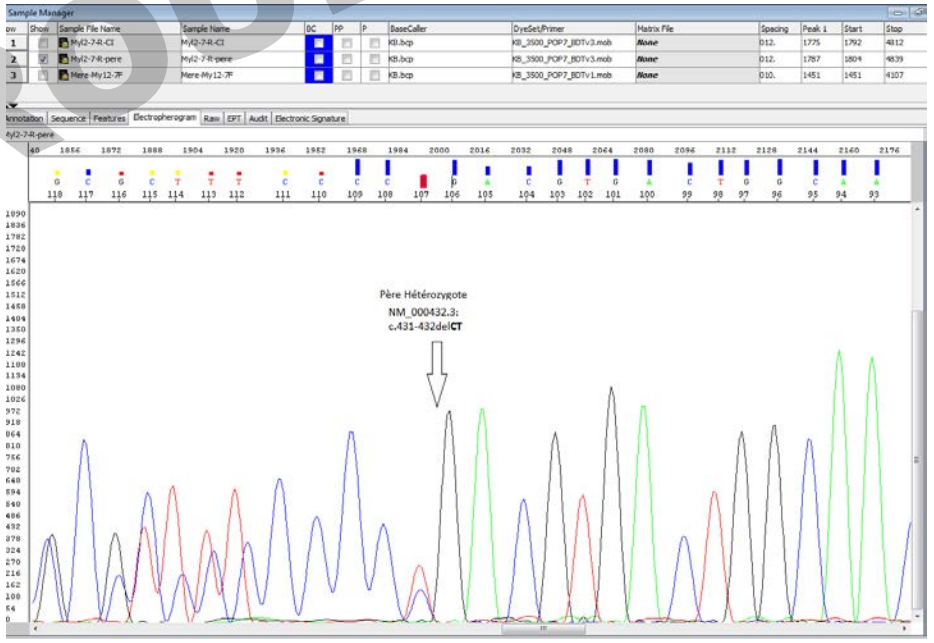
Mutation du gène *Myosin light chain 2 (MYL2/MLC-2V)*

- Homozygous frameshift variant (*MYL2: c.431-432delCT; MYL2: p.P144RfsX56)*, which alters the last 20 amino acids of the protein, and adds an additional 36 non-canonical amino acids to the c-terminal EF-hand domain
- The parents are heterozygous carriers of the variant
- This novel variant is not found in control cohorts from multiple public genomic databases including ExAC and the 1000 Genome Project.

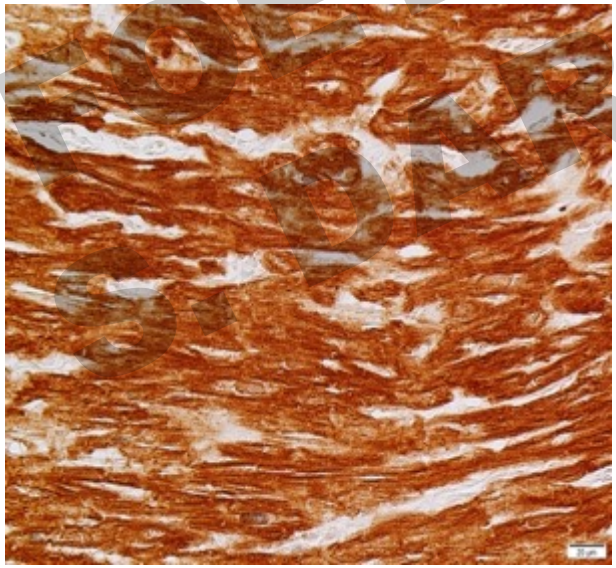
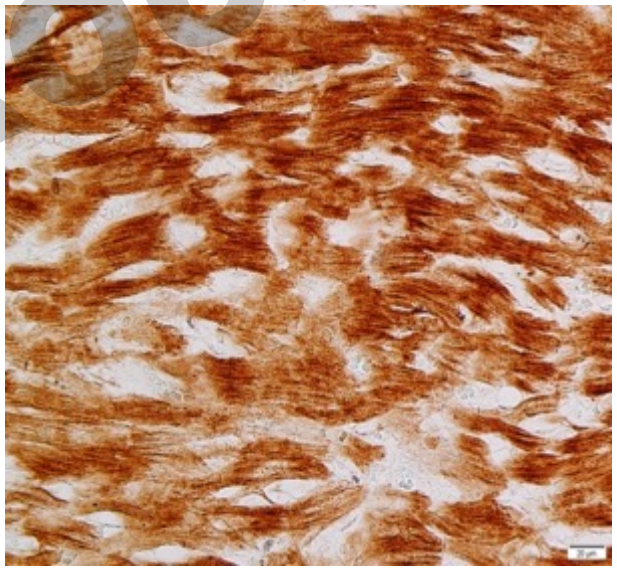
MYL2: c.431-432delCT



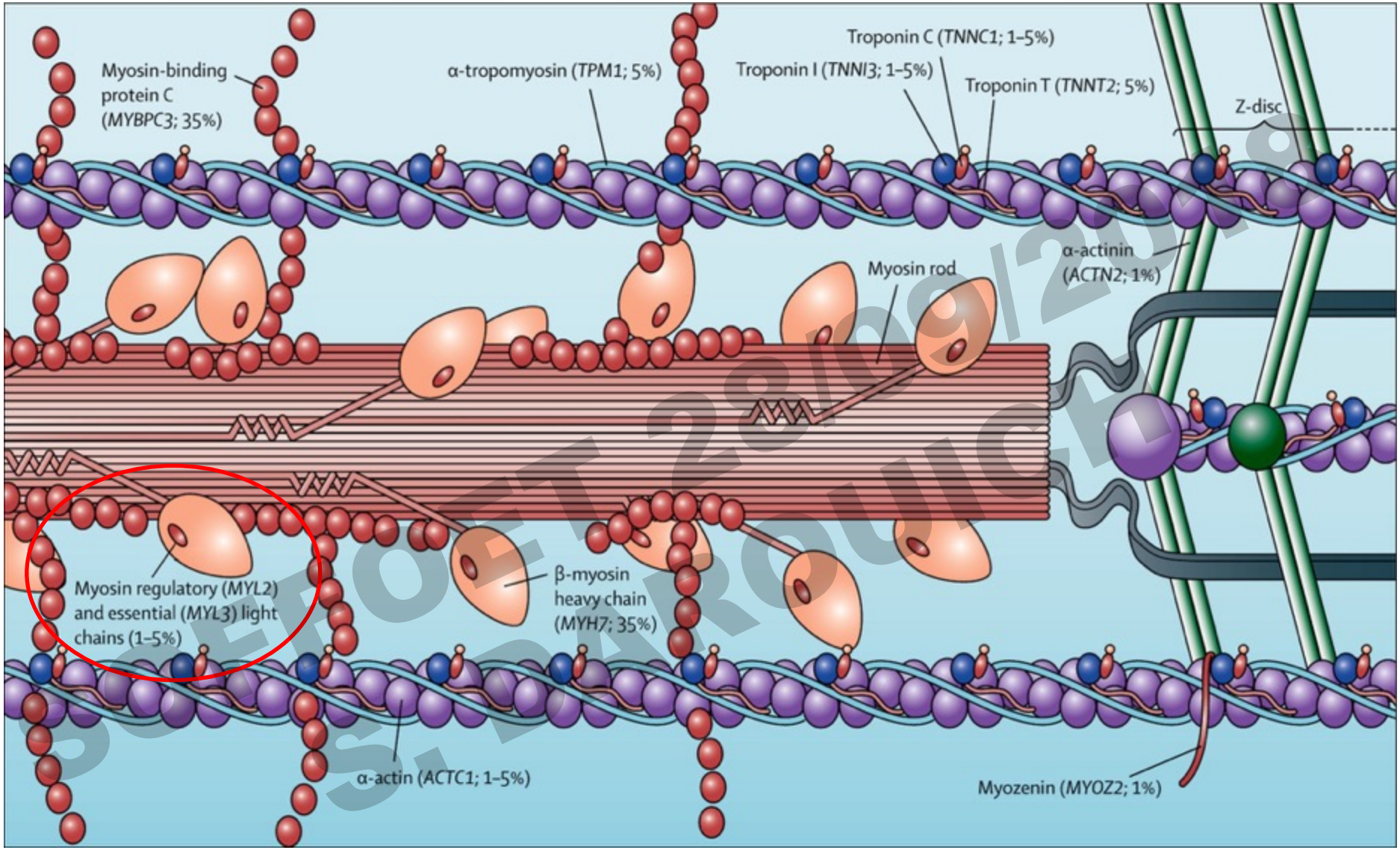




IHC

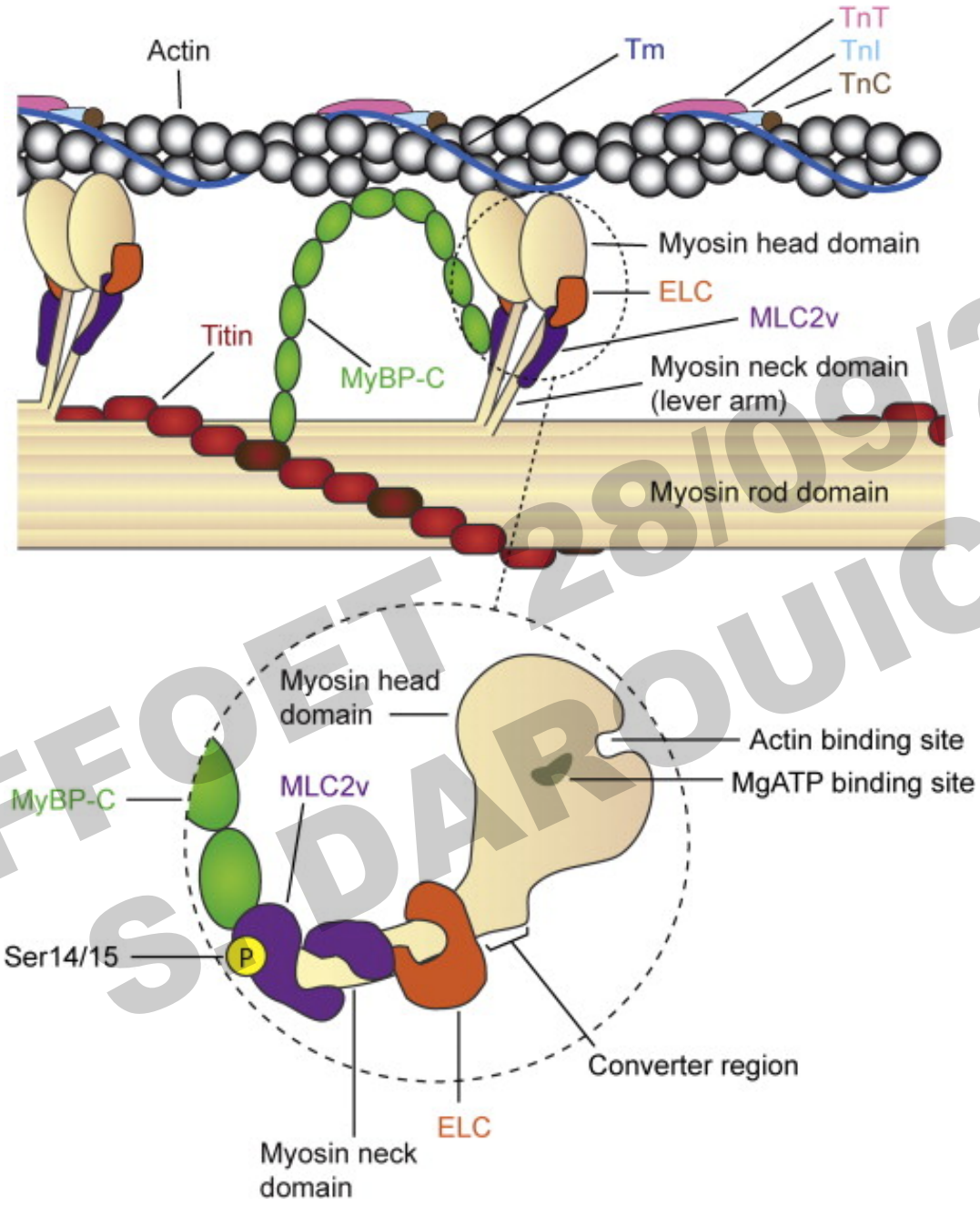
	Control ventricular muscle	Proband ventricular muscle
MYL2**		
cTnI		

** antibody detects both phosphorylated and unphosphorylated protein



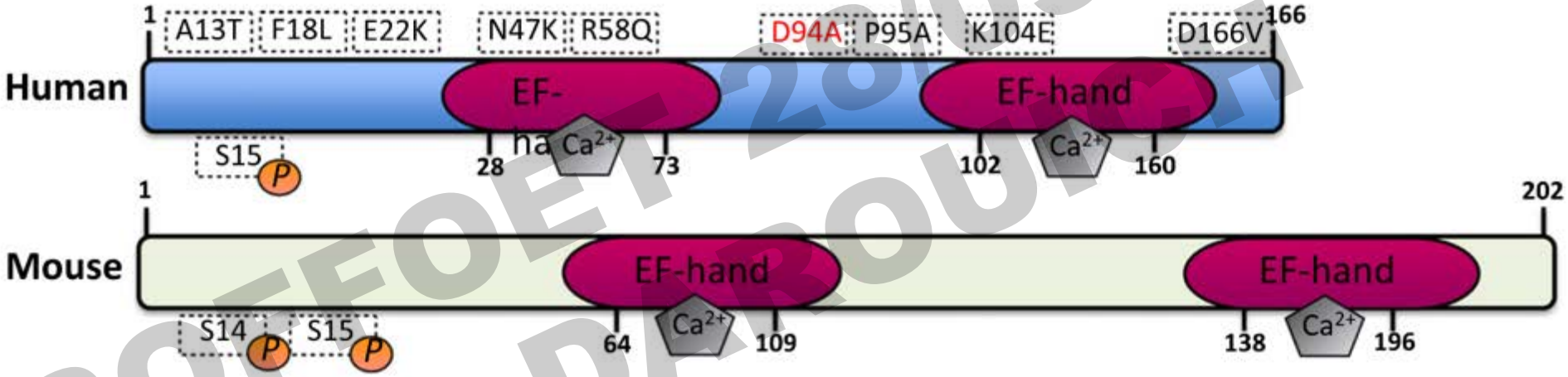
Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy

Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013;381(9862):242-55.



Sheikh et al. Getting theskinnyonthick filament regulationincardiac muscle biologyanddisease. Trends in Cardiovascular Medecine 24 (2014) 133-141.

Myosin light chain-2 (*MYL2/MLC-2*)



Sheikh et al. Functions of myosin light chain-2 (MYL2) in cardiac muscle and disease. Gene 569 (2015) 14–20.

doi:10.1093/brain/aws293 Brain 2013: 136; 282–293 | 282

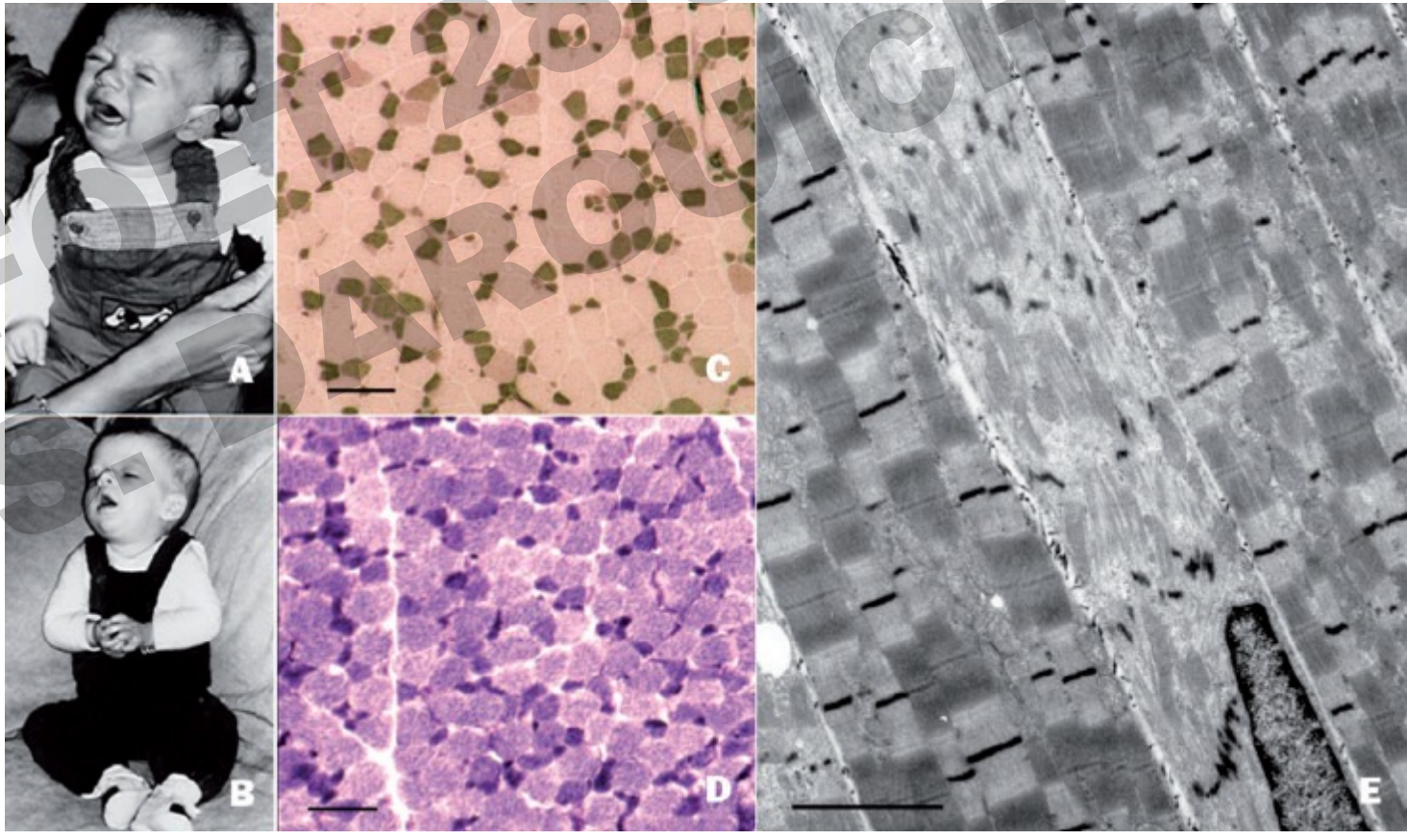
BRAIN
A JOURNAL OF NEUROLOGY

Recessive *MYL2* mutations cause infantile type I muscle fibre disease and cardiomyopathy

Marian A. J. Weterman,[1] Peter G. Barth,[2] Karin Y. van Spaendonck-Zwarts,[3,4] Eleonora Aronica,[5] Bwee-Tien Poll-The,[2] Oebele F. Brouwer,[6] J. Peter van Tintelen,[4] Zohal Qahar,[1] Edward J. Bradley,[1] Marit de Wissel,[1] Leonardo Salviati,[7] Corrado Angelini,[7,8] Lambertus van den Heuvel,[9] Yolande E. M. Thomasse,[10,*] Ad P. Backx,[11] Gudrun Nürnberg,[12,13] Peter Nürnberg[12,13,14] and Frank Baas[1]

c.431delC; p.Pro144LeufsX2 and c.432delT; p.Asp145ThrfsX2

c.403-1G4C



Link between MYL2 mutation and valvular dysplasia ?

- Myocardial development may also affect valve development.
- An example would be the link between MYH7 mutations and Ebstein's anomaly of the tricuspid valve (with associated LV non-compaction cardiomyopathy) as first reported by Postma et al. Circ Cardiovascular Genetics, 2011.
- Additional publications discussing this link are: Vermeer AM, et al. Am J Med Genet C, 2013; Bettinelli et al. Am J Med Genet A 2013 and Hirono K et al. J Thorac Cardiovasc Surg 2014.