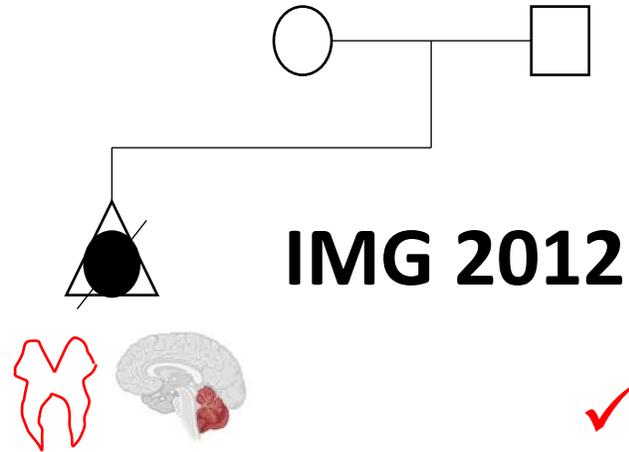


Une Laminopathie apparentée au syndrome de Joubert : étude génétique et histopathologique

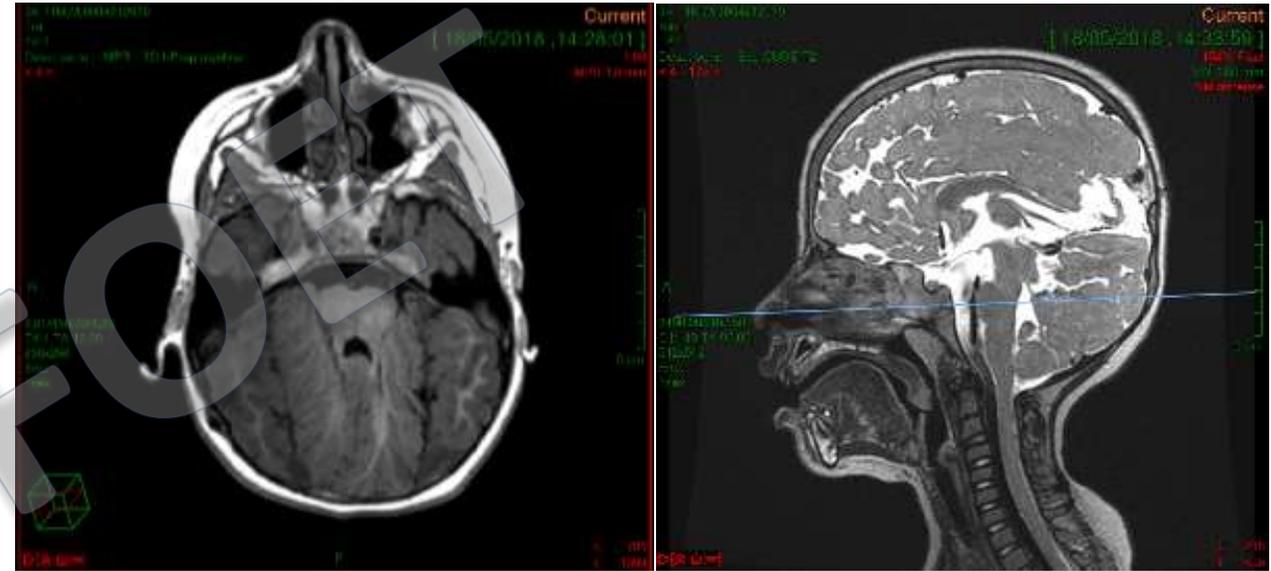
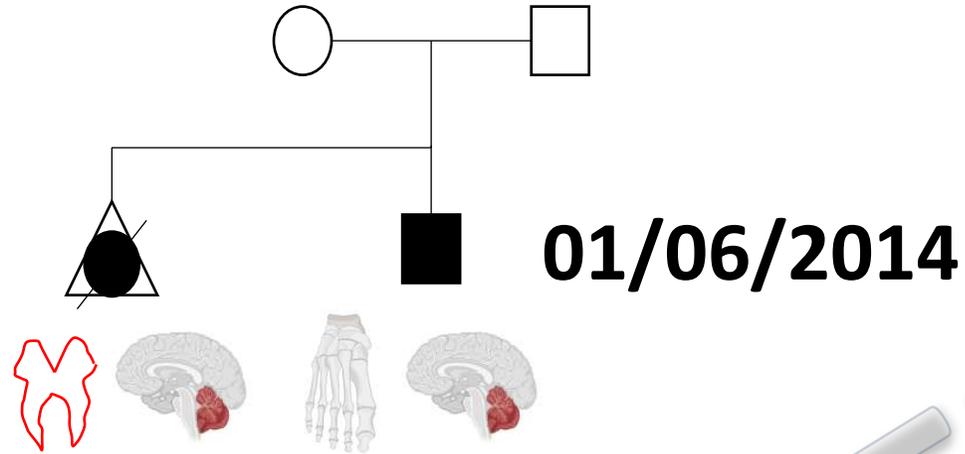
Clémence JACQUIN
Sophie THOMAS
Tania ATTIE-BITACH

Clinique



- ✓ Hypoplasie cérébelleuse et du vermis
 - ✓ Image de dent molaire à l'IRM
- Pas d'examen foetopathologique
Pas de prélèvement à visée génétique

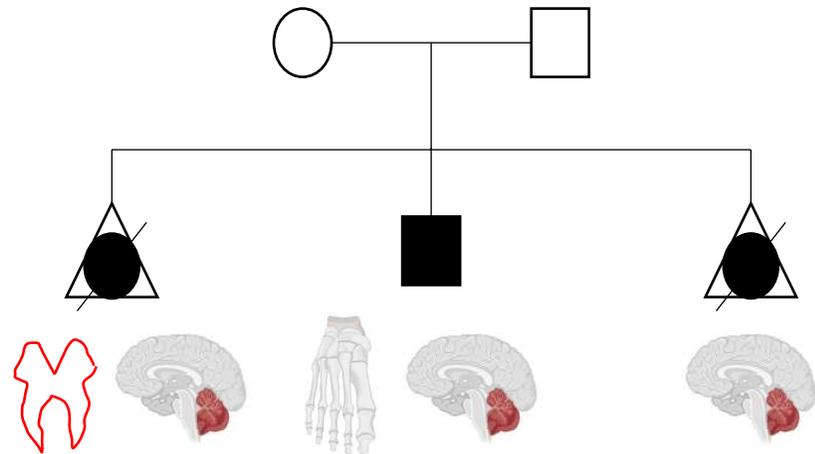
Clinique



- ✓ CIV
- ✓ Retard psychomoteur
- ✓ Apraxie oculomotrice

- ✓ Encéphalocèle occipitale (opérée)
- ✓ Dysplasie vermis+++ avec kystes cérébelleux
- ✓ PD post axiale MI (opérée)
- ✓ Polymicrogyrie

Clinique



IMG 2017 (17 SA)

Fœtus de sexe féminin

poids : 138 g (50^e)

VT 21 cm (75^e)

VC 14 cm (75^e)

PC 13cm (15^e)

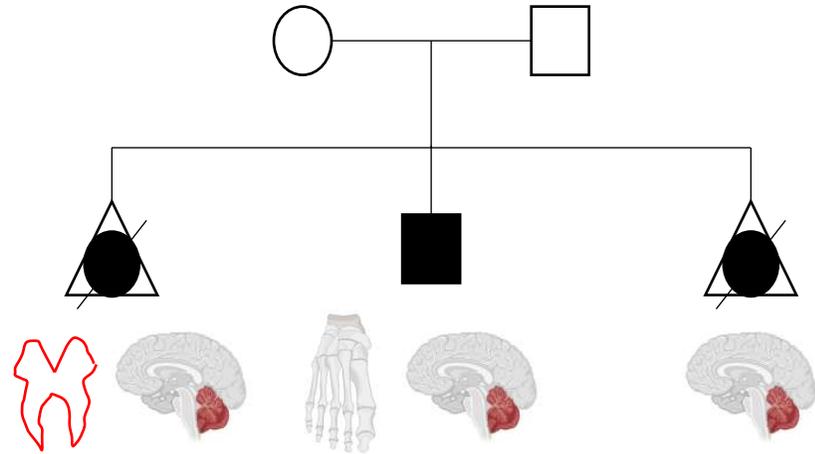
Pied 2.5cm (50^e)



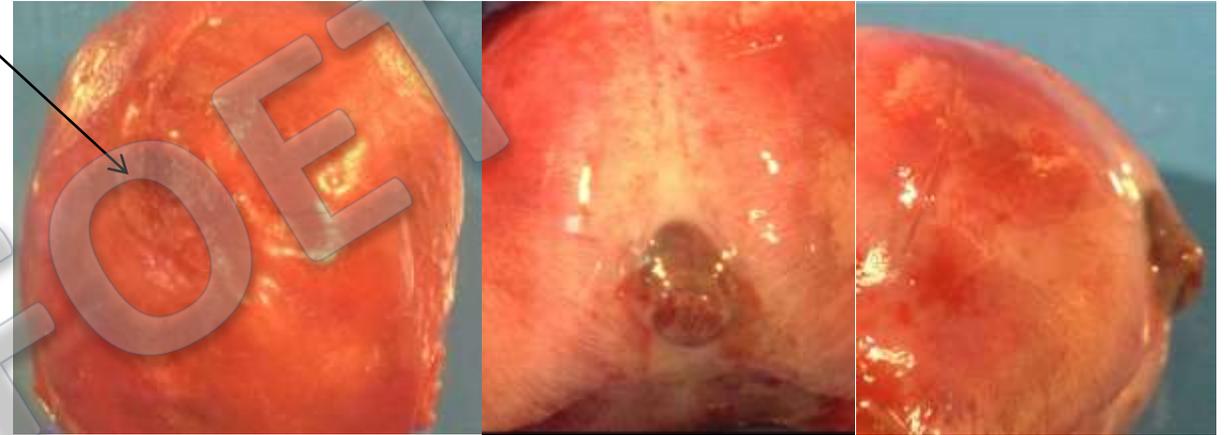
- Petit nez pincé
- Philtrum bombant
- Rétrognatisme
- Pas d'anomalie rénale
- Pas de polydactylie
- Pas d'anomalie osseuse



Clinique

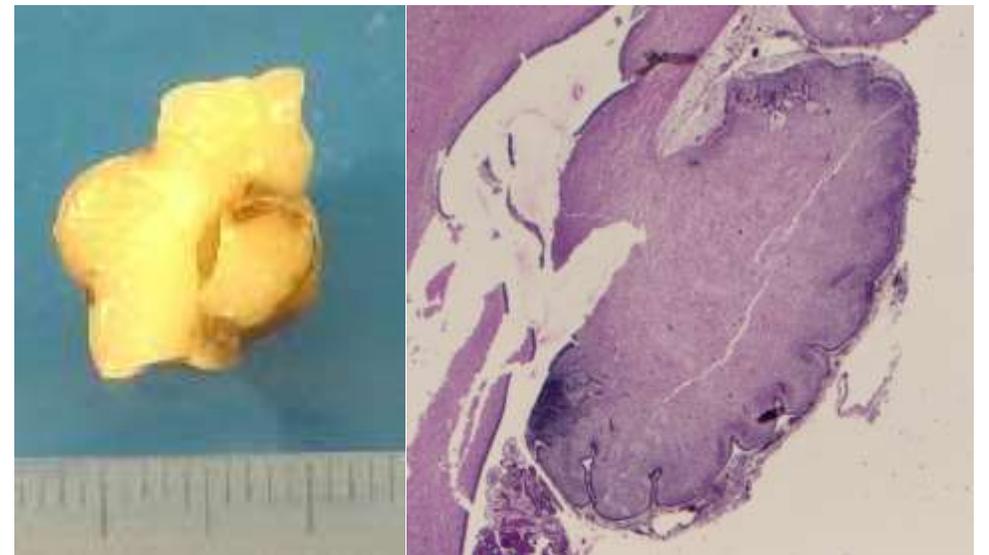


IMG 2017 (17 SA)



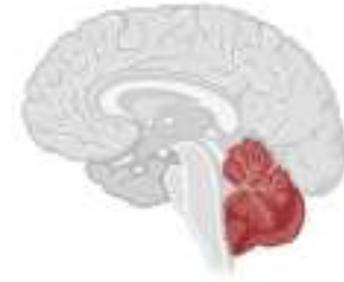
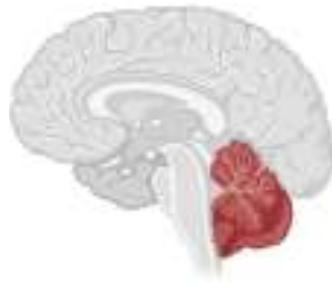
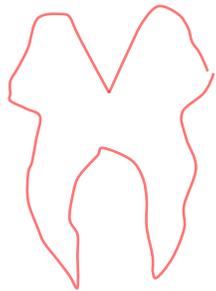
- ✓ Méningo-encéphalocèle isolée
- ✓ Dysplasie du cervelet

Dysplasie des folioles antérieurs avec discontinuité des cellules de la couche des grains externes



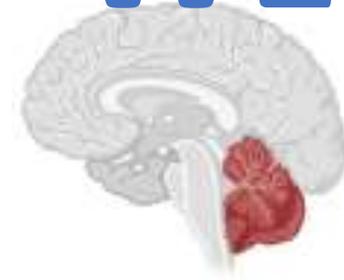
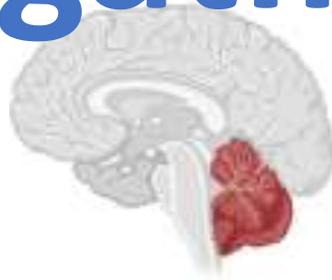
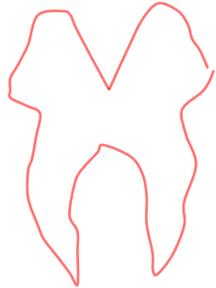
Clinique

Ciliopathie ?



Ciliopathie ?

IMG 2012 01/06/2014 IMG 2017 (17 SA)
Ciliome négatif → WES



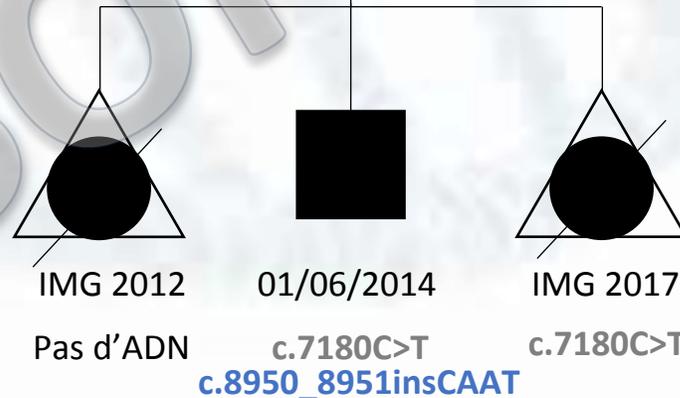
LAMA1 (63 exons/3075 AA) :

2 variants hétérozygotes composites retrouvés
chez les 2 atteints hérités chacun d'un des parents

NM_005559.3:c.7180C>T
p.Arg2394*



NM_005559.3:c.8950_8951insCAAT
p.Lys2984Thrfs*12



Syndrome de Poretti-Boltshauser

Dystrophie/anomalie rétinienne	12/25	48%
Myopie	17/25	68%
Apraxie oculomotrice	17/25	68%
Nystagmus	8/24	33%
Strabisme	13/24	54%
Retard de développement moteur	24/25	96%
Retard de langage	21/24	87%
DI	15/24	63%
Ataxie	17/17	100%

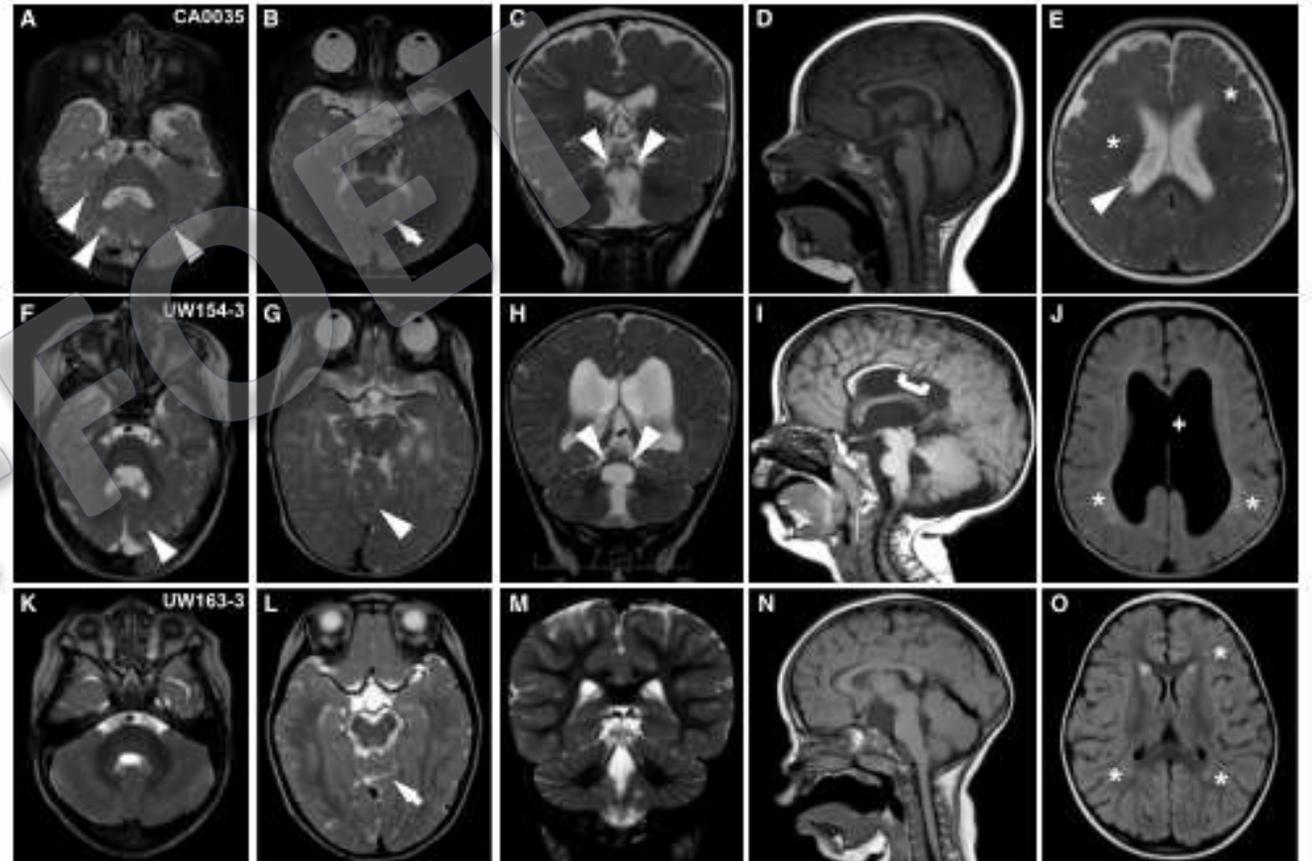
OMIM	#615960
Mode de transmission	AR
Gène	<i>LAMA1</i>



Autres : cataracte bilatérale (1), syndactylie 2-3 orteils (2 frères), trouble spectre autistique (1), épilepsie (1), anxiété/TOCS (2)

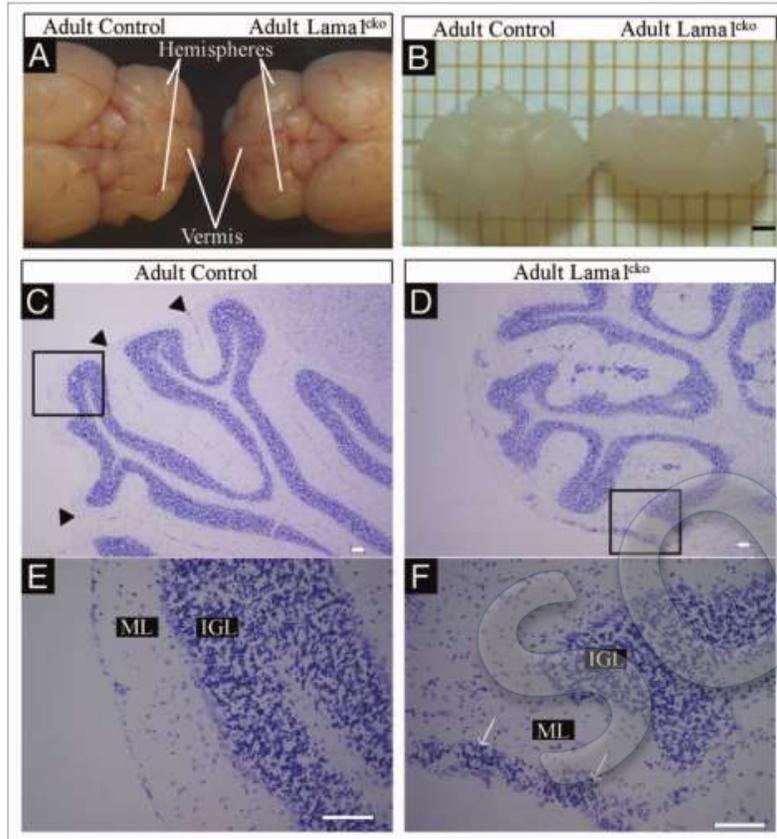
Syndrome de Poretti-Boltshauser

Dysplasie cérébelleuse	25/25	100%
Kystes cérébelleux	23/25	92%
Hypoplasie du vermis	17/25	68%
4 ^{ème} ventricule élargi	20/24	83%
Péduncules cérébelleux supérieurs évasés/surélevés	12/23	52%
Anomalies du tronc cérébral	11/24	46%
Anomalies supratentorielles	5/23	22%

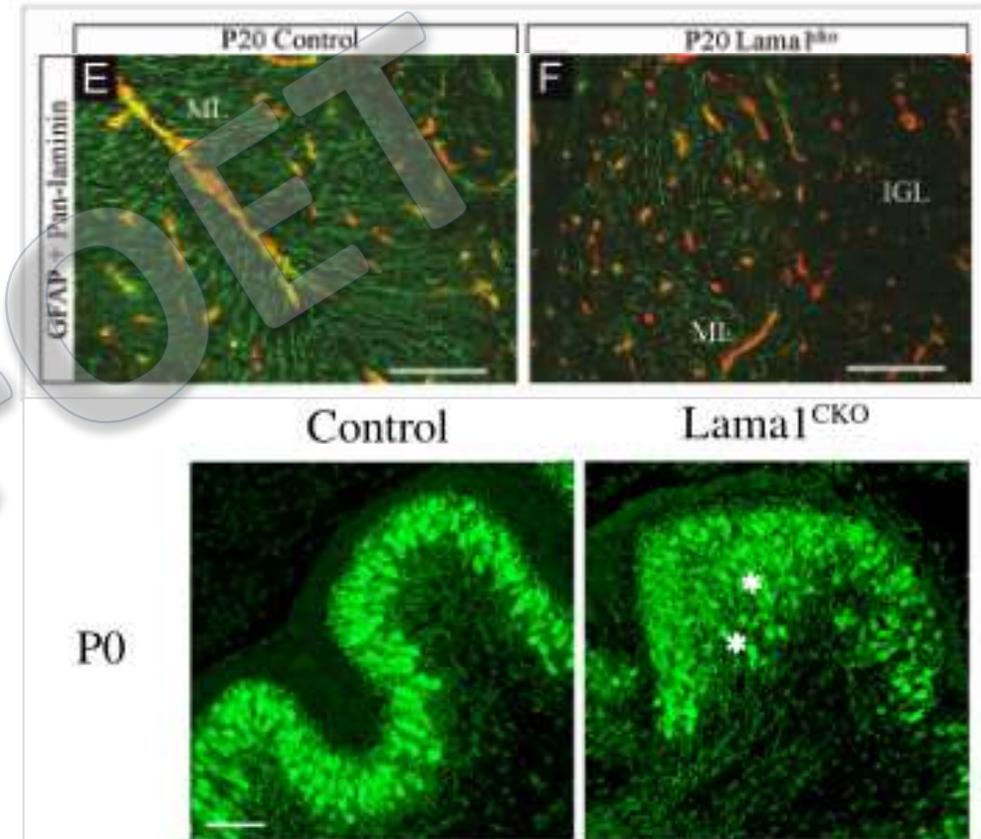


Dysplasie cérébelleuse, Kystes cérébelleux, Hypoplasie du vermis, Elargissement du 4^{ème} ventricule, Péduncules cérébelleux supérieurs évasés et surélevés, Anomalies du tronc cérébral et anomalies supratentorielles.

Modèles murins



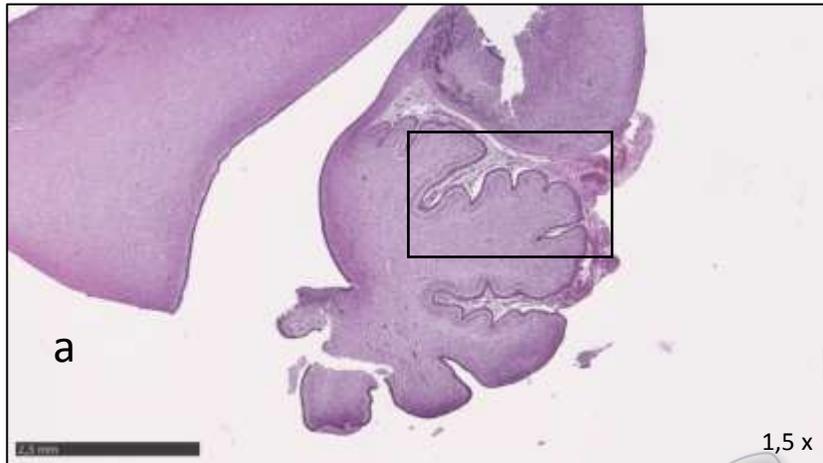
- Hypoplasie cérébelleuse
- Anomalie de foliation
- Perturbation des couches cellulaires:
agréats de cellules granulaires



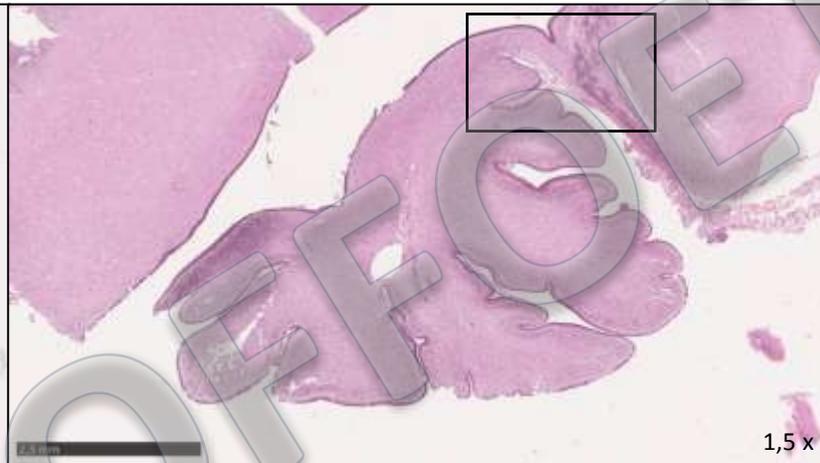
- Désorganisation de la Glie de Bergmann
- Anomalies de la membrane basale
- Désorganisation de la couche des cellules de Purkinje

Examen neurohistopathologique

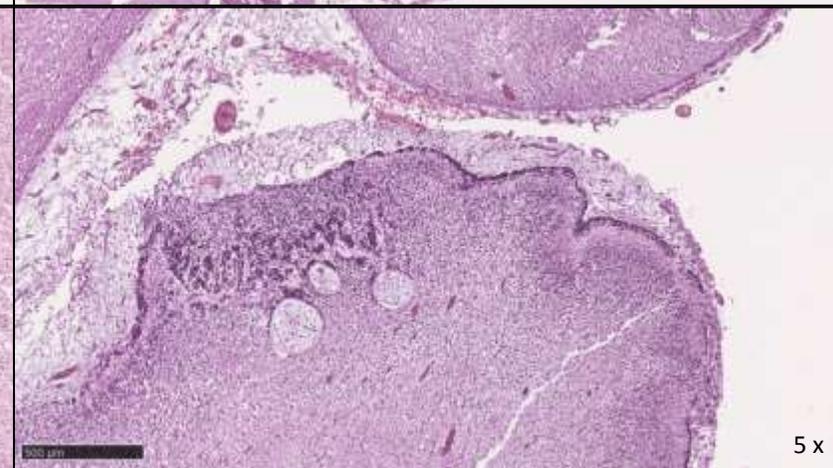
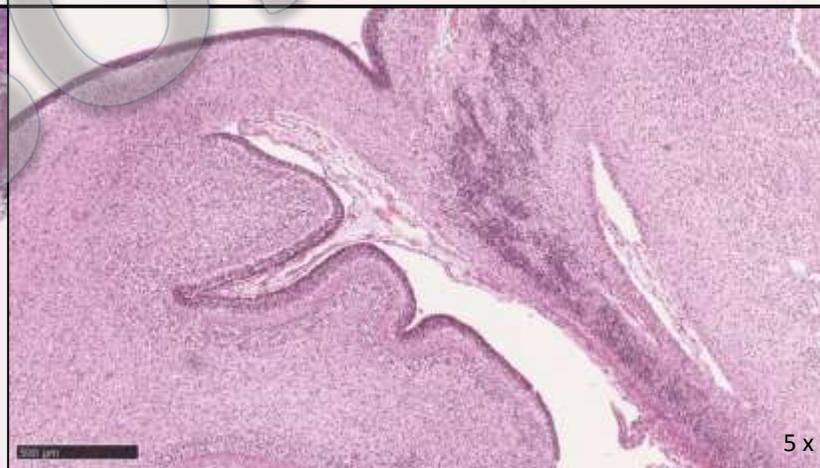
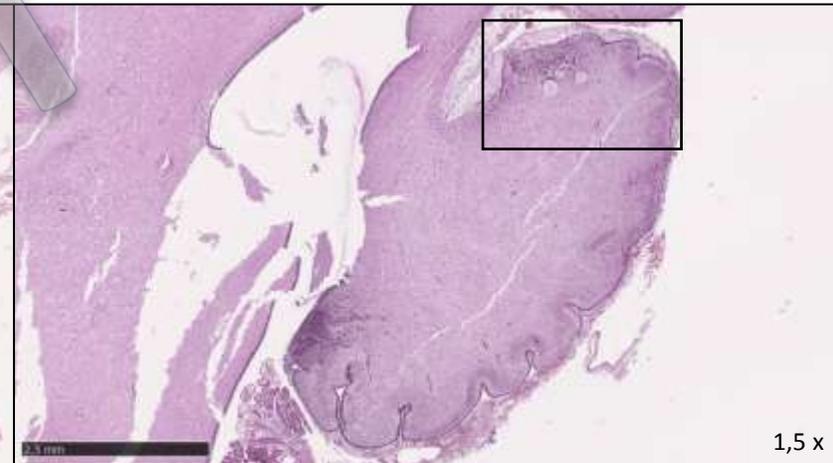
Témoin 16 SA



Témoin 18 SA



Fœtus atteint 17 SA



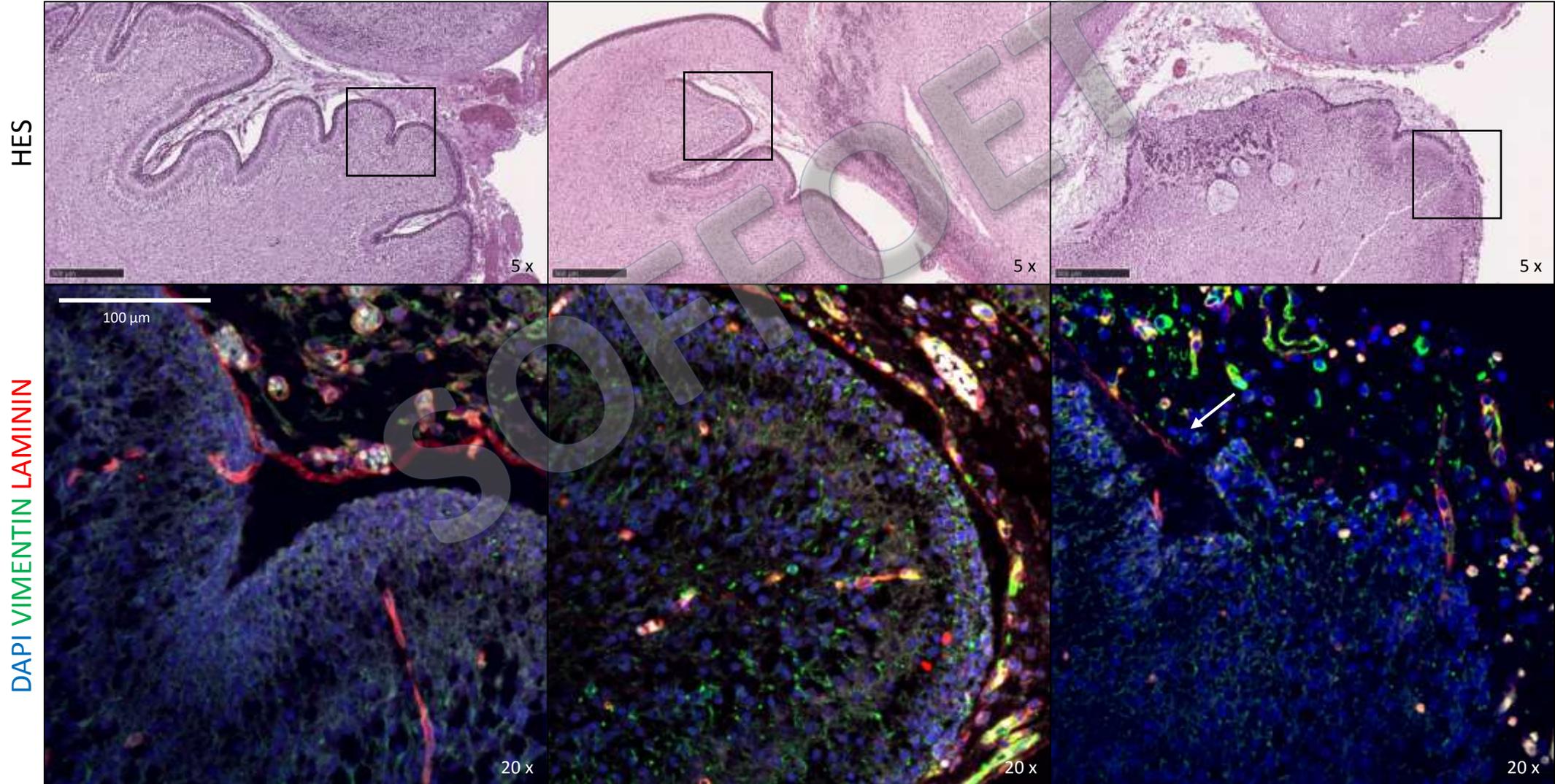
Examen neurohistopathologique

La membrane basale

Témoin 16 SA

Témoin 18 SA

Foetus atteint 17 SA



Examen neurohistopathologique

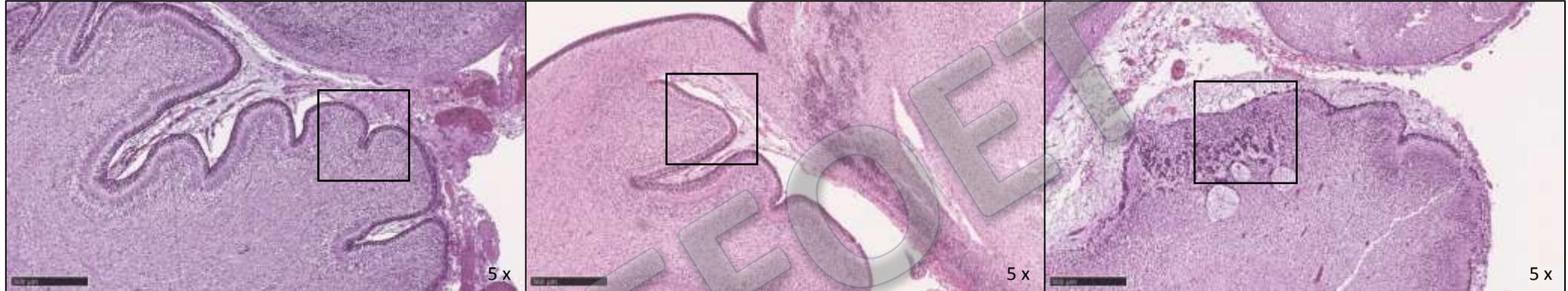
La membrane basale

Témoin 16 SA

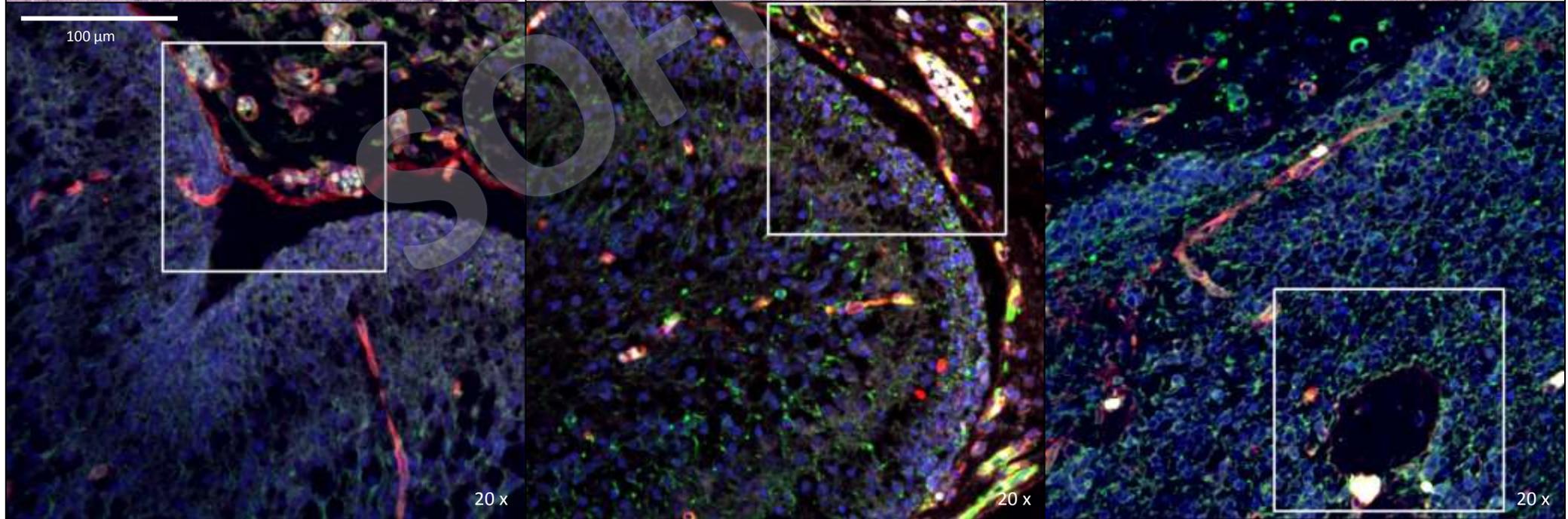
Témoin 18 SA

Foetus atteint 17 SA

HES



DAPI VIMENTIN LAMININ



Examen neurohistopathologique

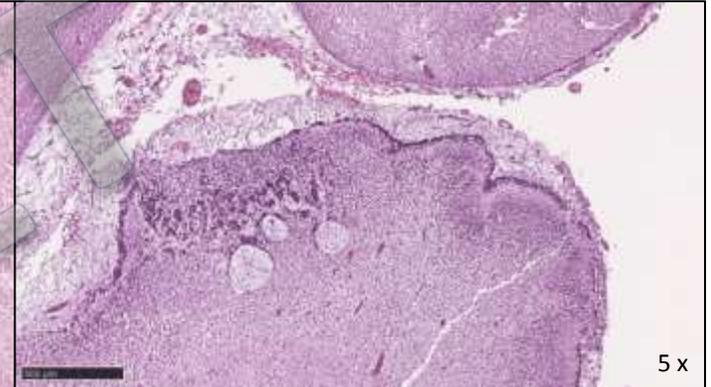
La membrane basale

Témoin 16 SA

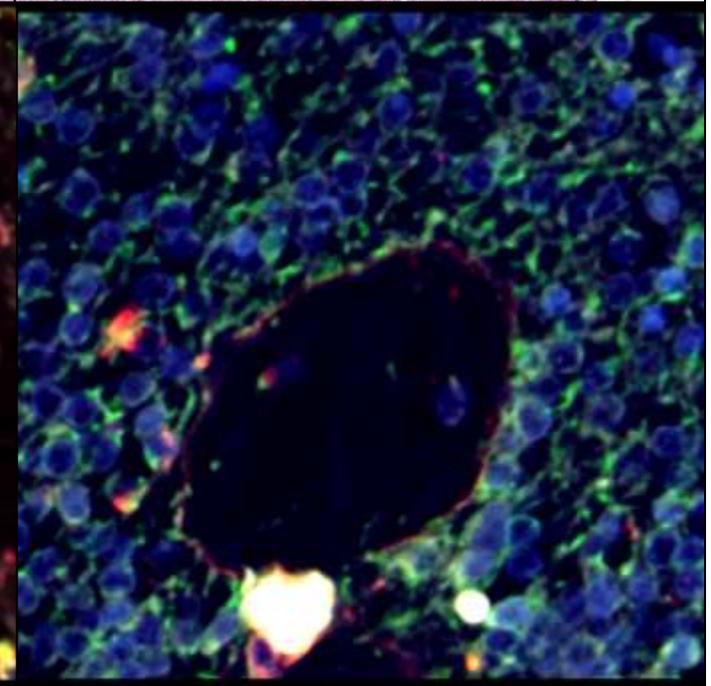
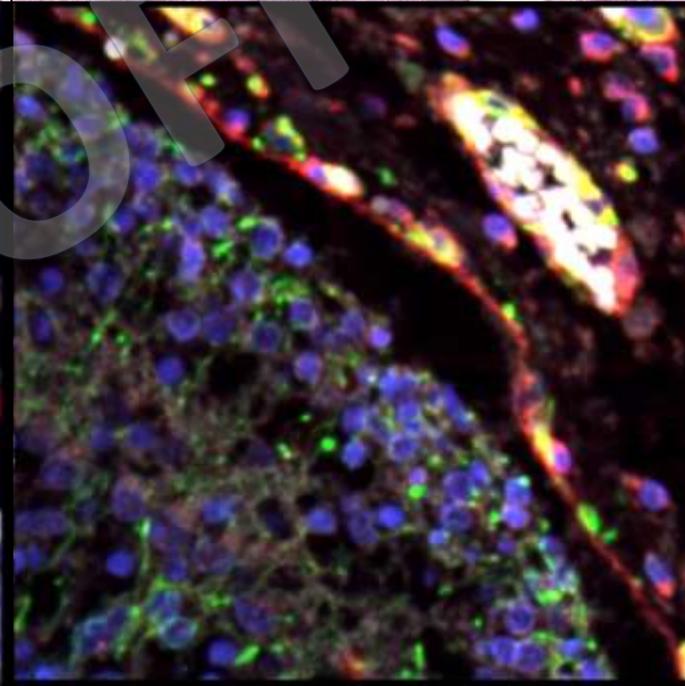
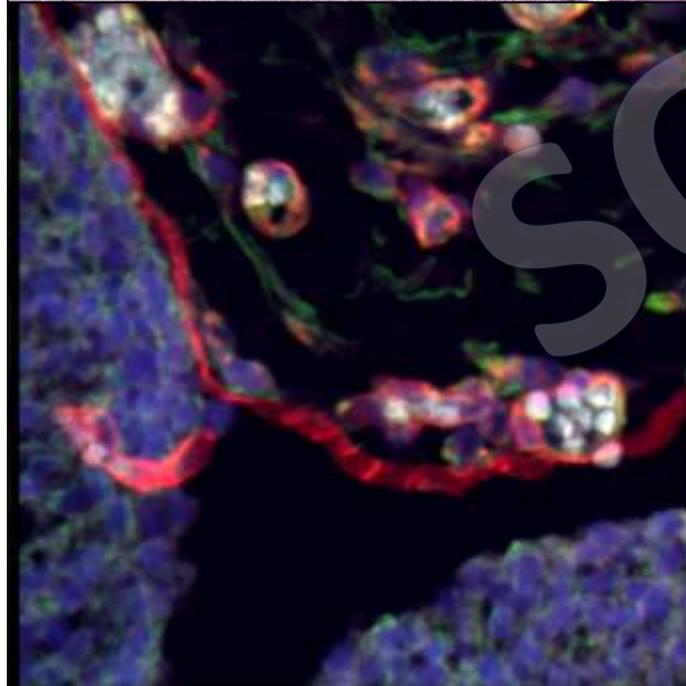
Témoin 18 SA

Foetus atteint 17 SA

HES



DAPI VIMENTIN LAMININ



Examen neurohistopathologique

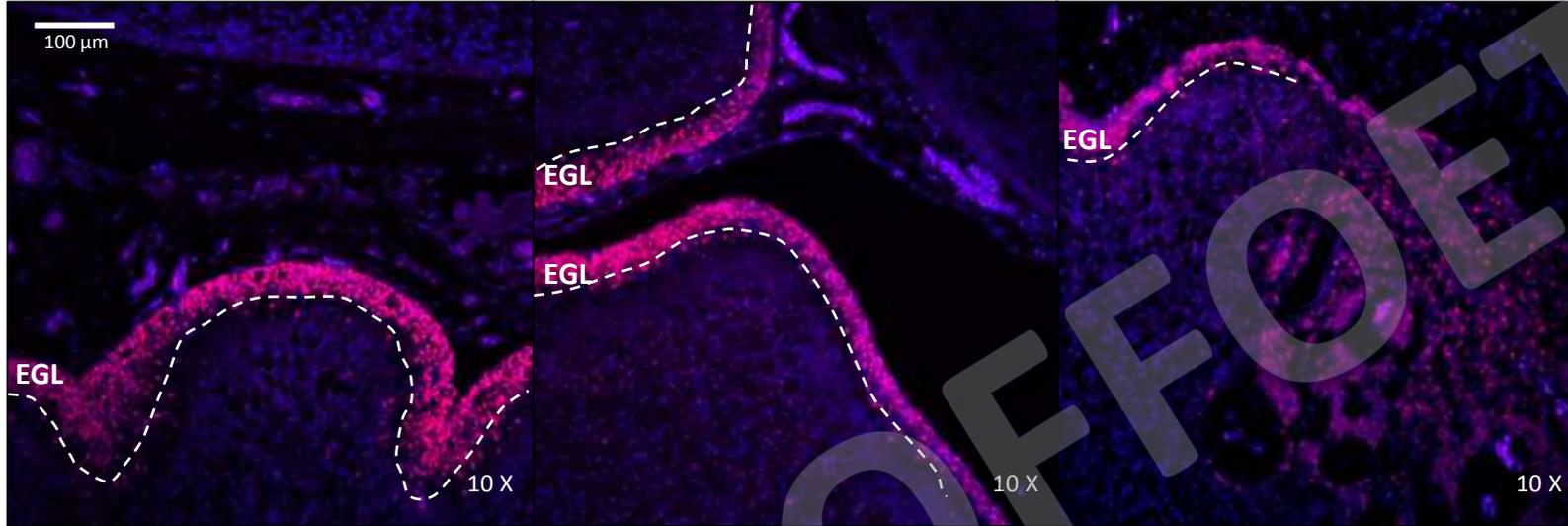
La lamination du cervelet

Témoin 16 SA

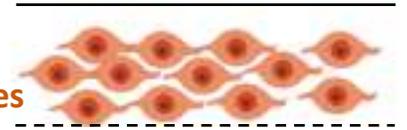
Témoin 18 SA

Foetus atteint 17 SA

DAPI PAX6

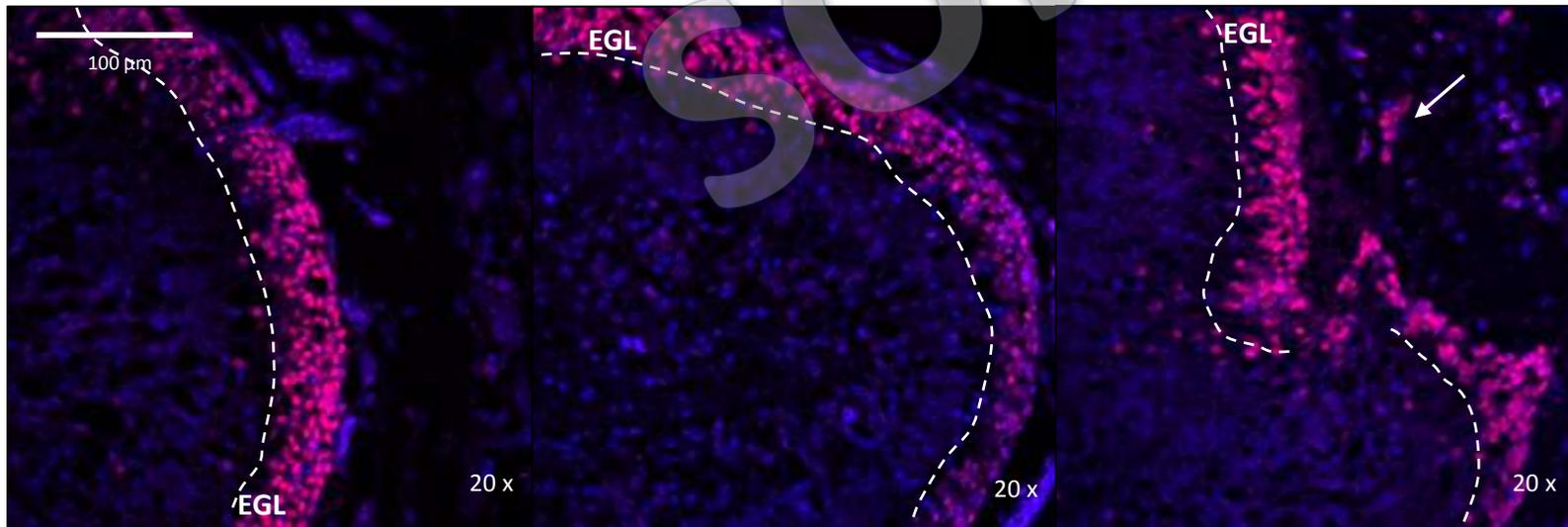


Précurseurs des
cellules granulaires



EGL

DAPI PAX6



Examen neurohistopathologique

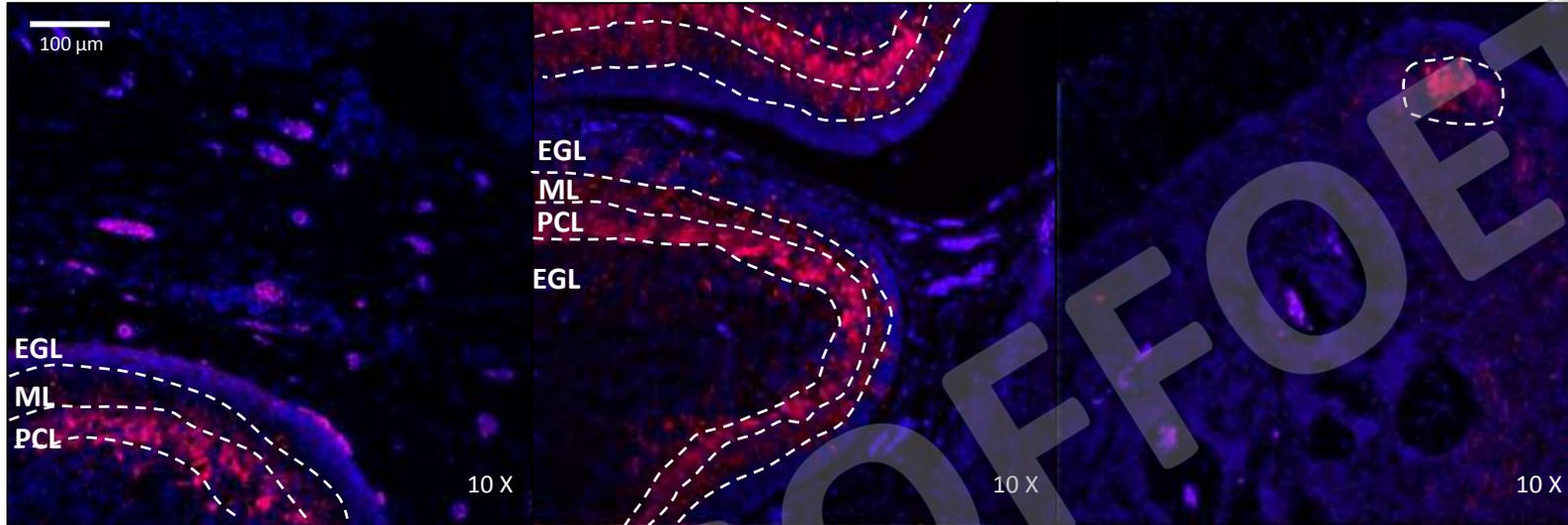
La lamination du cervelet

Témoin 16 SA

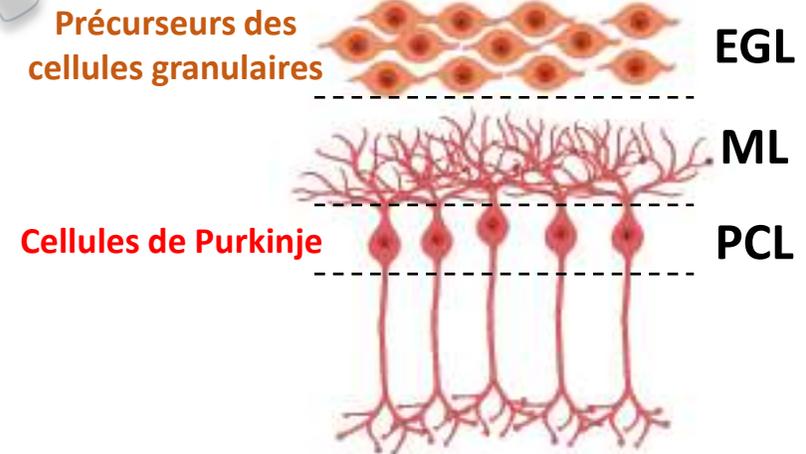
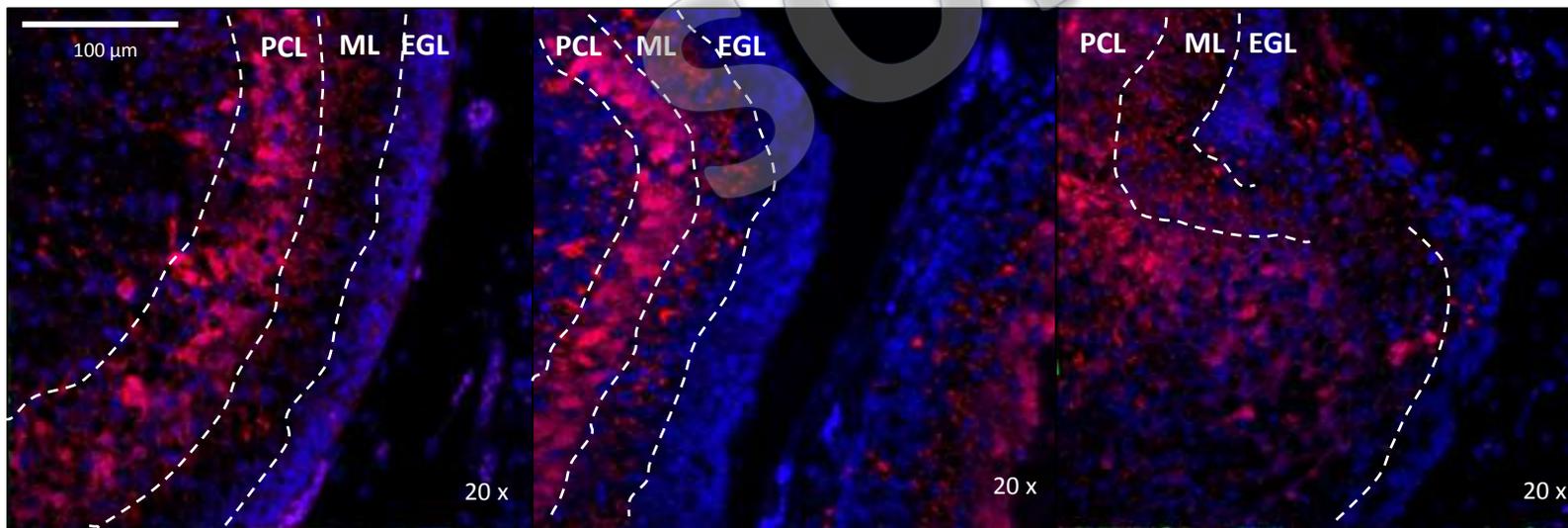
Témoin 18 SA

Fœtus atteint 17 SA

DAPI CALBINDIN



DAPI CALBINDIN



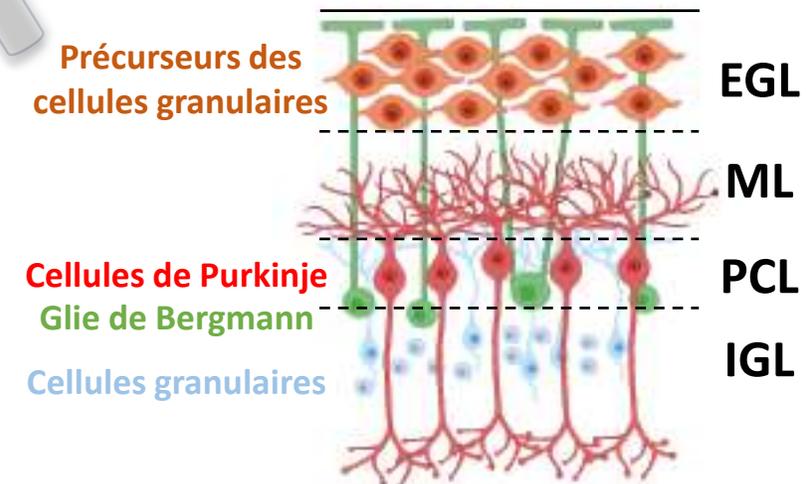
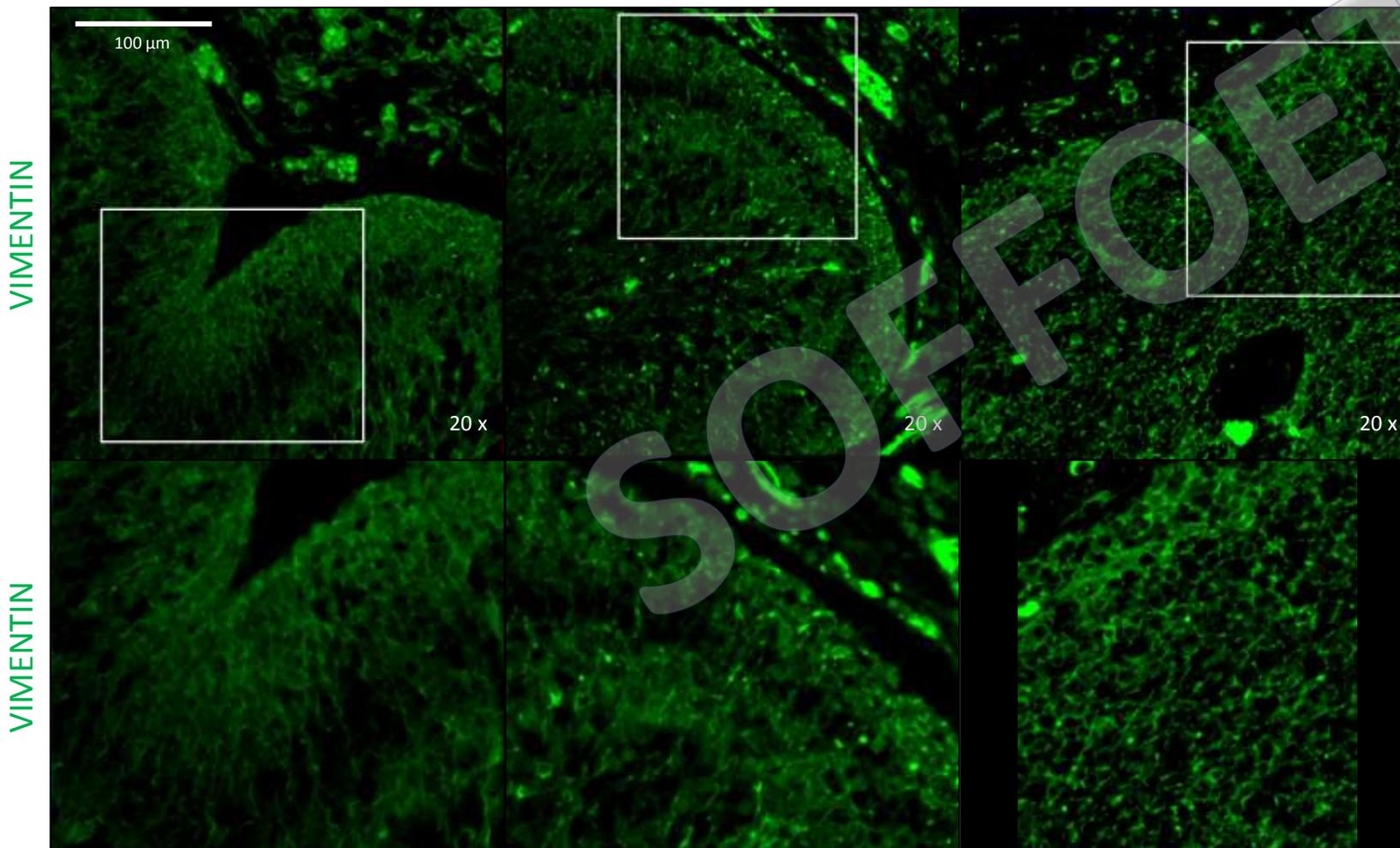
Examen neurohistopathologique

La glie de Bergmann

Témoin 16 SA

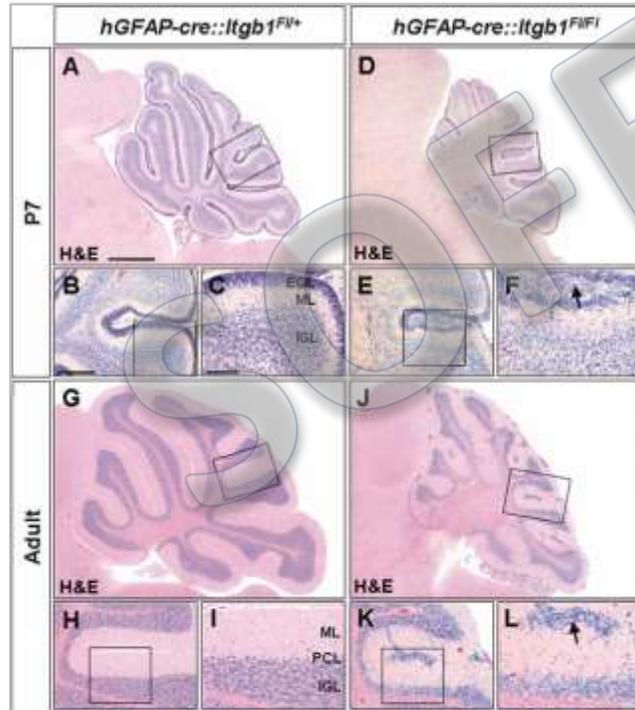
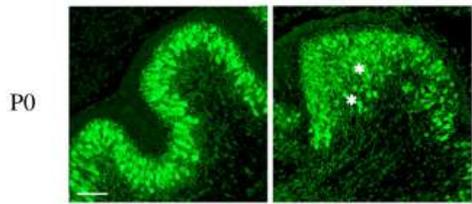
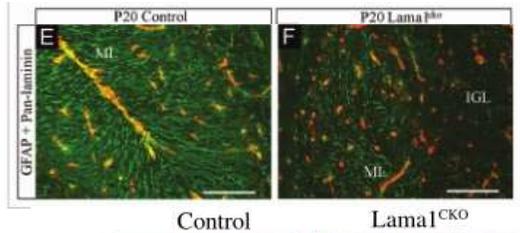
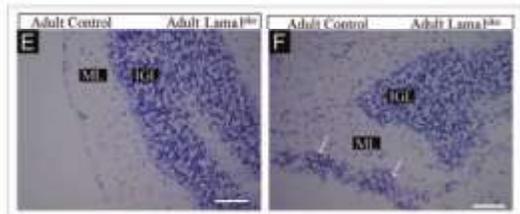
Témoin 18 SA

Fœtus atteint 17 SA



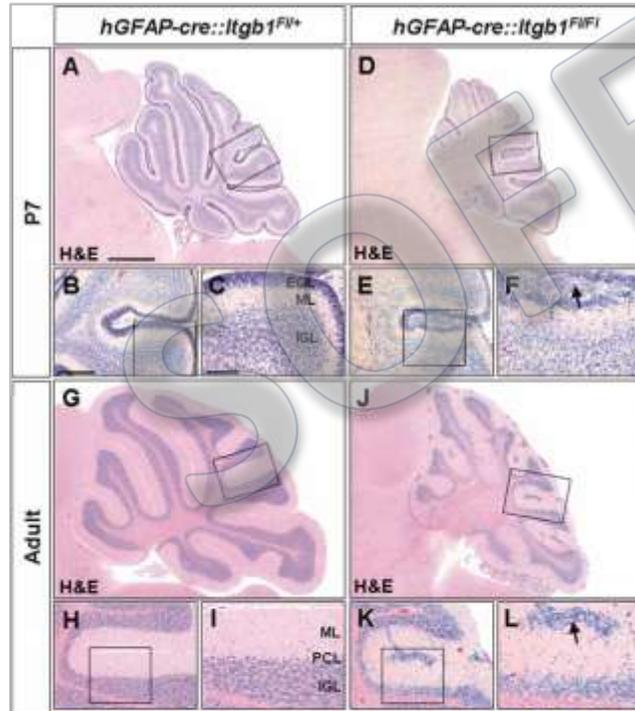
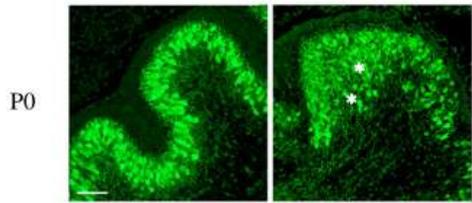
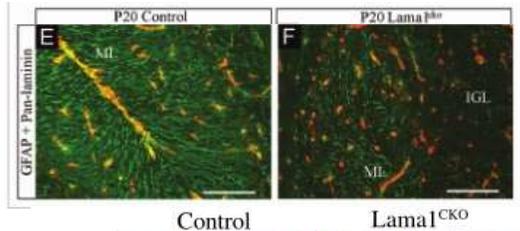
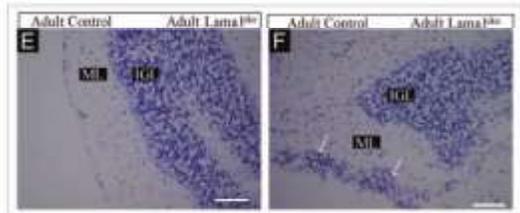
Examen neurohistopathologique

➤ Résultats concordants avec les modèles murins

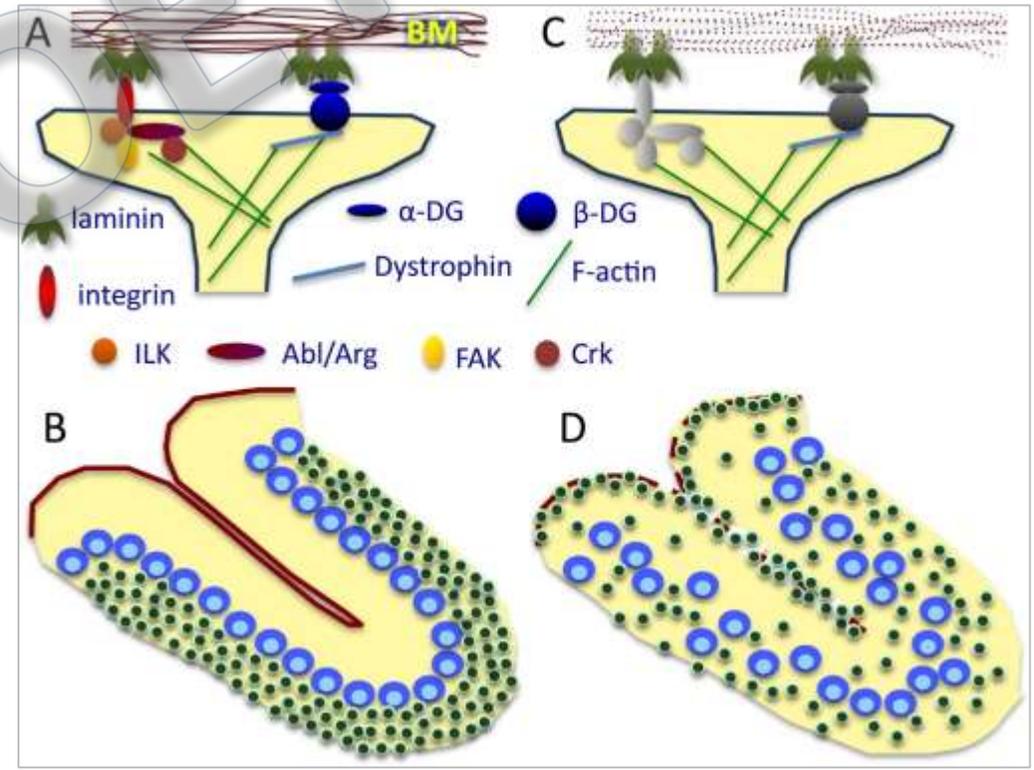


Examen neurohistopathologique

➤ Résultats concordants avec les modèles murins



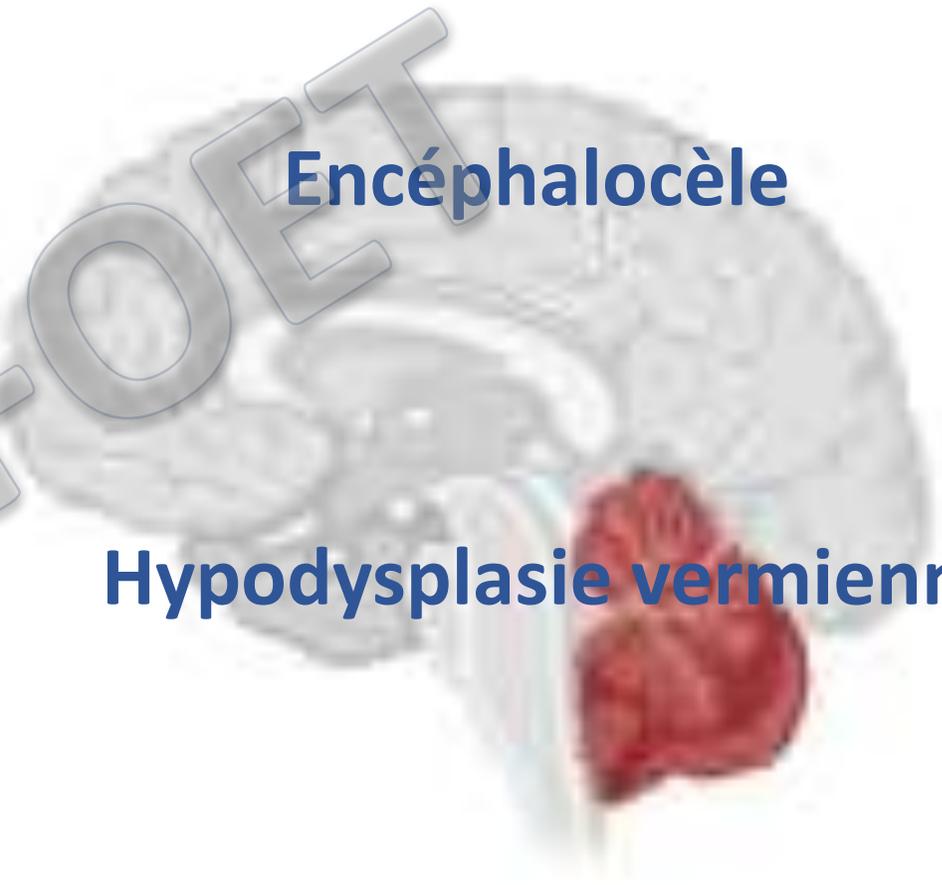
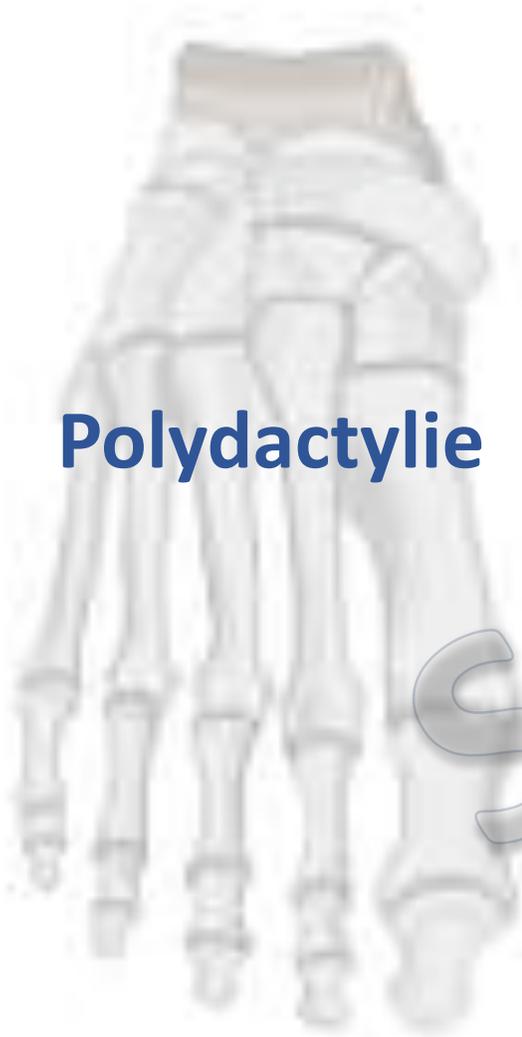
➤ Défaut d'ancrage de la glie de Bergmann à la membrane basale



Buffo *et al.* 2013.

→ défaut de la lamination du cortex cérébelleux

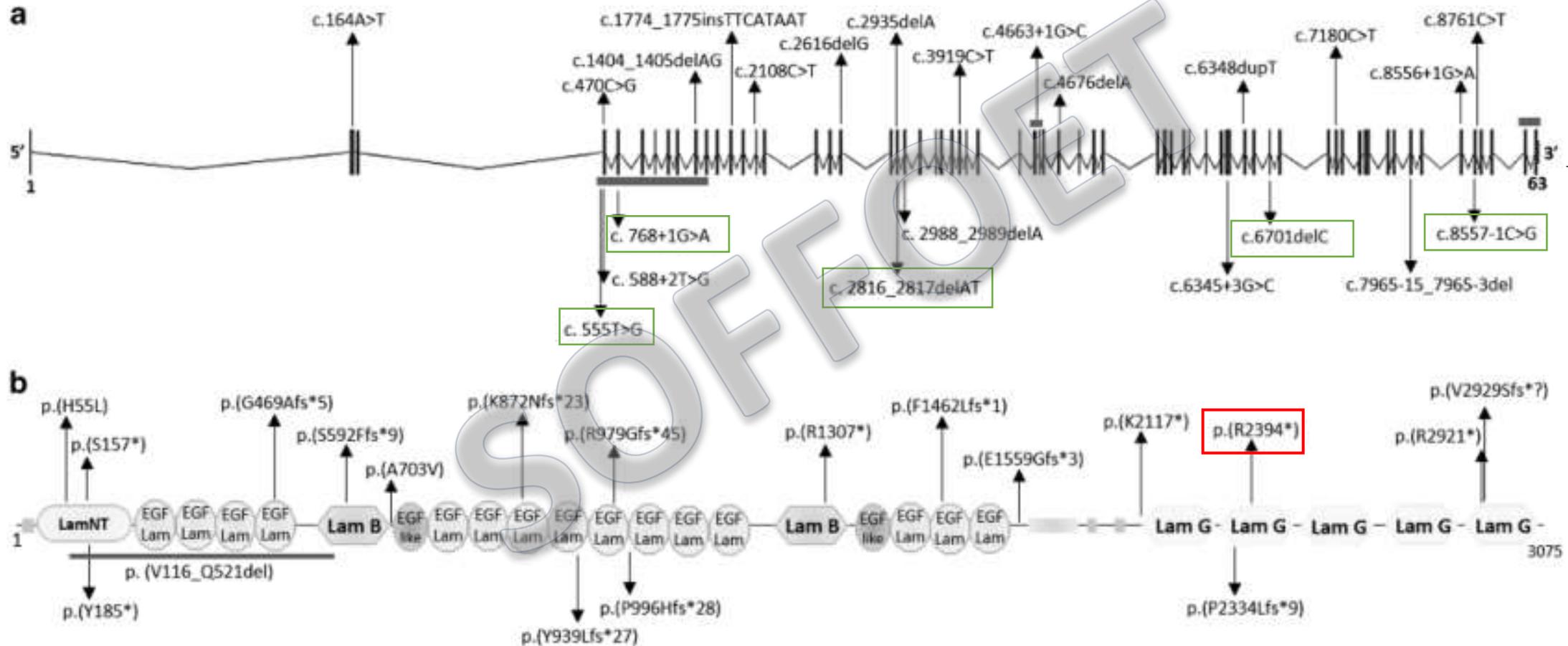
Clinique



Hypodysplasie vermiennne

→ Anomalie du cil primaire ?

Syndrôme de Poretti-Boltshauser



Micalizzi et al. 2016
 Aldinger et al. 2014

Patients initialement étiquetés Joubert

Poretti-Boltshauser / Joubert

Syndrome de Joubert

Signe de la « dent molaire » :

- fossette interpédunculaire
- élongation et horizontalisation des PCS
- hypoplasie du vermis

Anomalies respiratoires

Reins kystiques

Anomalies hépatiques

Polydactylie

Encéphalocèle occipitale

Syndrome de Poretti-Boltshauser

Ataxie

Apraxie oculomotrice

RPM / DI

Hypotonie

Dystrophie rétinienne

Hypoplasie vermienne

Dysplasie cérébelleuse

Kystes cérébelleux

PCS évasés/surélevés

V4 élargi

Poretti-Boltshauser / Joubert

Syndrome de Joubert

Signe de la « dent molaire » :

- fossette interpédonculaire
- élongation et horizontalisation des PCS
- hypoplasie du vermis

Anomalies respiratoires

Reins kystiques

Anomalies hépatiques

Syndrome de Poretti-Boltshauser

Ataxie

Apraxie oculomotrice

RPM / DI

Hypotonie

Dystrophie rétinienne

Hypoplasie vermienne

Polydactylie

Encéphalocèle occipitale

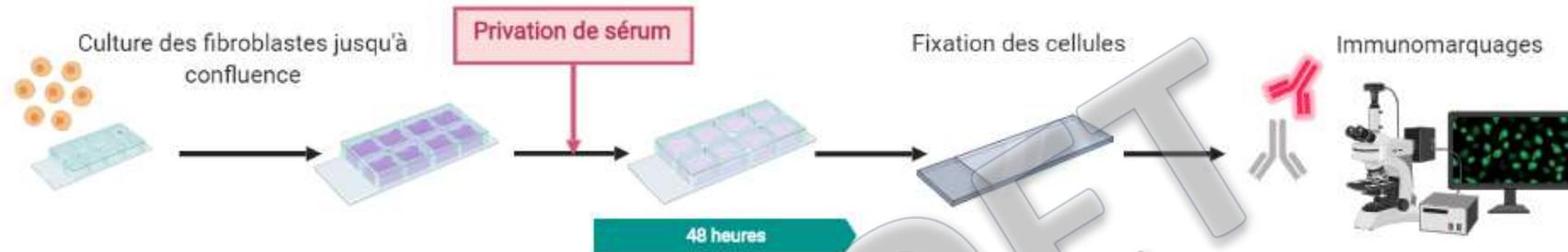
Dysplasie cérébelleuse

Kystes cérébelleux

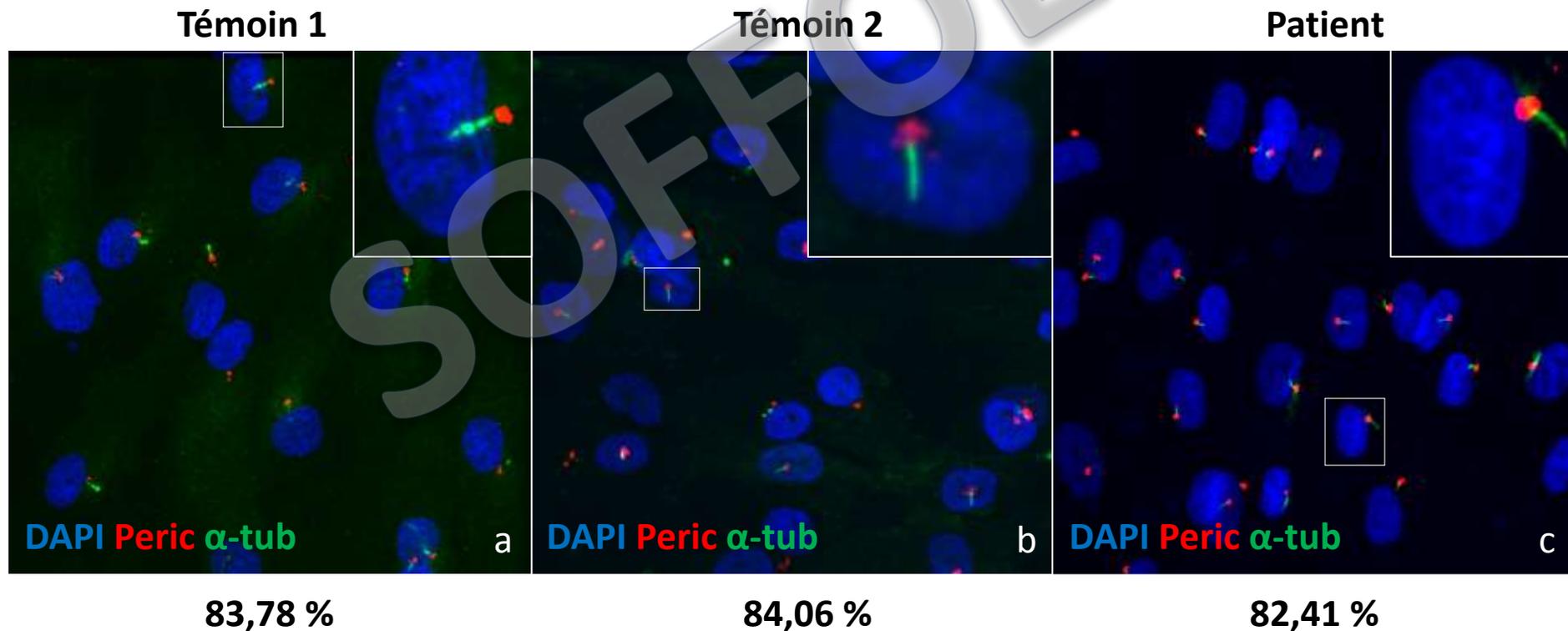
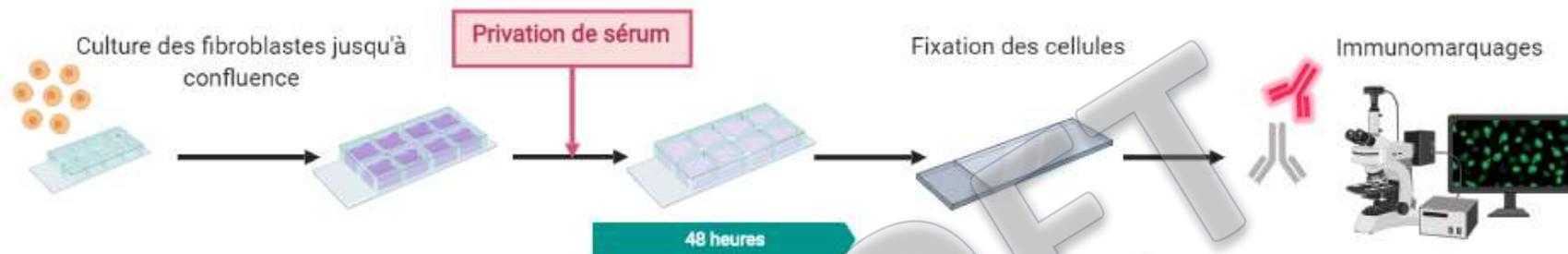
PCS évasés/surélevés

V4 élargi

Etude du cil primaire



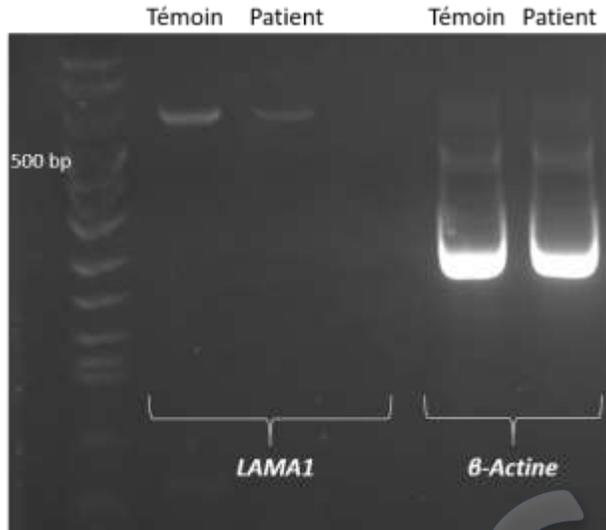
Etude du cil primaire



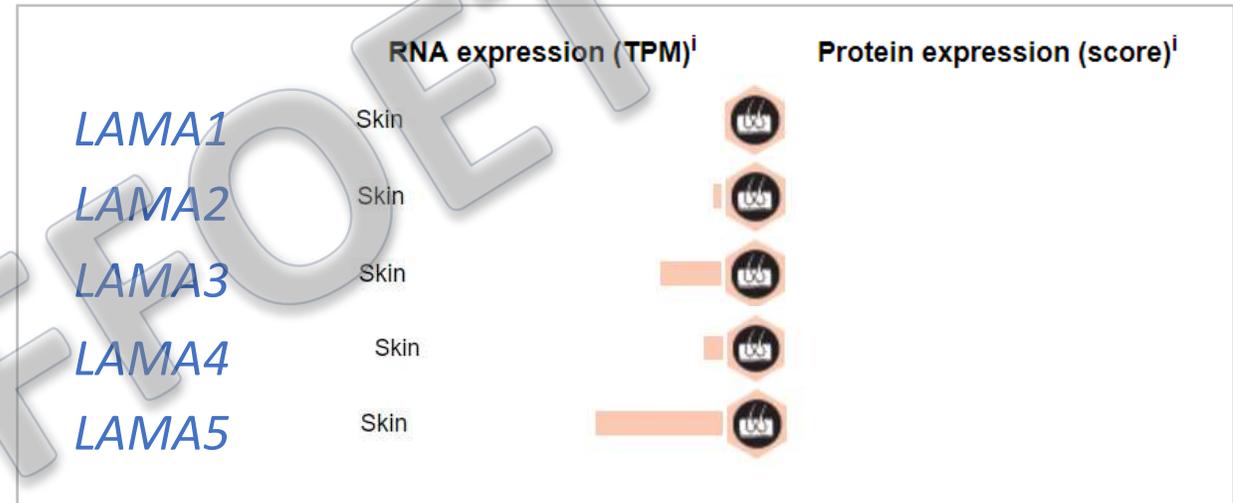
Pourcentage de
cellules ciliées

Etude du cil primaire

➤ Expression faible de *LAMA1* dans les fibroblastes



RT-PCR à partir de l'ARN extrait de fibroblastes



Vérifier l'intégrité du cil primaire dans un tissu pathologique : le cerveaulet

Conclusion

- 1^{ère} description de **polydactylie/encéphalocèle** dans le SPB
→ **extension du phénotype**
- Diagnostic différentiel du syndrome de Joubert
- Pas d'anomalie du cil primaire dans les fibroblastes
→ **analyse sur le tissu pathologique (cervelet)**
- 1^{er} cas foetal rapporté → **étude histopathologique** dans le cervelet humain :
 - **discontinuité de la membrane basale**
 - **perturbation de la lamination du cortex cérébelleux**

Remerciements

Tania ATTIE-BITACH

Lucile BOUTAUD

Camille Maillard

Genetics and Development of
Cerebral Cortex
Alessandra PIERANI

Sophie THOMAS

Thuih Linh Le

Embryology and Genetics of
human malformation
S. LYONNET, J. AMIEL

Aude TESSIER

Ferechté RAVAZI

Laurence LOEUILLET

Amel SEKOUR

Elodie LUNEL

Nadia ELKHARTOUFI

Amale ACHAIAA

Bettina BESSIERES

Nathalie ROUX

Unité d'embryo-foetopathologie,
Hôpital Necker-enfants malades



Merci de votre attention

Les laminines impliquées en pathologie

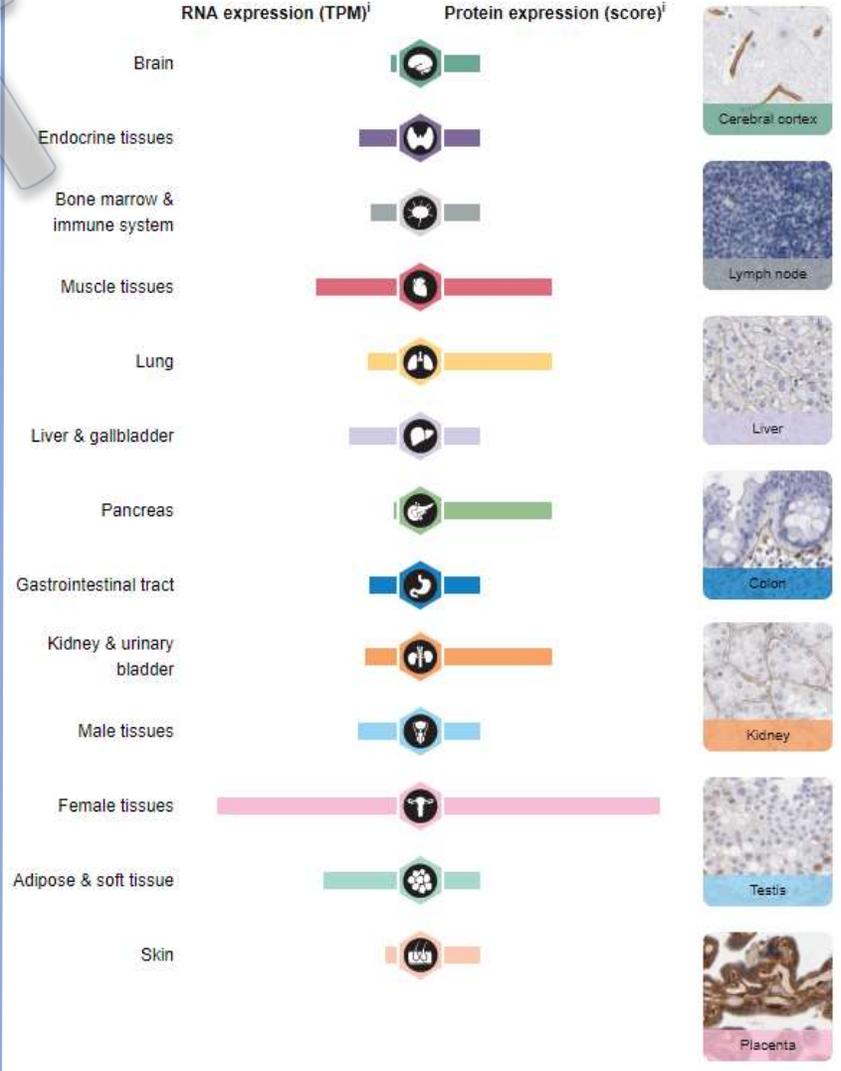
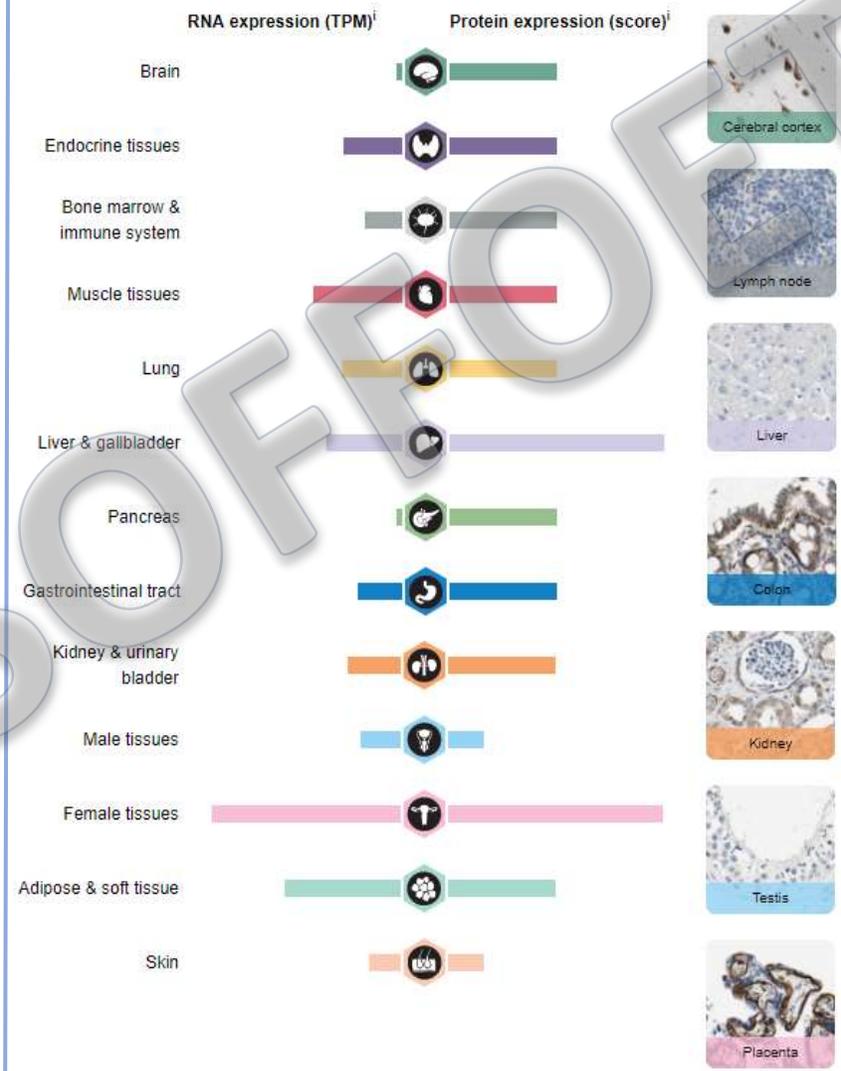
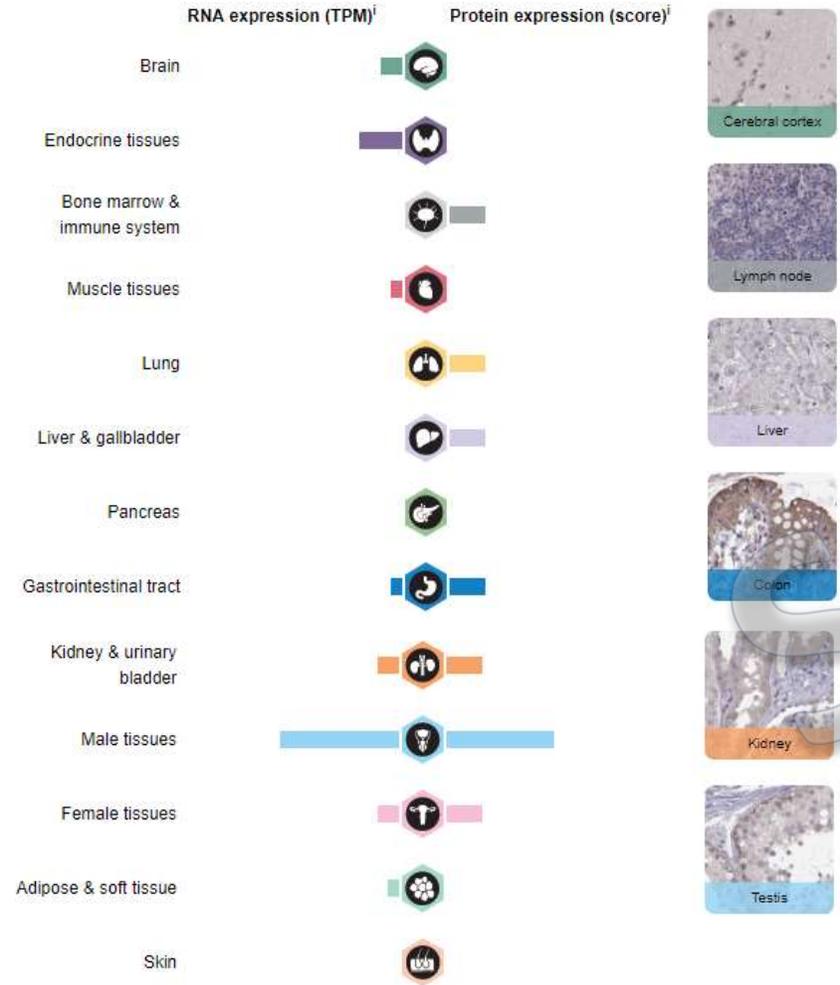
Gene	Protein	Human Disease	Phenotype MIM number	Mode of inheritance
LAMA1	Laminin α 1	Cystic cerebellar dysplasia associated with degenerative myopia/ Poretti-Boltshauser syndrome	615960	AR
LAMA2	Laminin α 2	Congenital muscular dystrophy with diffuse cerebral gray and white matter abnormalities	618138, 607855	AR
LAMA4	Laminin α 4	Dilated cardiomyopathy	615235	AD
LAMB1	Laminin β 1	Cobblestone lissencephaly without ocular or muscular abnormalities with posterior encephalocele	615191	AR
LAMB2	Laminin β 2	Nephrotic syndrome with or without ocular anomalies (Pierson syndrome)	614199, 609049	AR
LAMA3	Laminin α 3	Epidermolysis bullosa	226650, 226700, 245660	AR
LAMB3	Laminin β 3	Epidermolysis bullosa	226700, 226650	AR
	Laminin β 3	Amelogenesis imperfecta, type IA	104530	AD
LAMC1	Laminin γ 1	Autosomal dominant Dandy-Walker malformation and occipital encephaloceles	(ADDWOC; 609222)	
LAMC2	Laminin γ 2	Epidermolysis bullosa	226700, 226650	AR
LAMC3	Laminin γ 3	Cerebral cortical malformations, occipital	614115	AR

Expression :

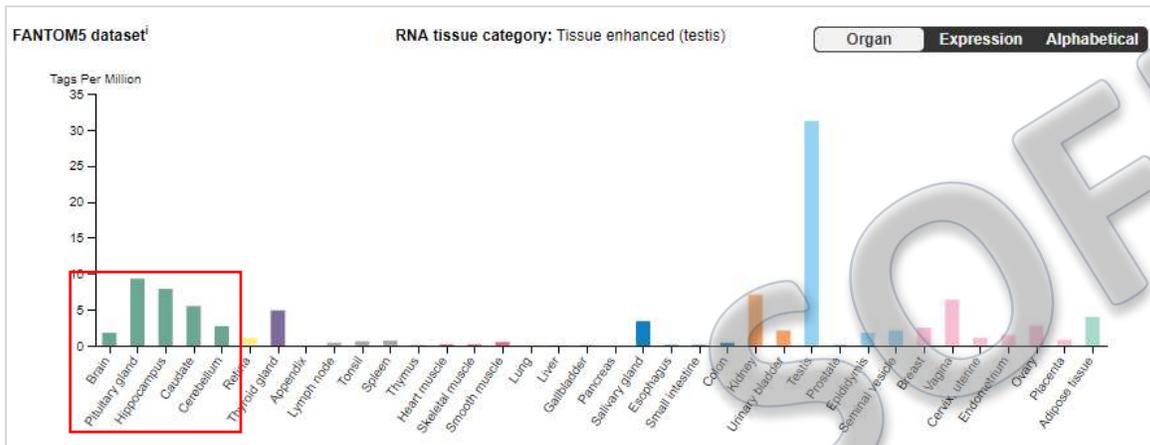
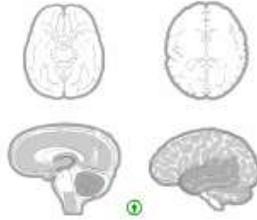
LAMA1

LAMB1

LAMC1



LAMA1 : Expression :



■ High ■ Medium ■ Low

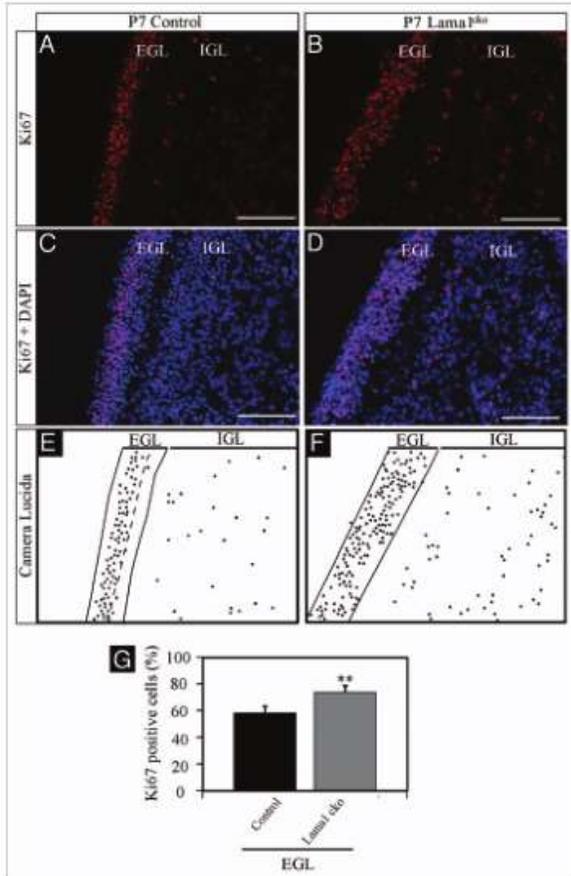
□ Below cutoff ⓘ

□ No data available



Modèle murin : *Lama1*^{cko}

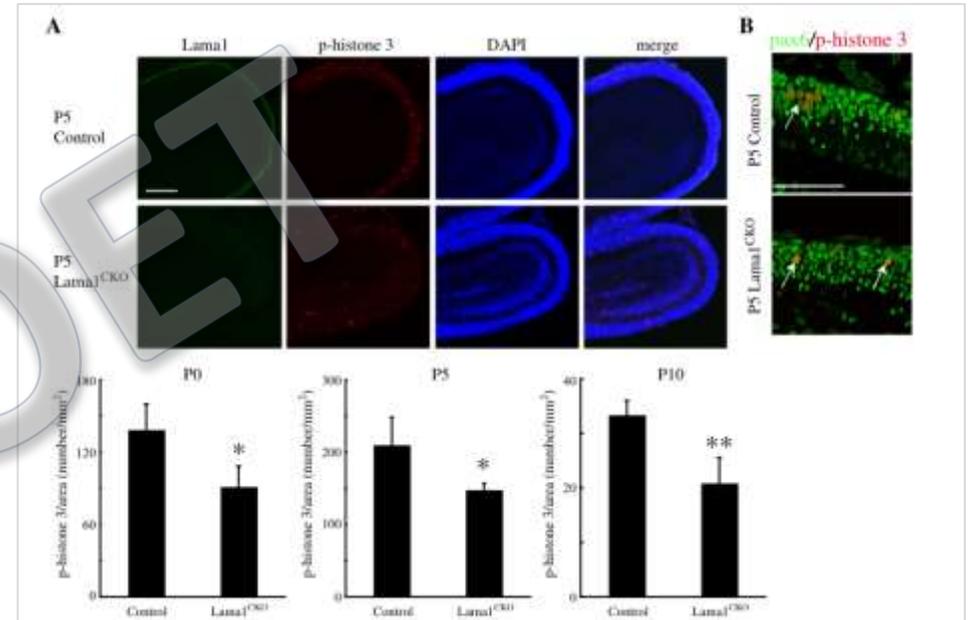
Heng *et al.* 2011.



- ↗ cellules prolifératives (KI67+, PH3+) dans la couche granulaire externe
- Cellules prolifératives détectées dans toute l'épaisseur de la couche granulaire externe chez les souris *LAMA1*^{cko}
- ↗ nombre de cellules Caspase-3+ chez les souris *LAMA1*^{cko}

Augmentation de la prolifération cellulaire et augmentation de l'apoptose

Ichikawa-Tomikawa *et al.* 2011.



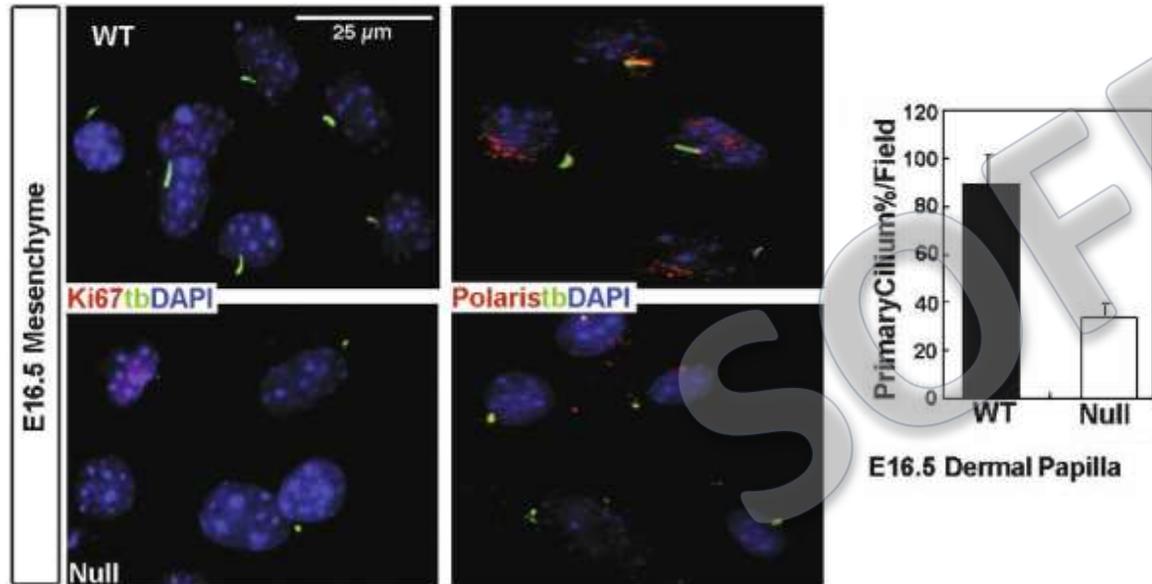
- Réduction du nombre de cellules prolifératives
- TUNEL (P0, P5, P10, P21 et adulte) : pas de différence concernant la mort cellulaire

Diminution de la prolifération cellulaire

Laminines et cil primaire

Laminin-511 is an epithelial message promoting dermal papilla development and function during early hair morphogenesis

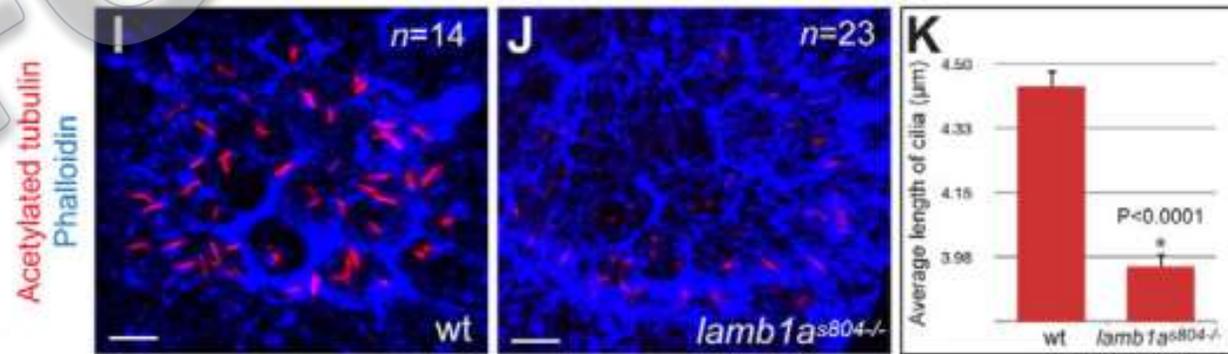
Jing Gao,¹ Mindy C. DeRouen,¹ Chih-Hsin Chen,¹ Michael Nguyen,¹ Ngon T. Nguyen,¹ Hiroyuki Ido,² Kenji Harada,² Kiyotoshi Sekiguchi,² Bruce A. Morgan,³ Jeffery H. Miner,⁴ Anthony E. Oro,¹ and M. Peter Marinkovich^{1,5,6}



Laminine-511 (α5β1γ1) est impliquée dans la formation et la longueur du cil primaire dans le derme papillaire chez la souris

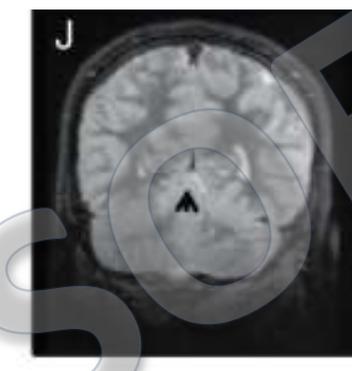
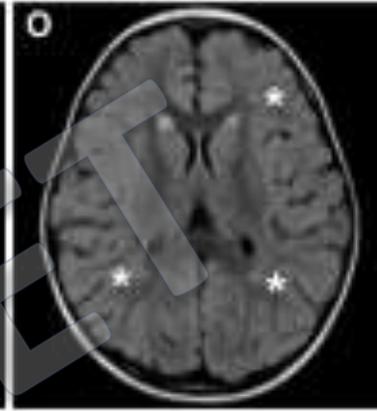
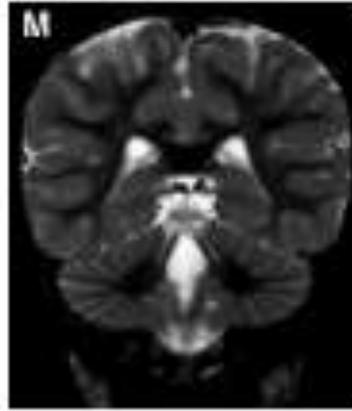
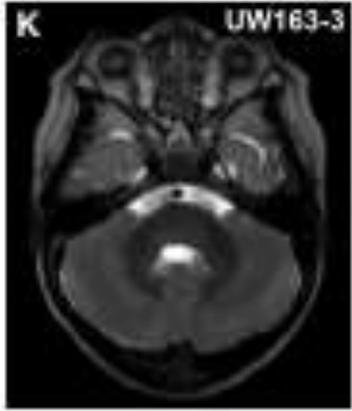
Laminin β1a controls distinct steps during the establishment of digestive organ laterality

Tatiana Hochgreb-Hägele^{1,2,*}, Chunyue Yin^{1,4,*}, Daniel E. S. Koo², Marianne E. Bronner² and Didier Y. R. Stainier^{1,5,1}



Lamb1a contrôle la longueur du cil dans la vésicule de Kupfer chez le poisson zèbre

Patients étiquetés Joubert like



K-O : UW 163-3 : dysplasie cérébelleuse, pas de kyste, anomalie de signal, pédoncules cérébelleux et 4^{ème} ventricule normaux

H,I,J : UW 160-3 : hypoplasie et dysplasie cérébelleuse, avec kystes, 4^{ème} ventricule élargi et rectangulaire

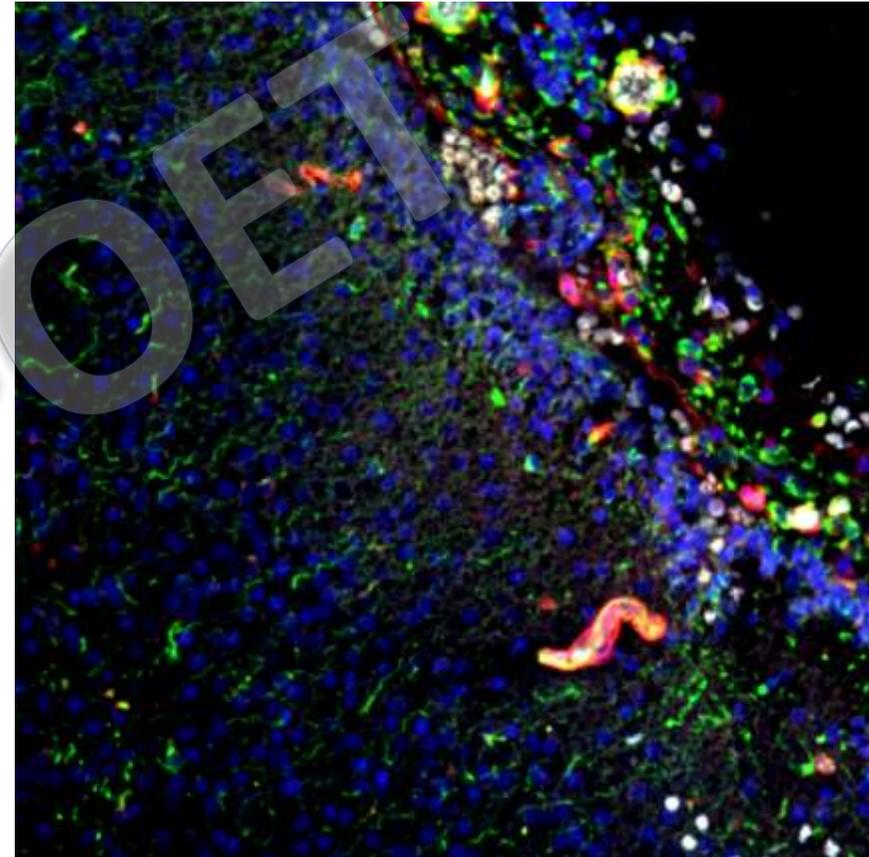
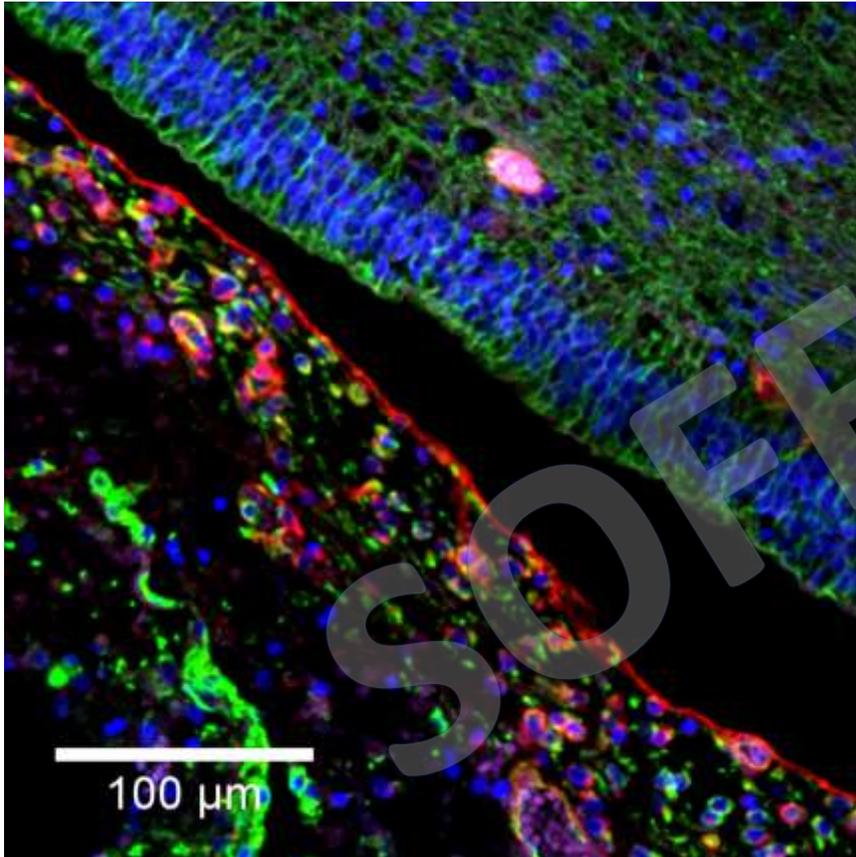


K,L,M : UW 160-4 : hypoplasie et dysplasie cérébelleuse avec kystes, 4^{ème} ventricule élargi

Témoïn 16 SA

Fœtus atteint 17 SA

DAPI VIMENTIN LAMININ



Search results: 1 to 5 of 5 (out of 277 total)

Show: Sequence Variants Filter...

DECIPHER ID	Variant	Sex	Size	Pathogenicity / Contribution	Inheritance	Phenotype(s)	Patient Open-Access Variants	Contact
271064	18 ⁷⁰⁴⁰²¹⁶ ⁷⁰⁴⁰²¹⁶ G > T	46XY	SNV	Pathogenic Full	Paternally inherited, constitutive in father	Aplasia/Hypoplasia of the cerebellar vermis, Cognitive impairment, Gait ataxia, Impaired social interactions, Oculomotor apraxia, Recurrent hand flapping	2	✉
271064	18 ⁷⁰²⁶⁰³⁶ ⁷⁰²⁶⁰³⁶ G > A	46XY	SNV	Pathogenic Full	Maternally inherited, constitutive in mother	Aplasia/Hypoplasia of the cerebellar vermis, Cognitive impairment, Gait ataxia, Impaired social interactions, Oculomotor apraxia, Recurrent hand flapping	2	✉
285238	18 ⁷⁰⁴⁴⁸⁰⁶ ⁷⁰⁴⁴⁸⁰⁶ G > T	46XX	SNV	Likely pathogenic Full	Paternally inherited, constitutive in father	Abnormality of eye movement, Abnormality of the cerebellum, Achilles tendon contracture, Central hypotonia, Clinodactyly of the 5th finger, Molar tooth sign on MRI	2	✉
285238	18 ⁶⁹⁸⁶³⁰¹ ⁶⁹⁸⁶³⁰² C T > C	46XX	-1 bp	Likely pathogenic Full	Maternally inherited, constitutive in mother	Abnormality of eye movement, Abnormality of the cerebellum, Achilles tendon contracture, Central hypotonia, Clinodactyly of the 5th finger, Molar tooth sign on MRI	2	✉
323516	18 ⁷⁰⁵⁰⁹¹⁷ ⁷⁰⁵⁰⁹¹⁹ C A T > C	46XX	-2 bp	Likely pathogenic Full	Biparental	Abnormality of the nervous system	1	✉

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