

# Dystroglycan in brain, eye, and nerve: the non-muscle, neuropathology of dystroglycanopathies.

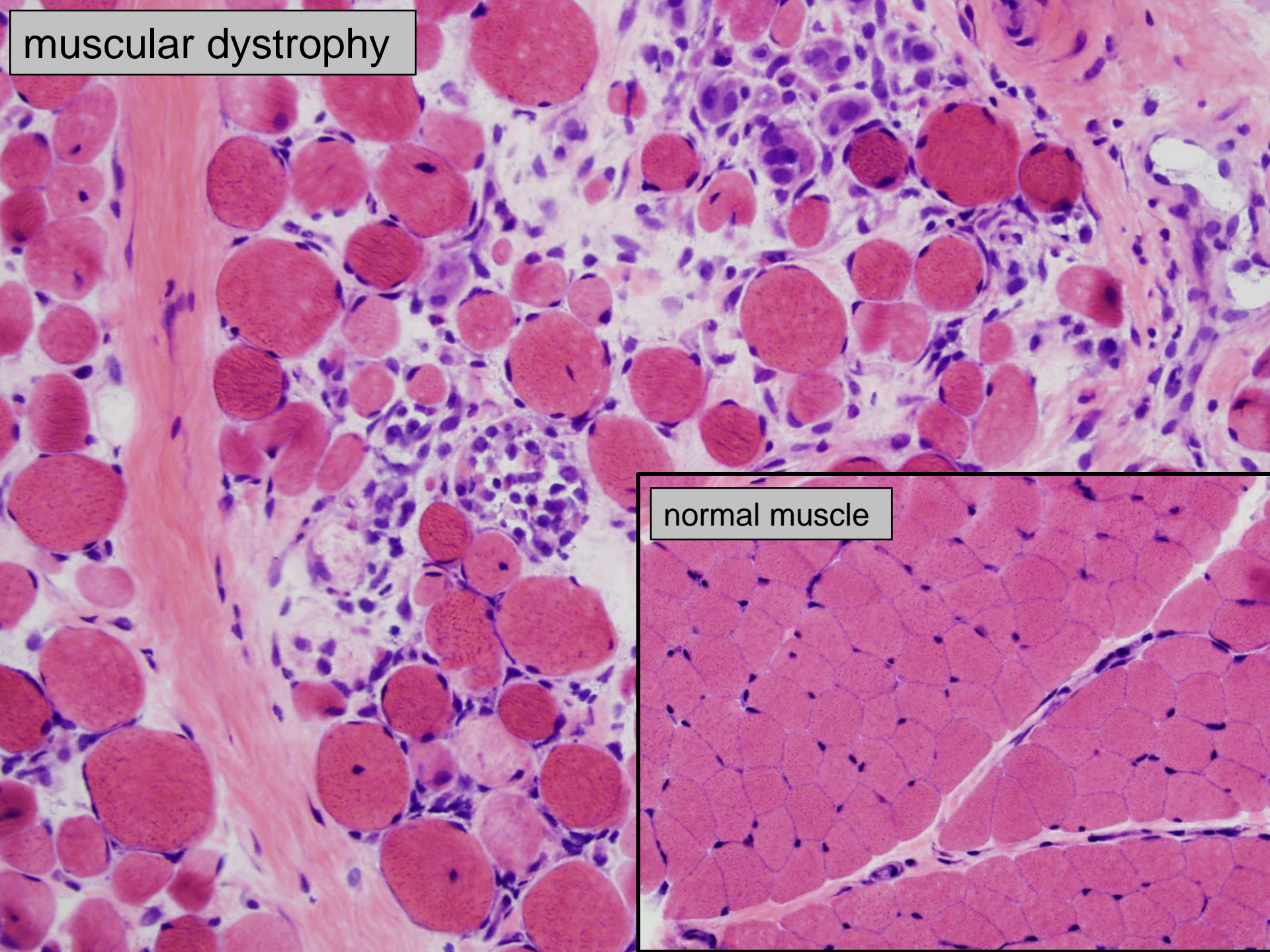


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Professor, Department of Pathology, and  
Wellstone Muscular Dystrophy Cooperative Research Center

No conflicts of  
interest to declare.



muscular dystrophy



normal muscle



basement  
membrane

This electron micrograph shows a cross-section of a skeletal muscle fiber. The fiber is bounded by a basement membrane (top left) and a cell surface membrane (top right). The interior is filled with a dense network of contractile proteins. Several mitochondria are visible as dark, oval structures. An inset in the bottom left corner shows a light micrograph of skeletal muscle tissue, highlighting the striated appearance and nuclei of the fibers.

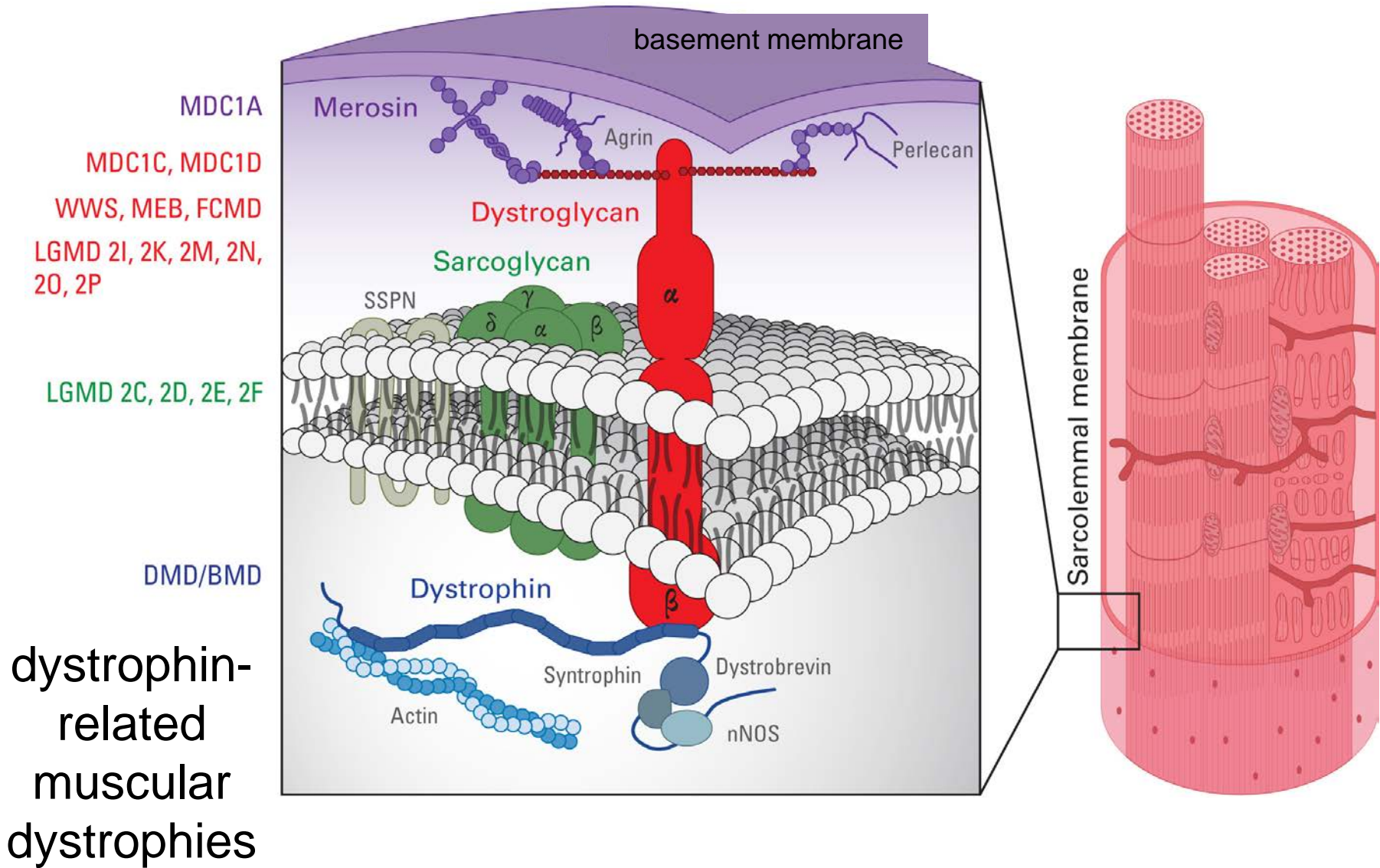
cell  
surface  
membrane

contractile  
proteins

electron micrograph of skeletal muscle fiber

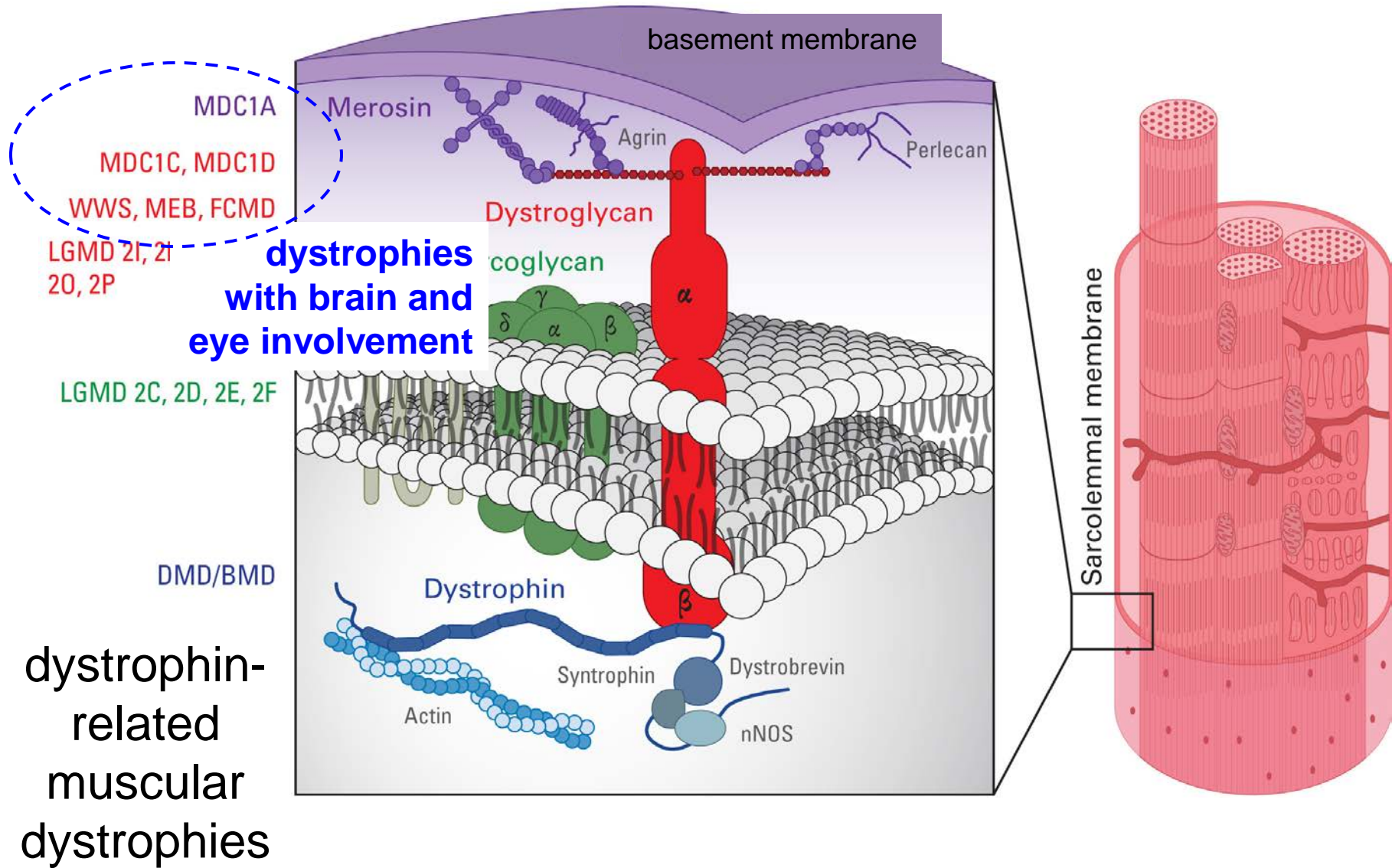


# dystrophin-glycoprotein complex (DGC)





# dystrophin-glycoprotein complex (DGC)



*drawing by Huy Nguyen*

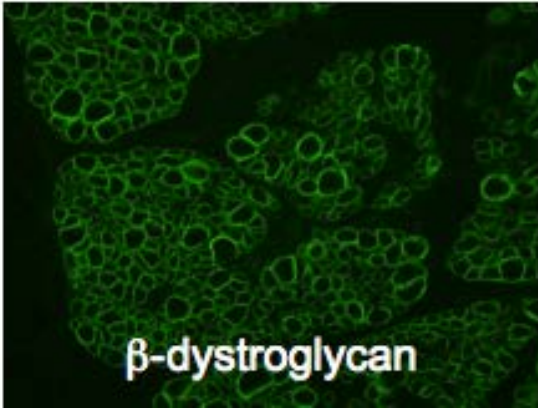
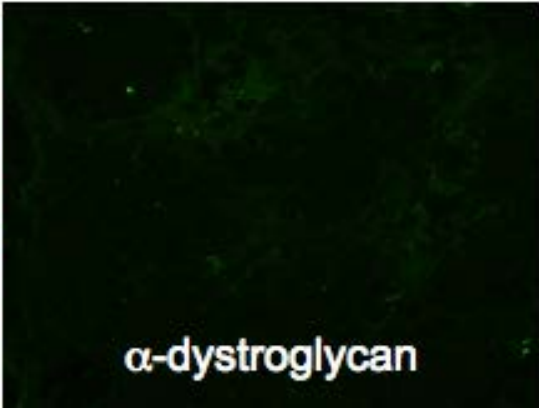
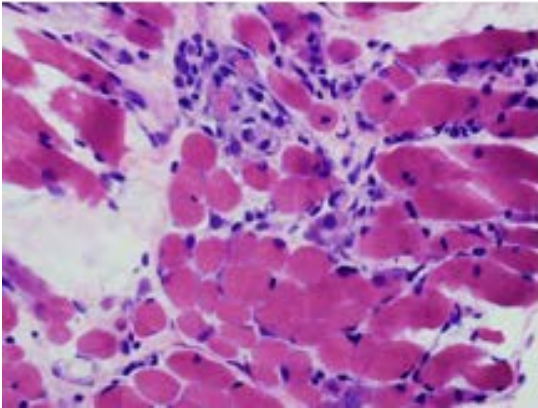
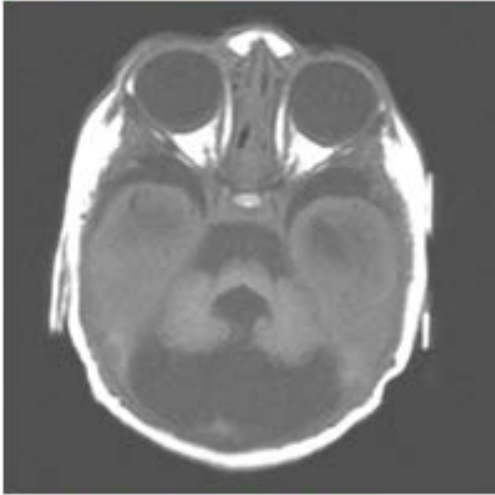
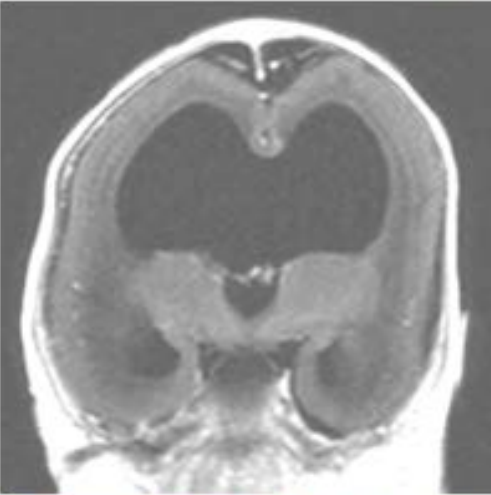


# dystroglycanopathies with brain and eye involvement

- Walker-Warburg syndrome - WWS
- muscle-eye-brain disease – MEB
- Fukuyama congenital muscular dystrophy – FCMD
- congenital muscular dystrophy (CMD) or limb-girdle muscular dystrophy (LGMD) with cognitive impairment



# WWS with *POMT1* mutations

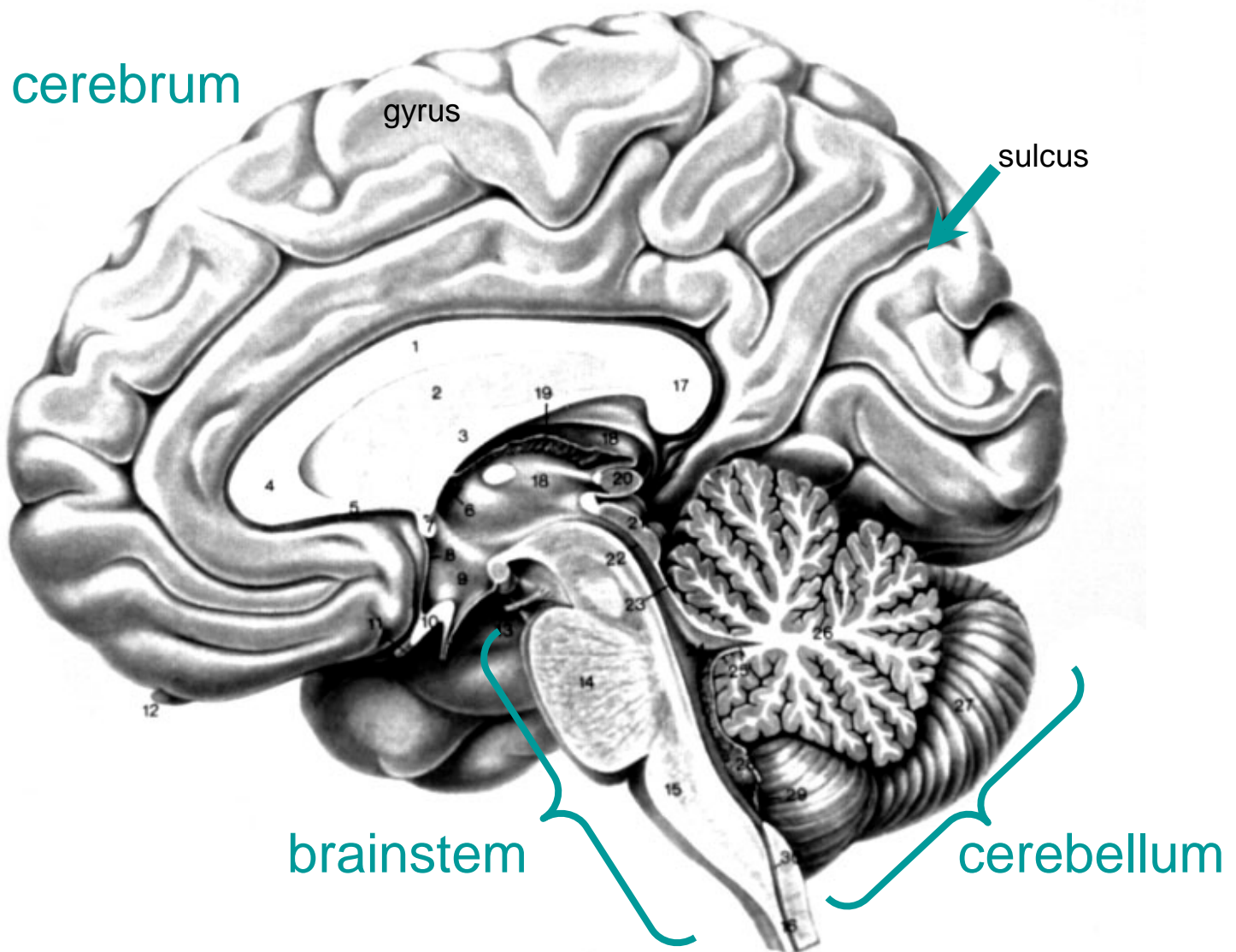




neuroanatomy

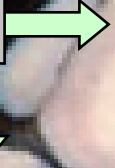


# brain





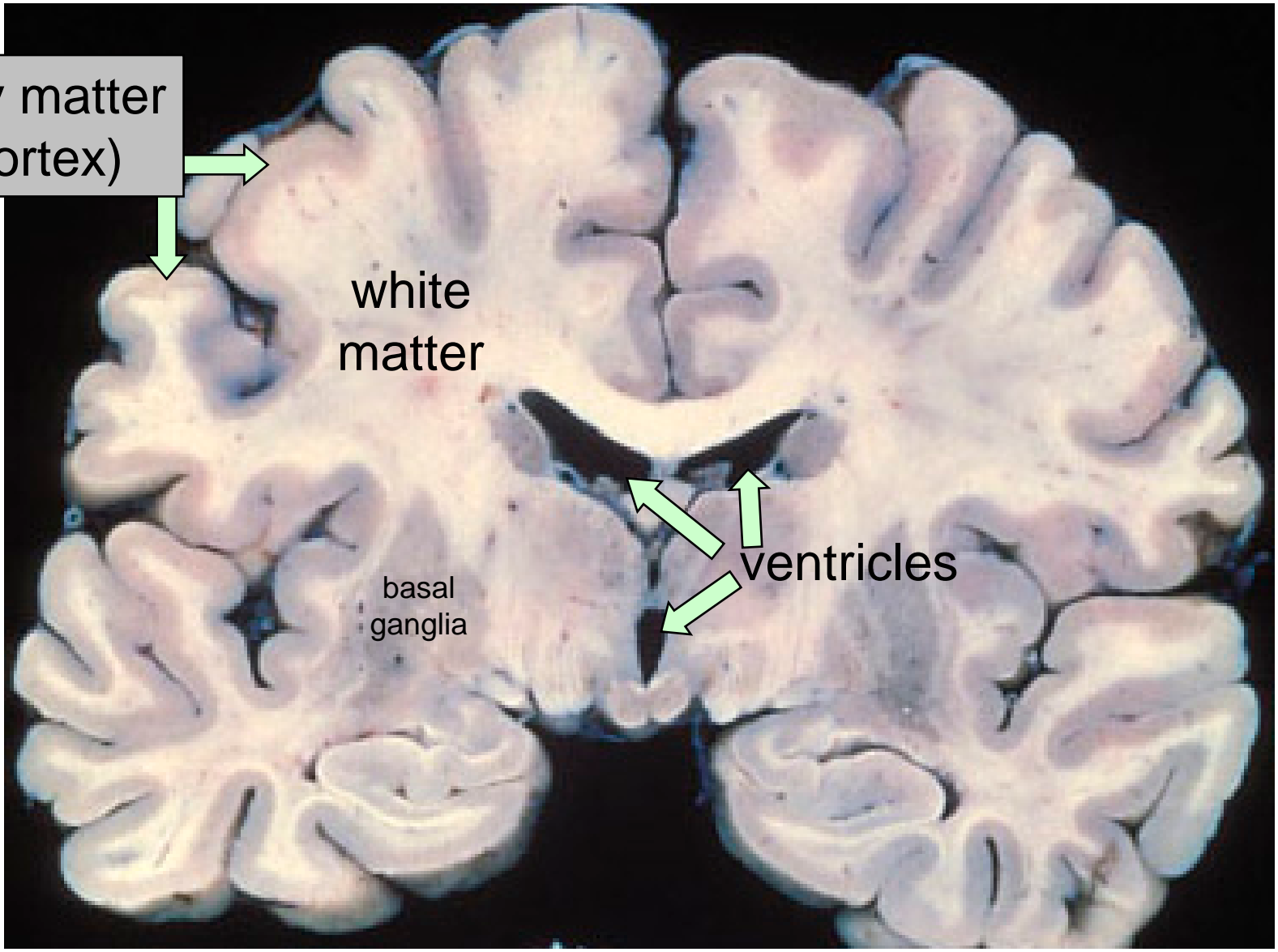
grey matter  
(cortex)



white  
matter

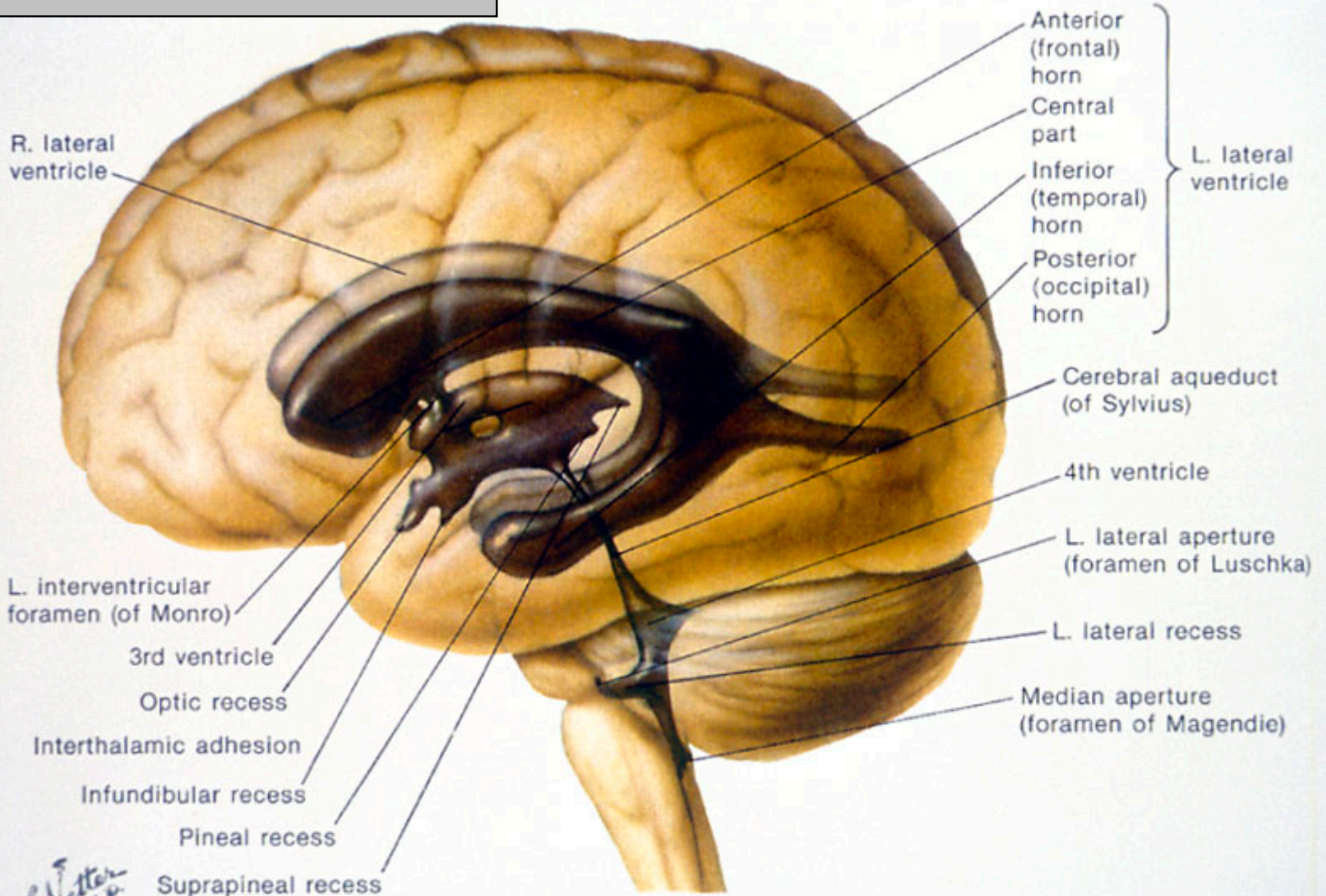
basal  
ganglia

ventricles

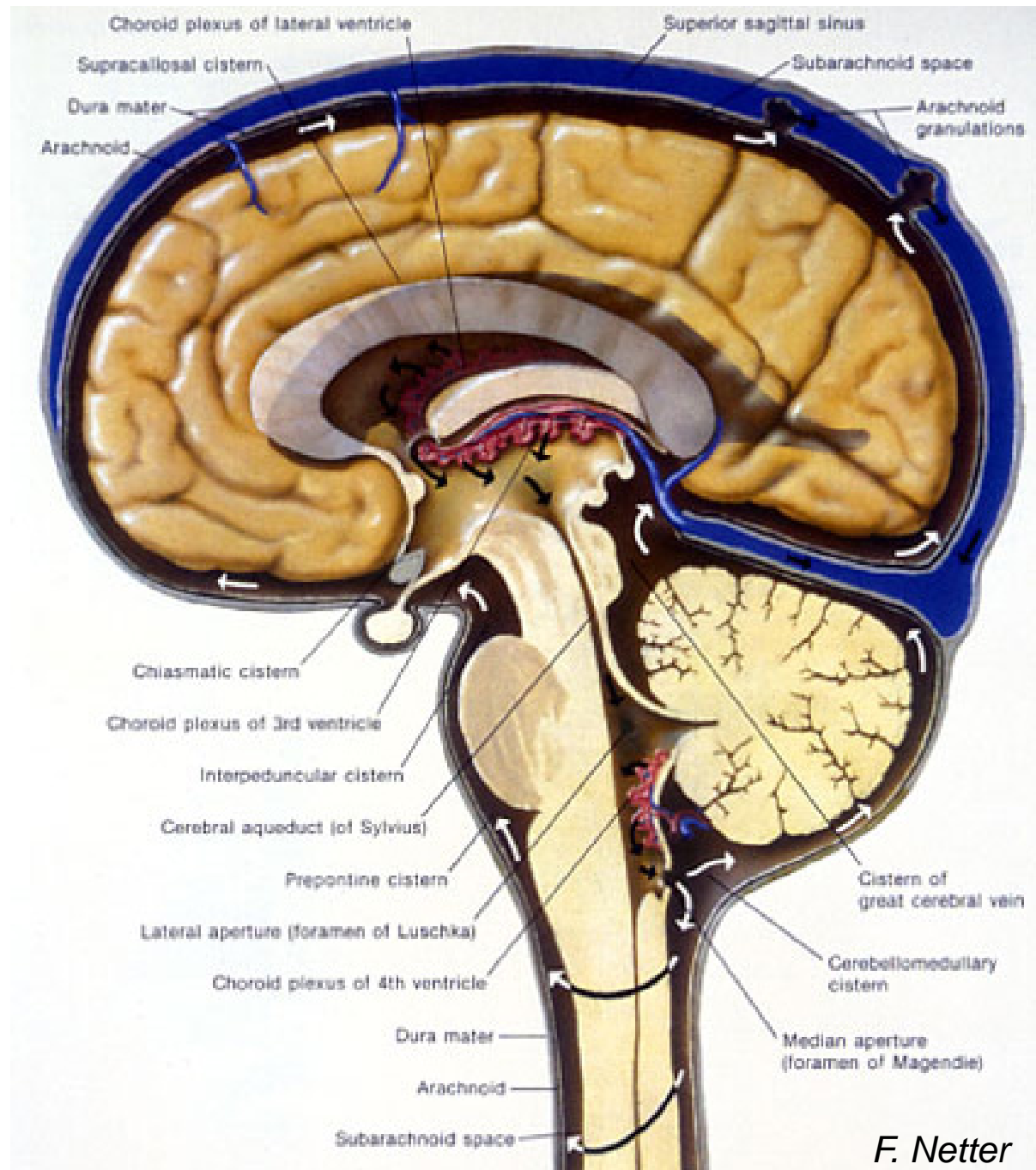




# brain ventricles

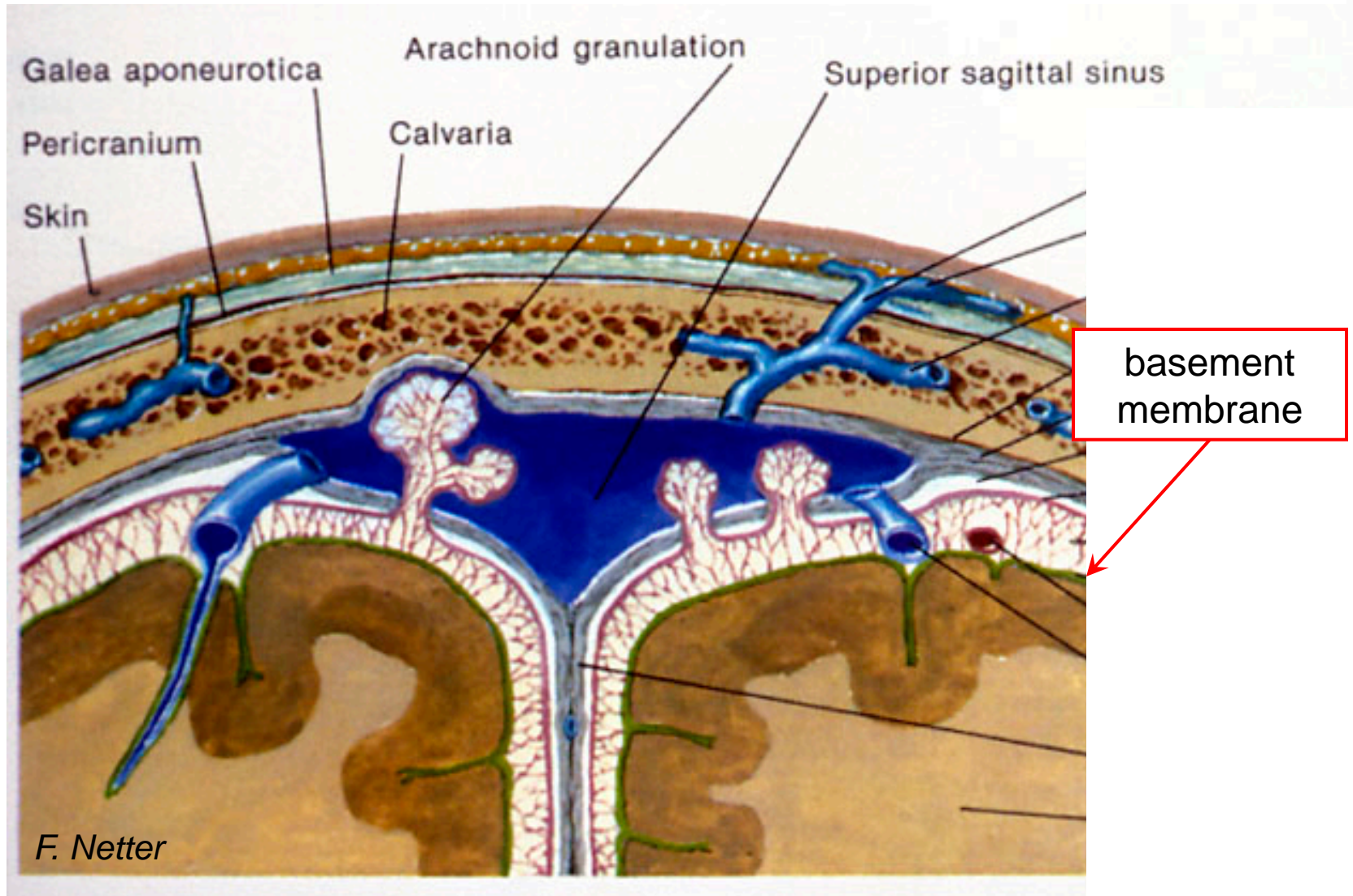


# CSF circulation





# CSF reabsorption

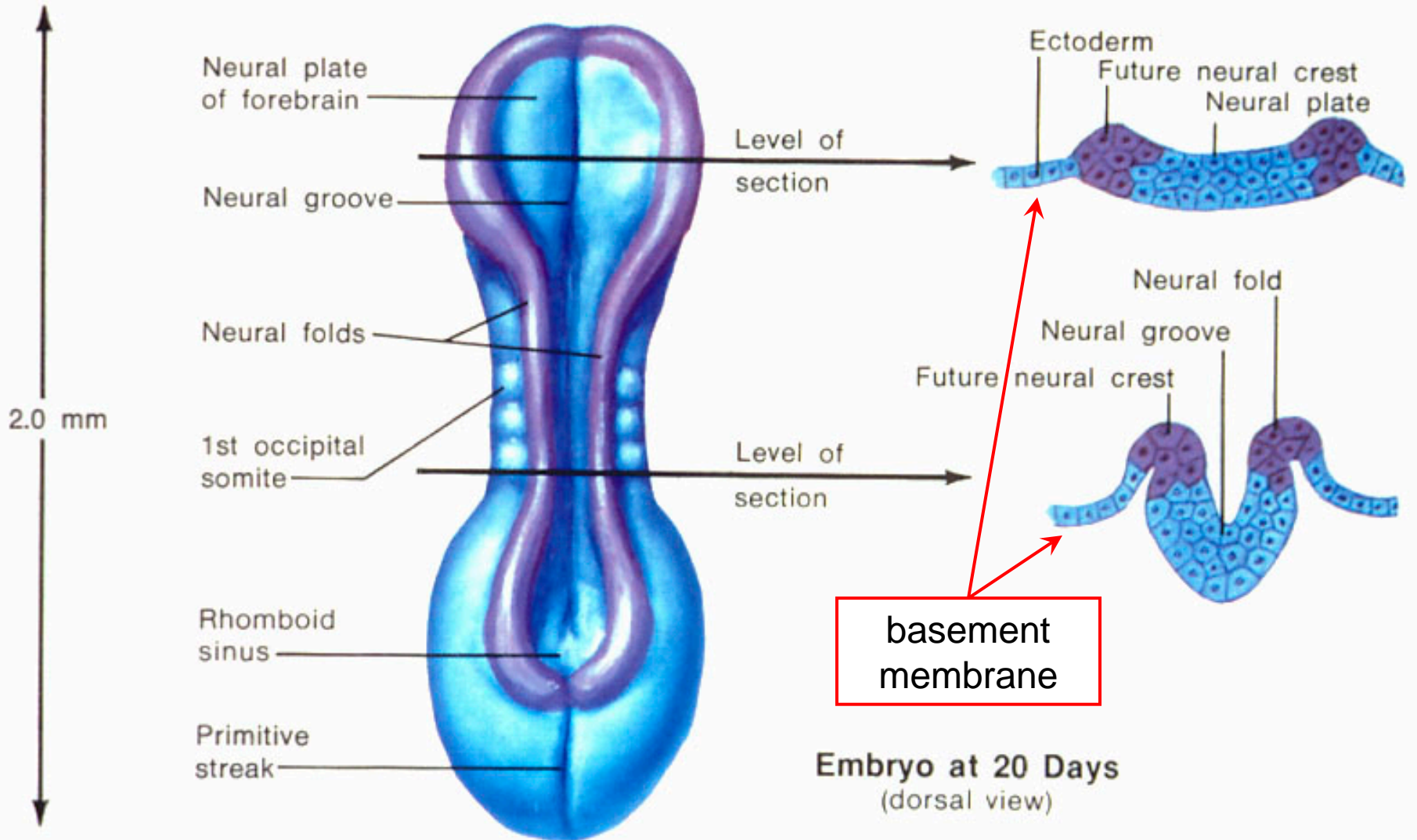


# developmental neurobiology

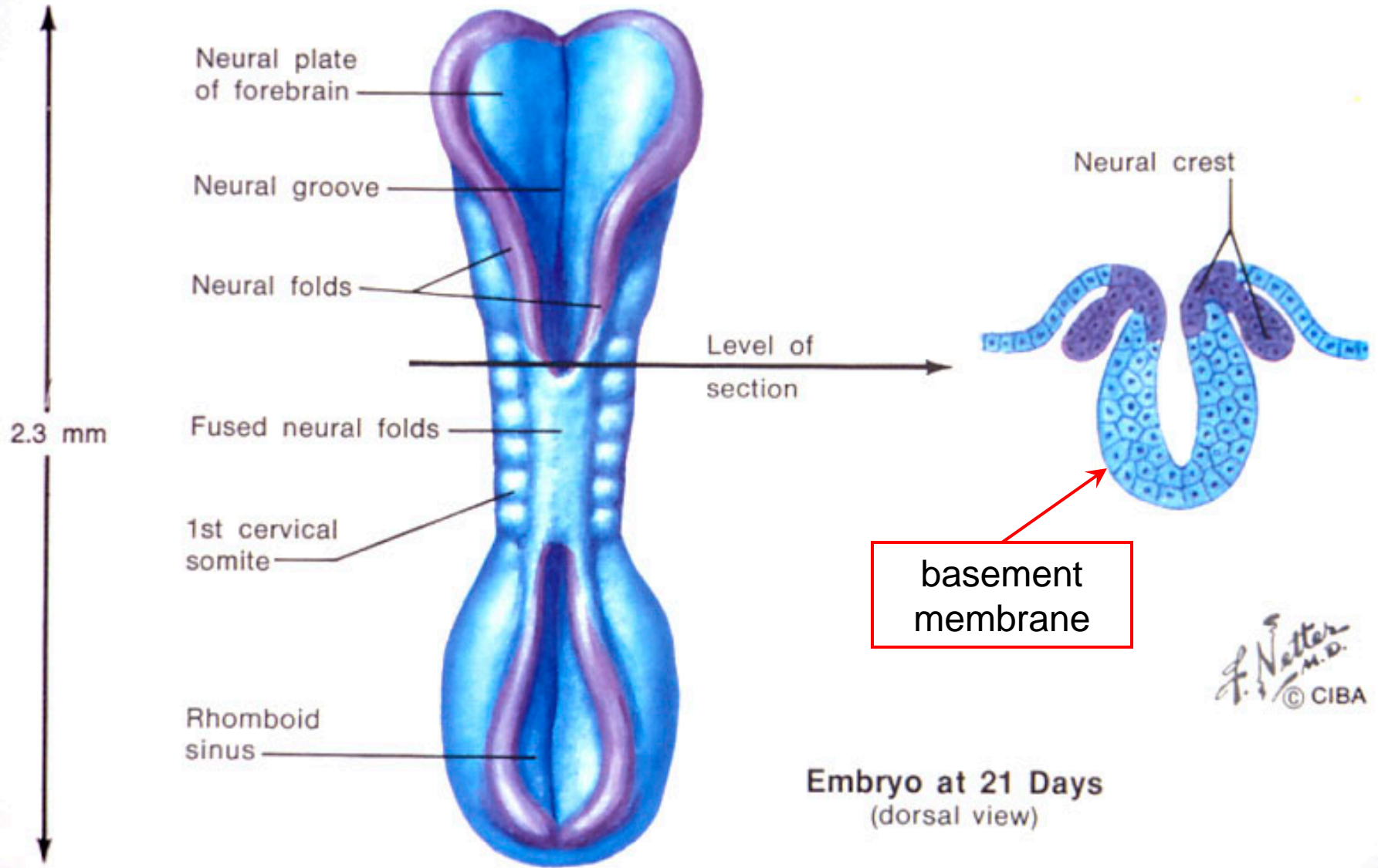
- normal brain development in five slides -



# normal neural tube closure

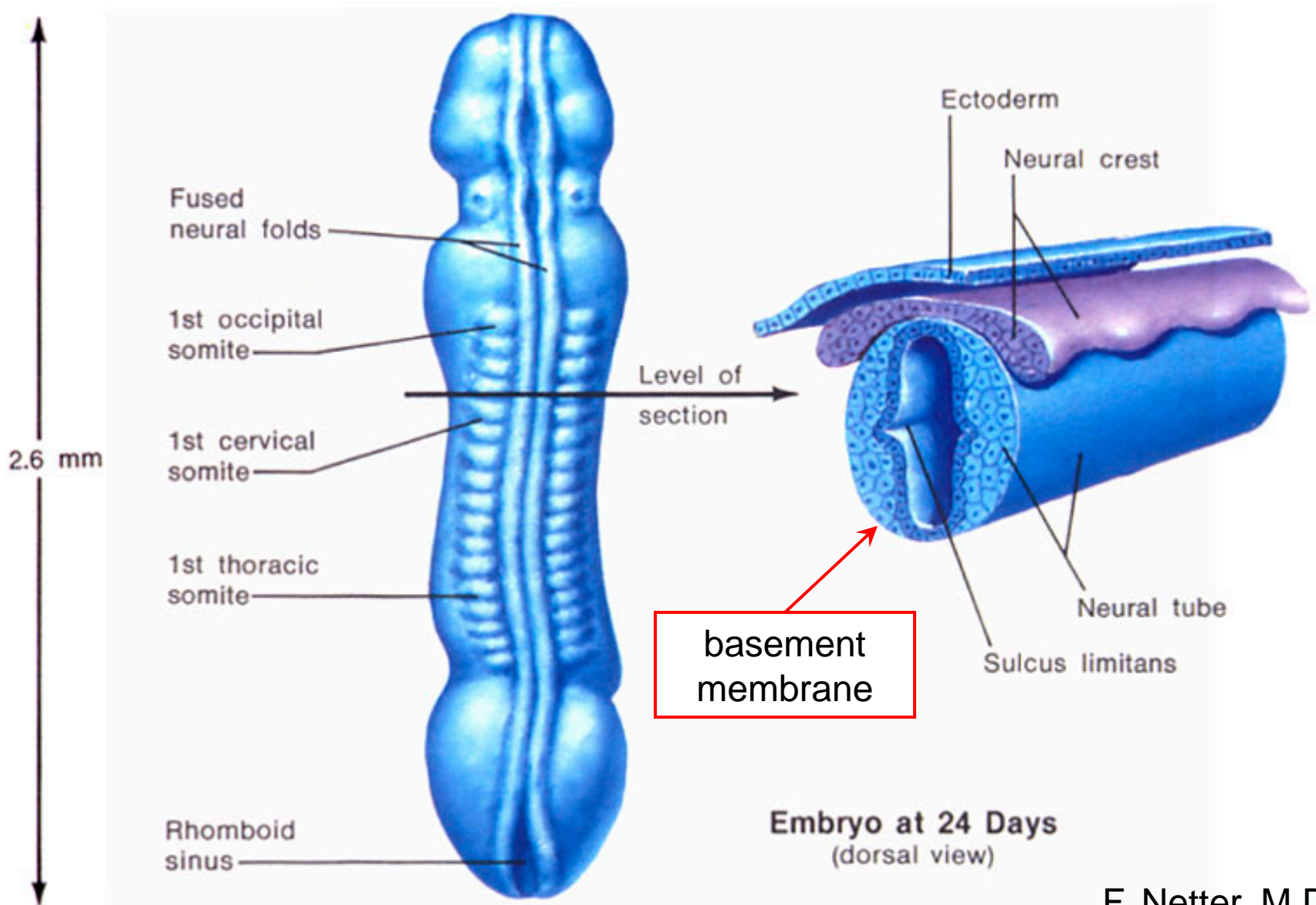


# normal neural tube closure

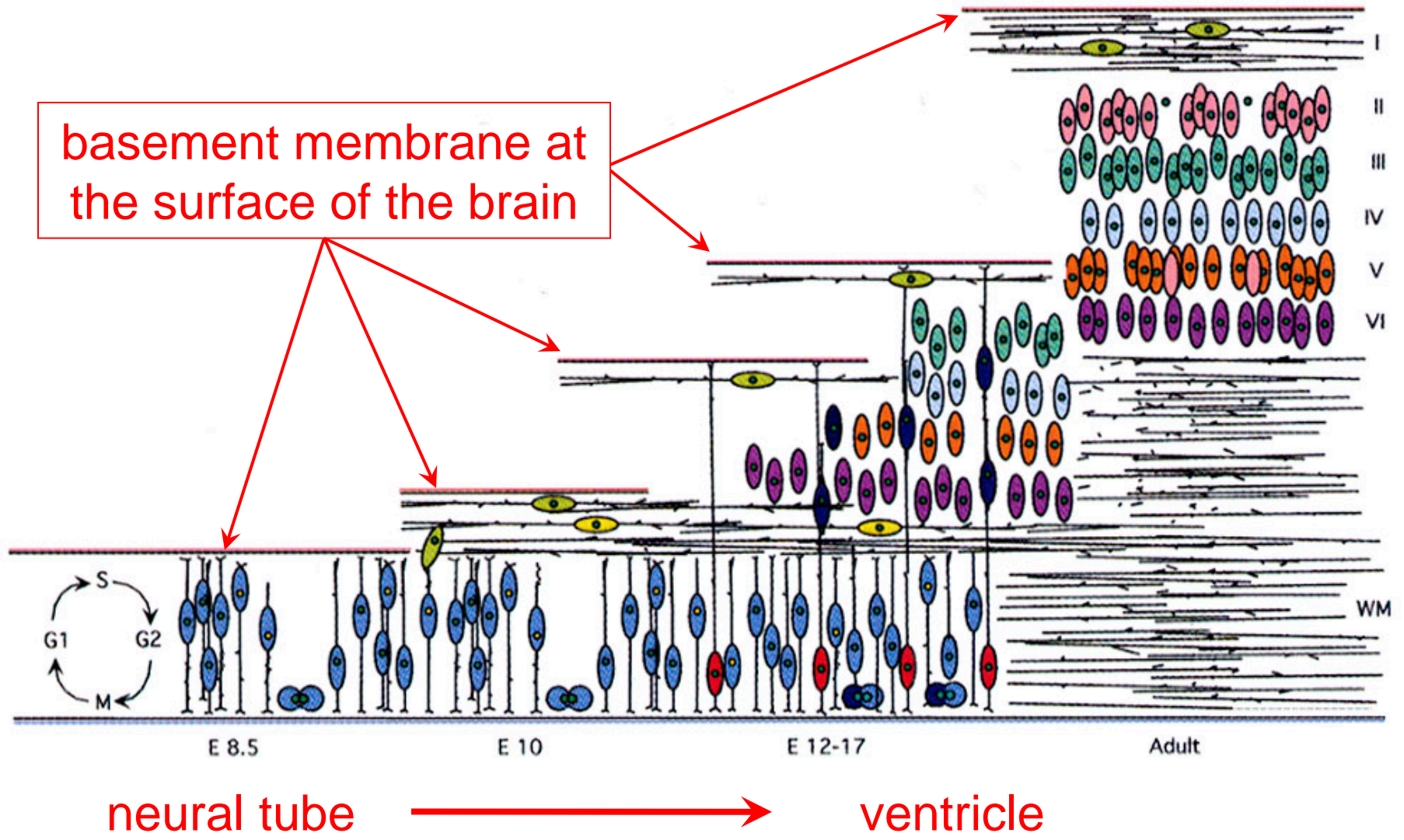




# normal neural tube closure



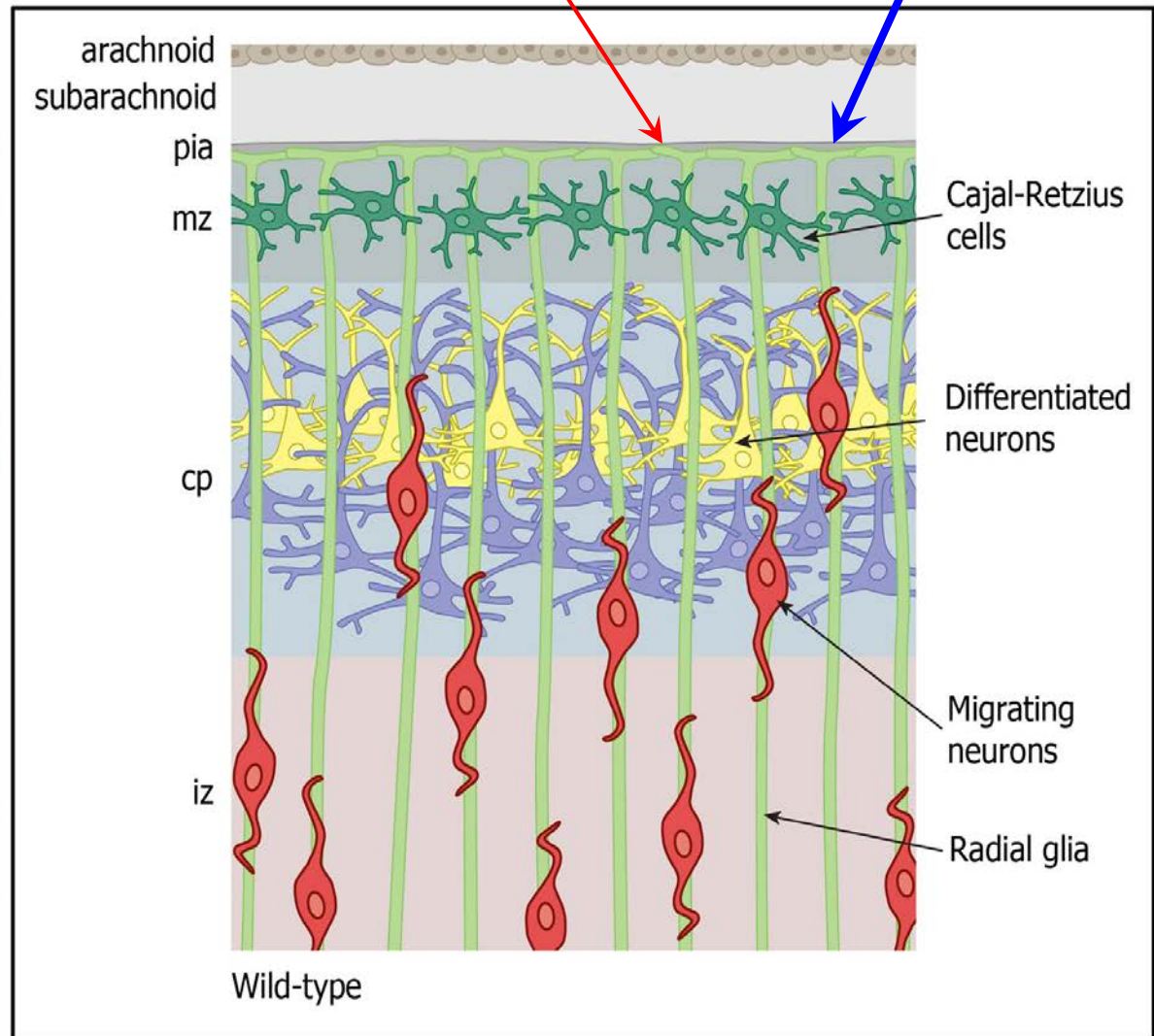
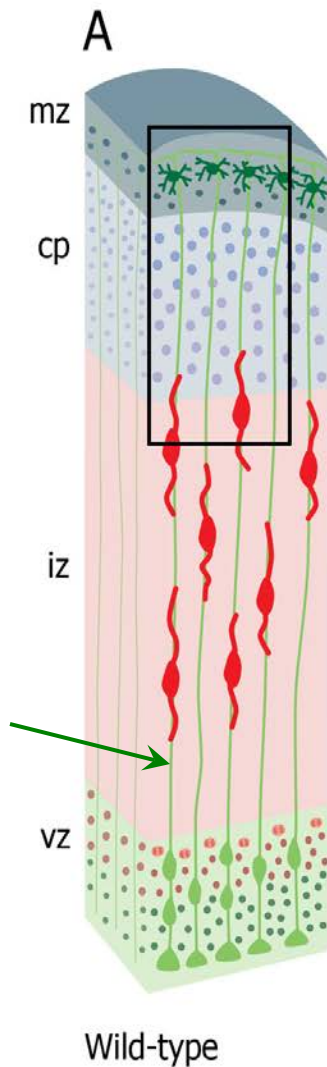
# normal cerebral cortex development





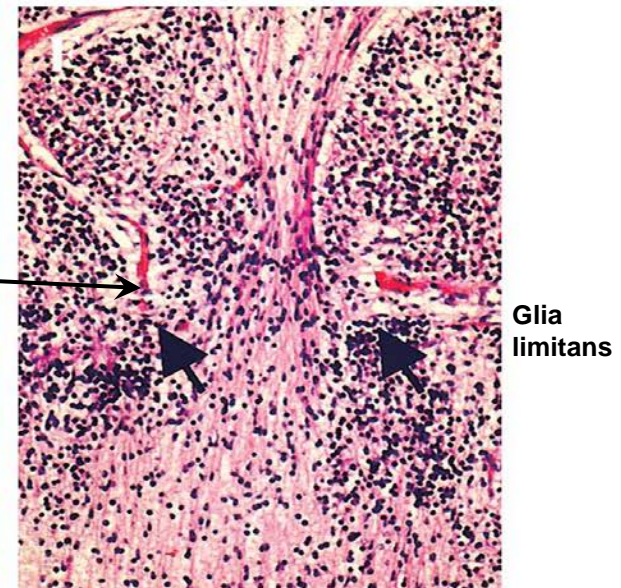
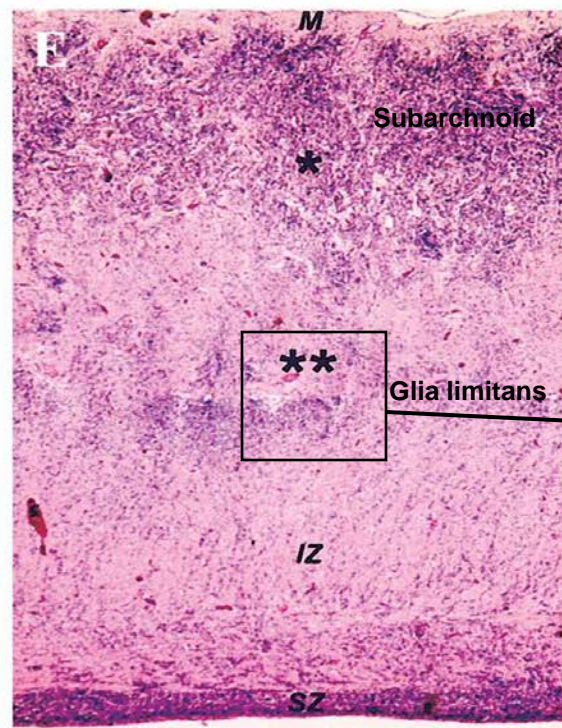
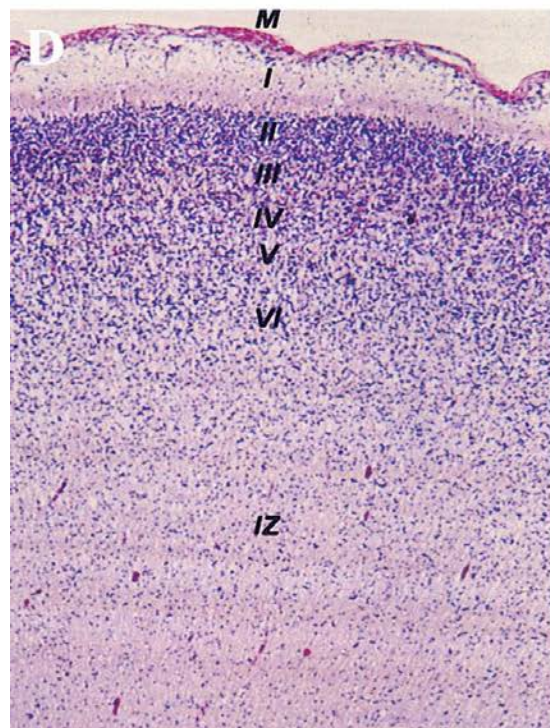
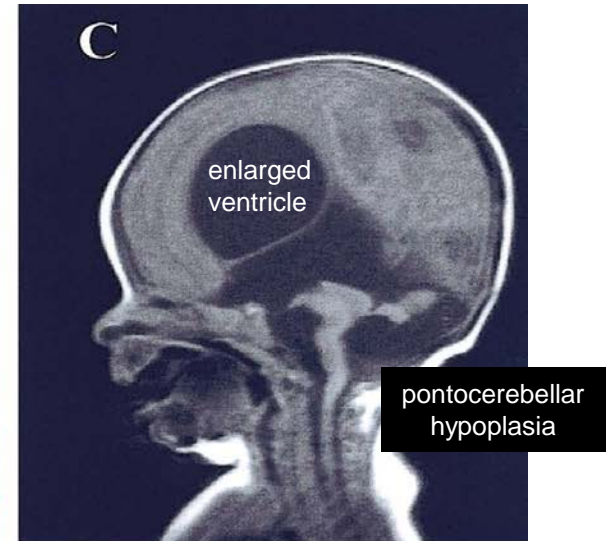
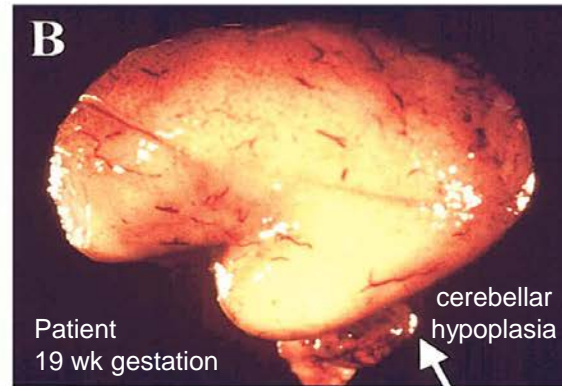
# normal development

radial  
glia





# Brain malformations in WWS patients with *POMT1* mutations

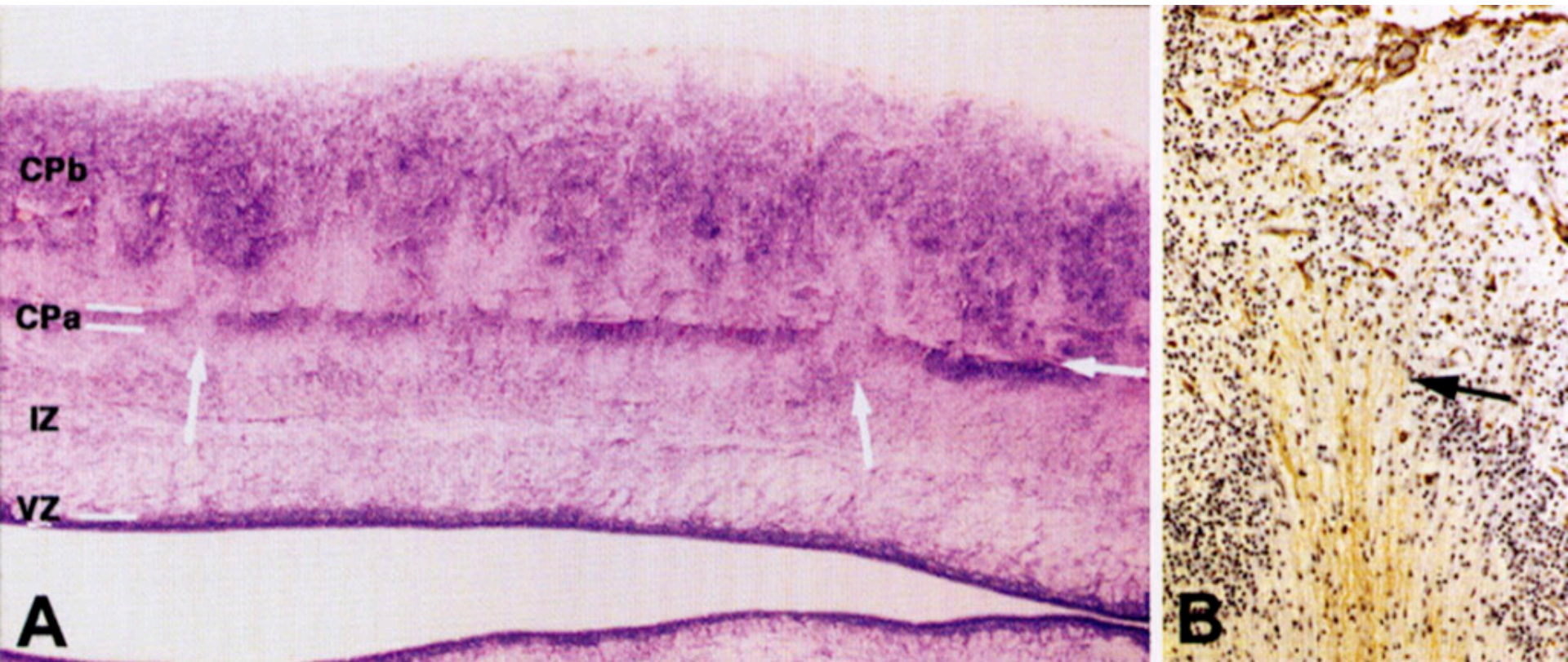


Normal

Patient

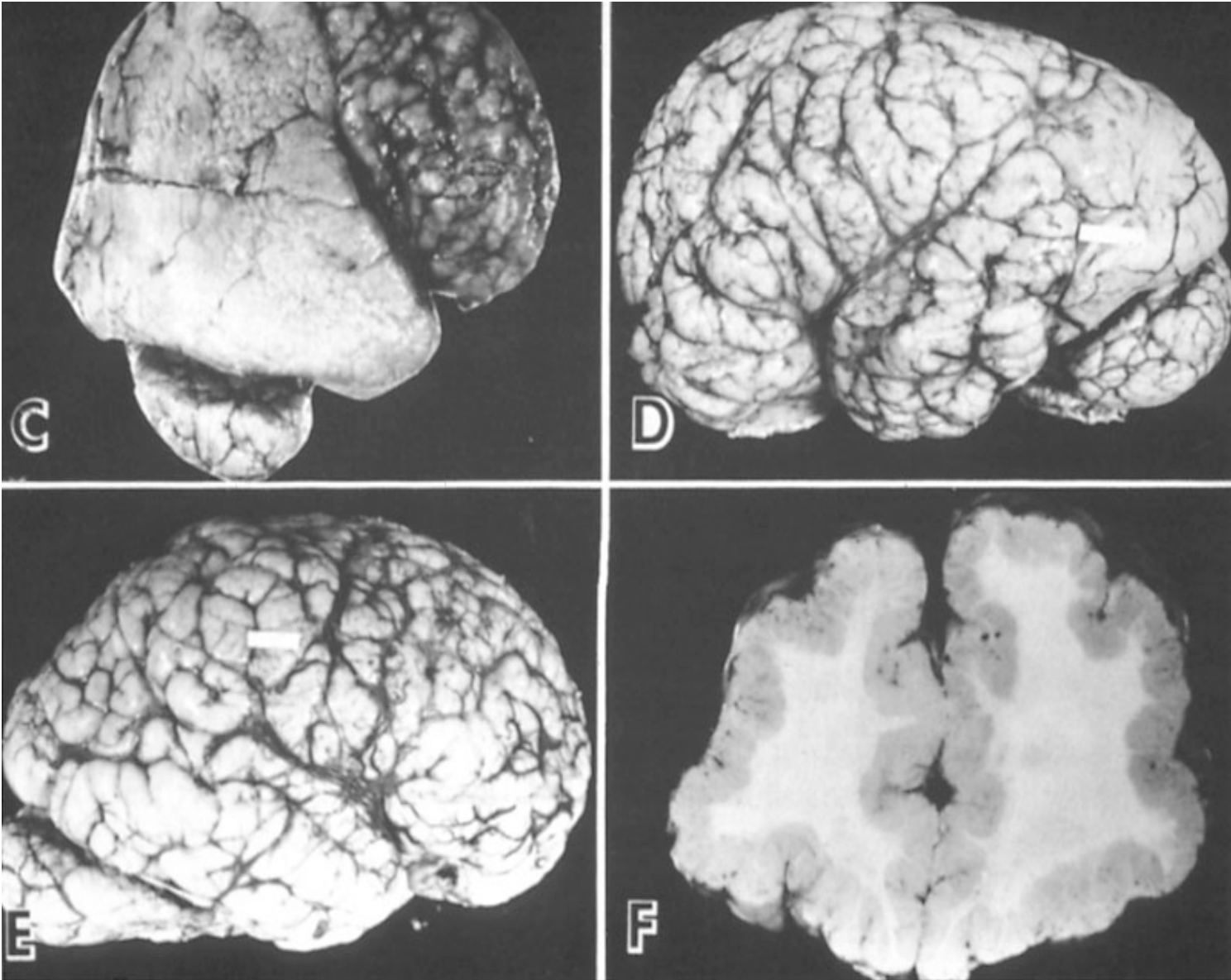


# abnormal cerebral development



Walker-Warburg syndrome cerebrum - 21 week fetus

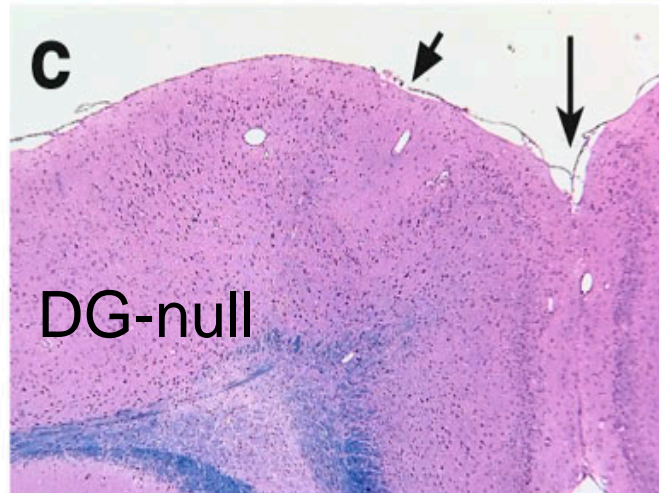
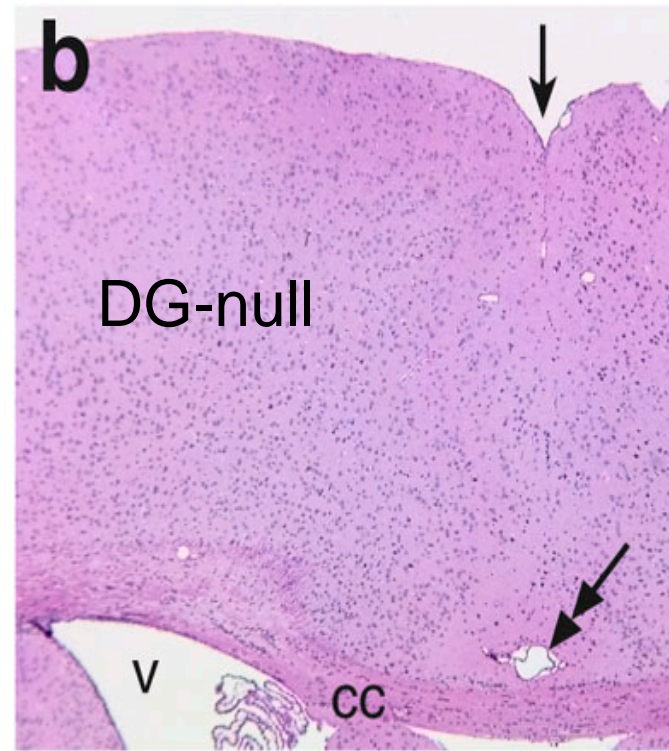
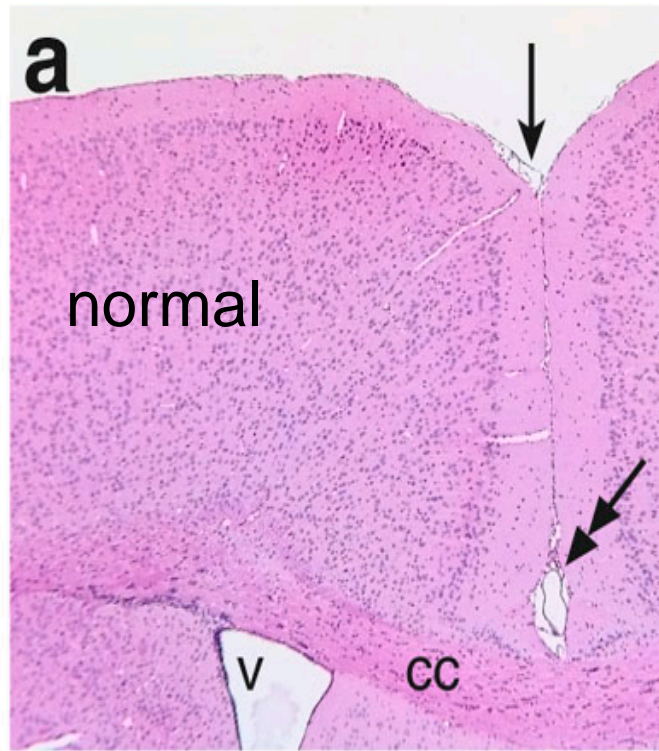
# Fukuyama CMD - cobblestone lissencephaly





abnormal cerebral development in mice without dystroglycan (DG-null)

- midline fusion
- cortical heterotopia

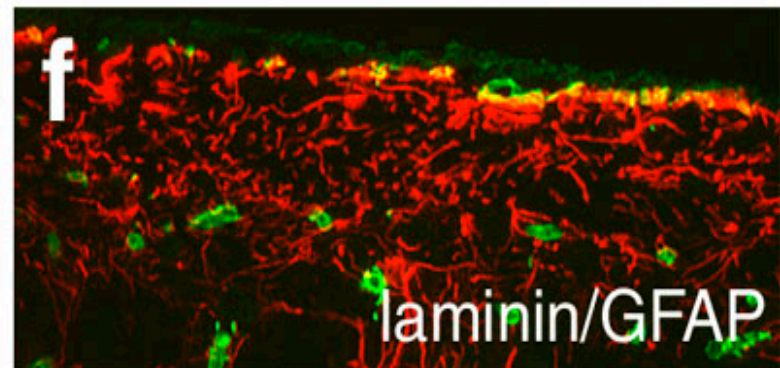
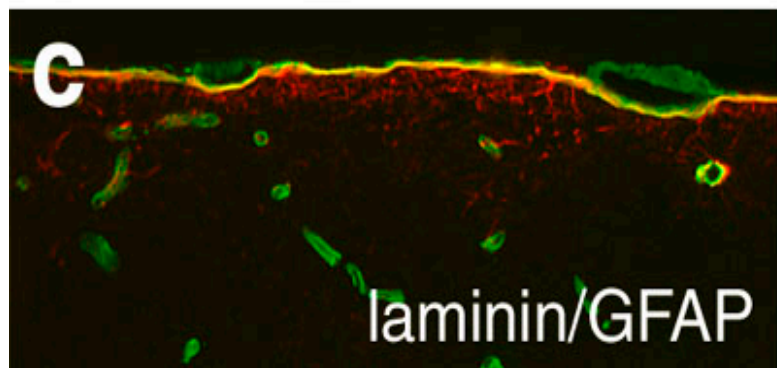
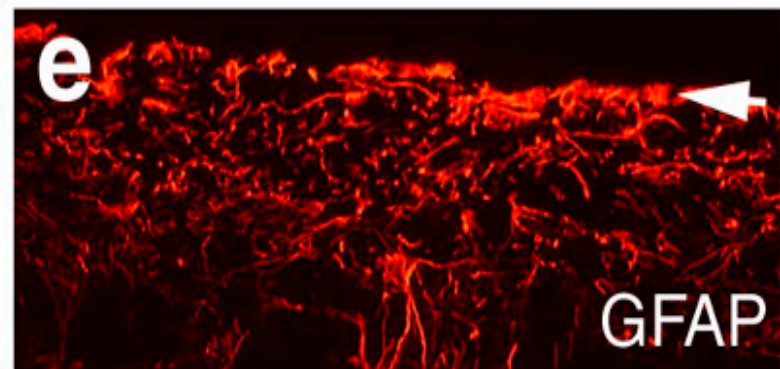
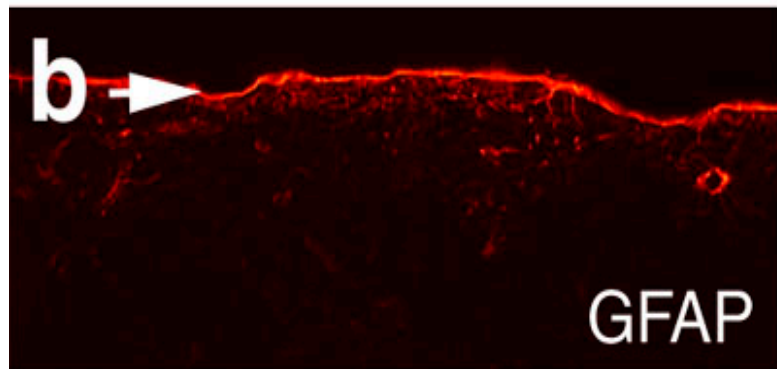
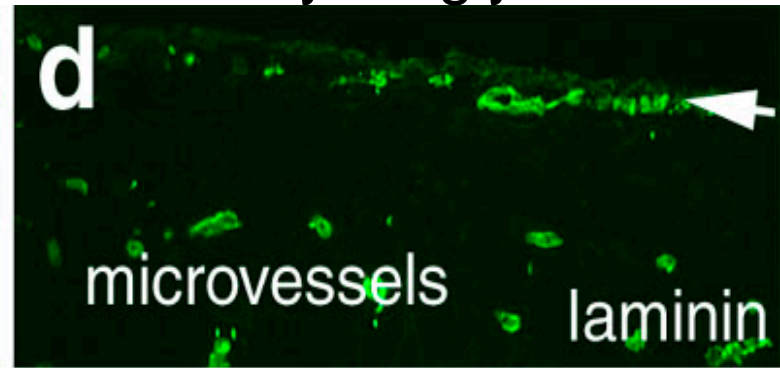
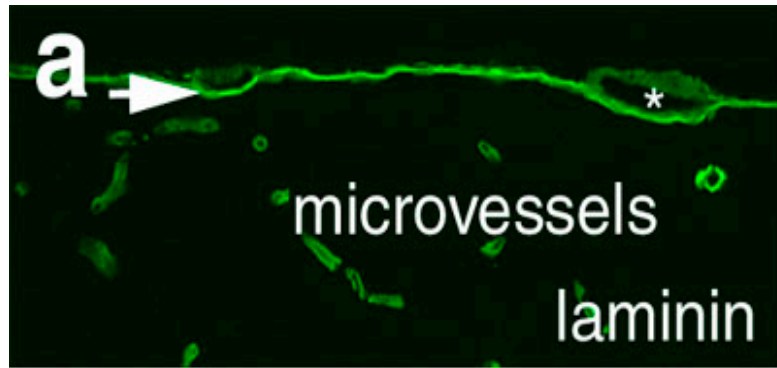




# basement membrane disruptions

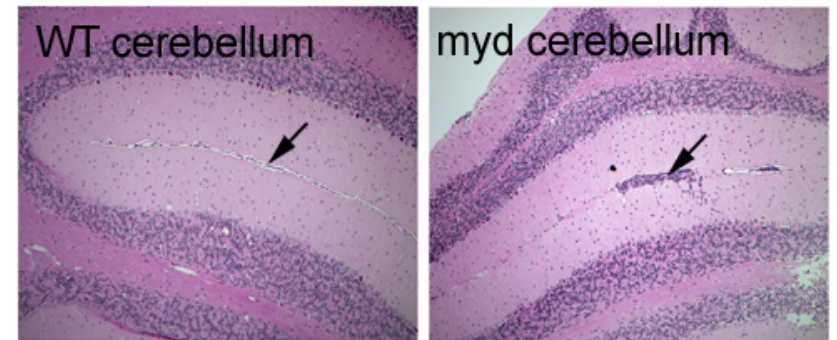
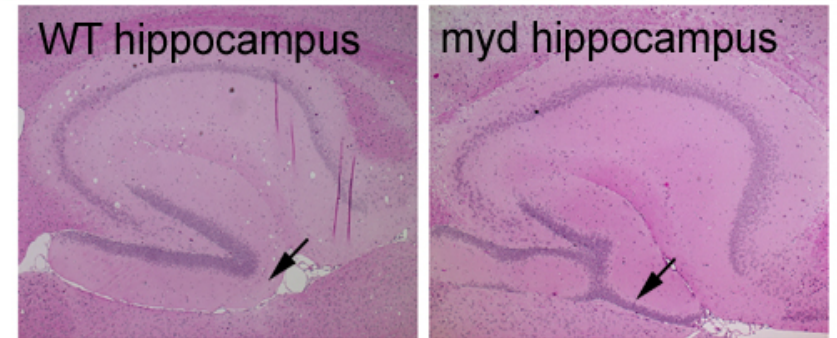
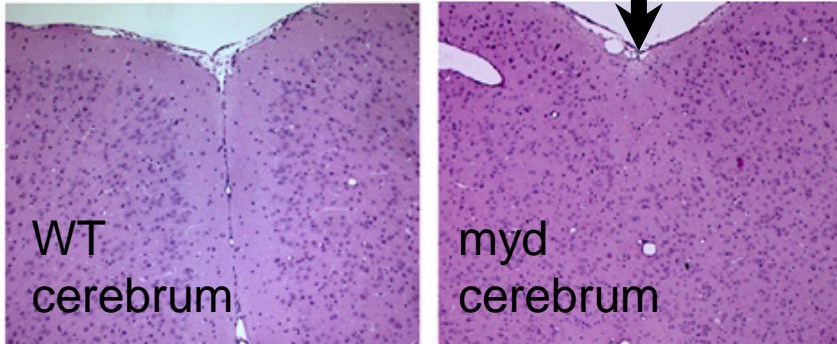
normal

no dystroglycan

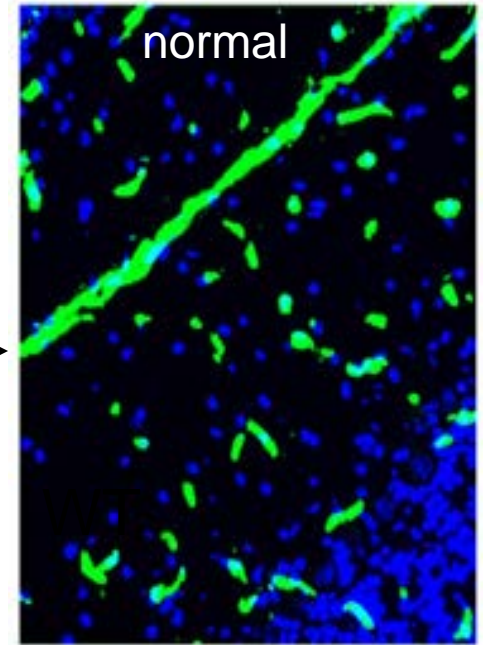


# Large<sup>myd</sup> mice

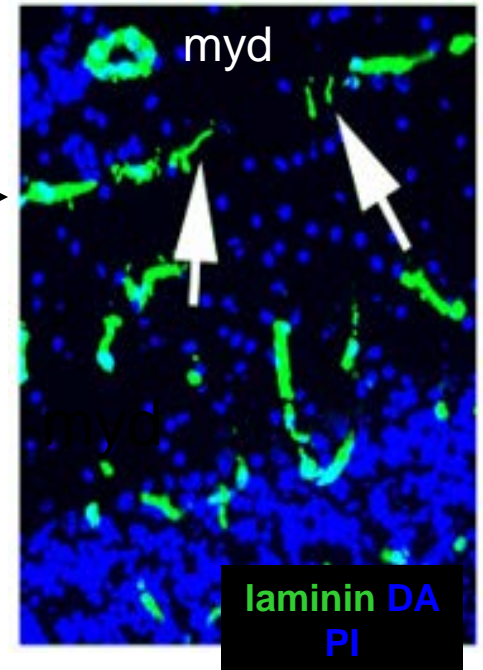
midline fusion



basement membrane



disrupted basement membrane

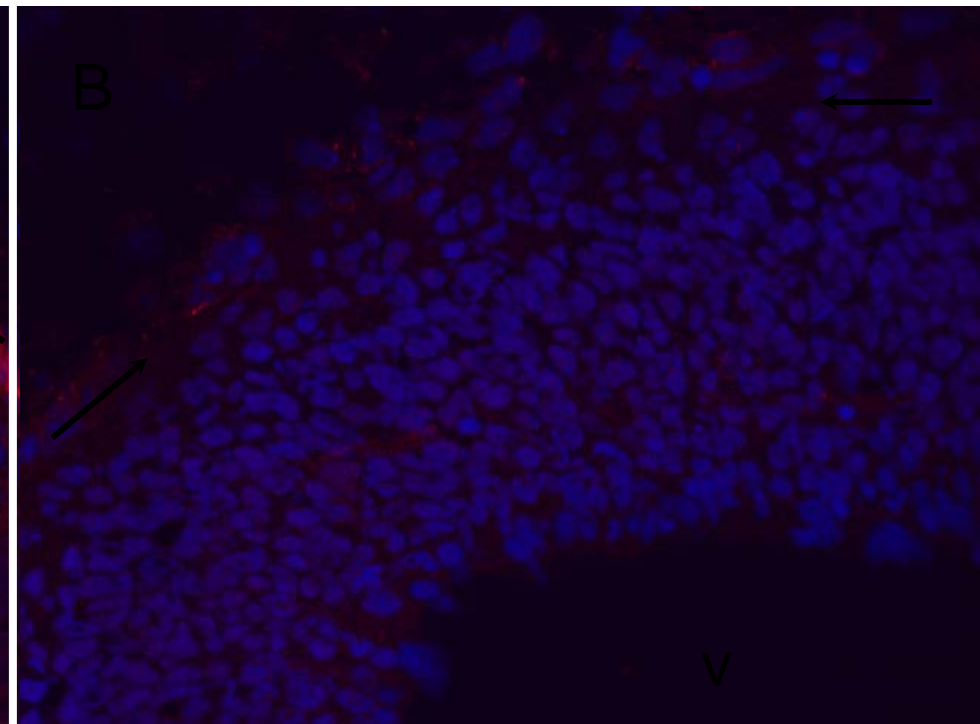
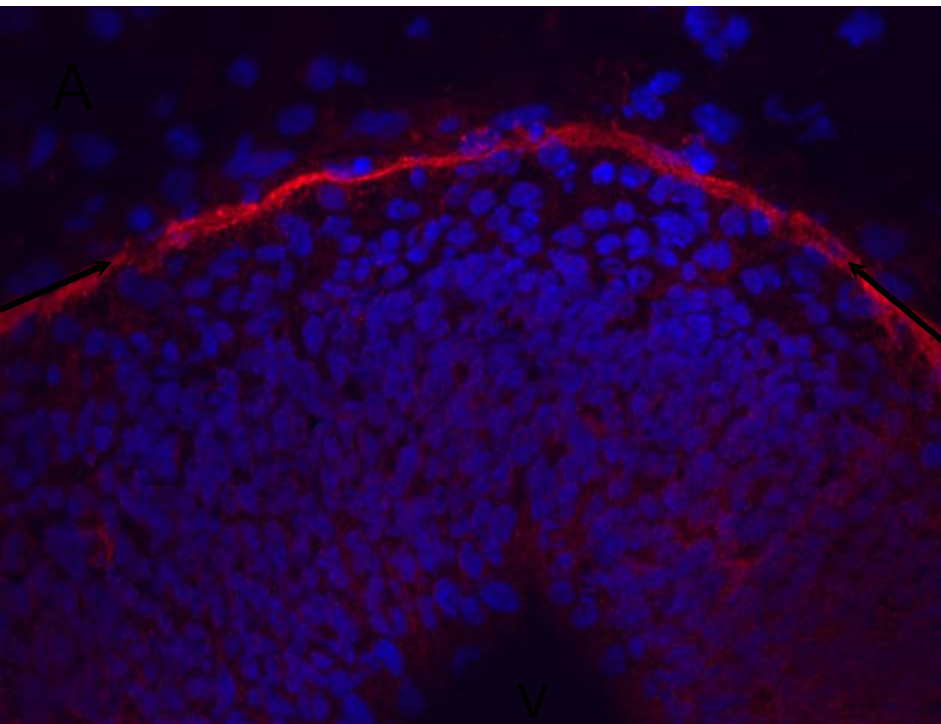




# dystroglycan immunofluorescence in DG-null brain

wt E13.5 cerebrum

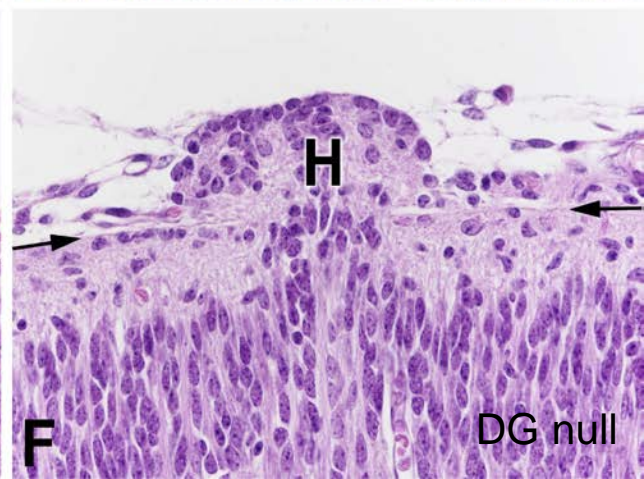
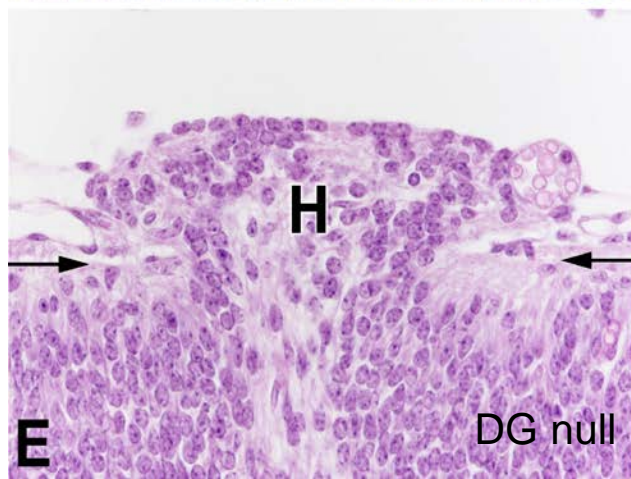
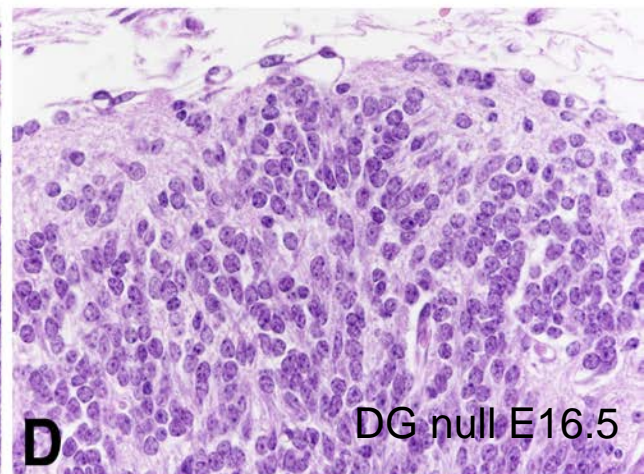
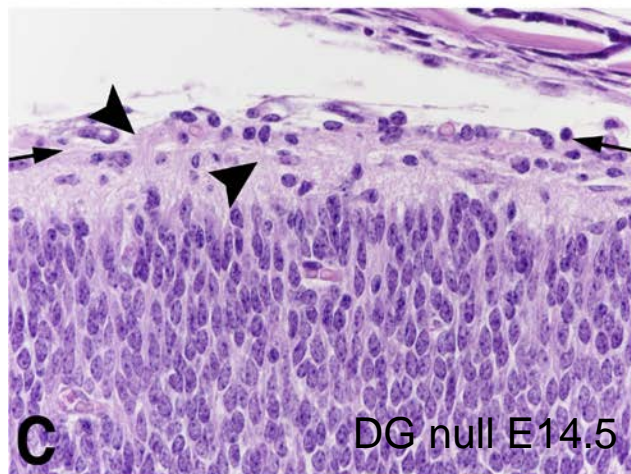
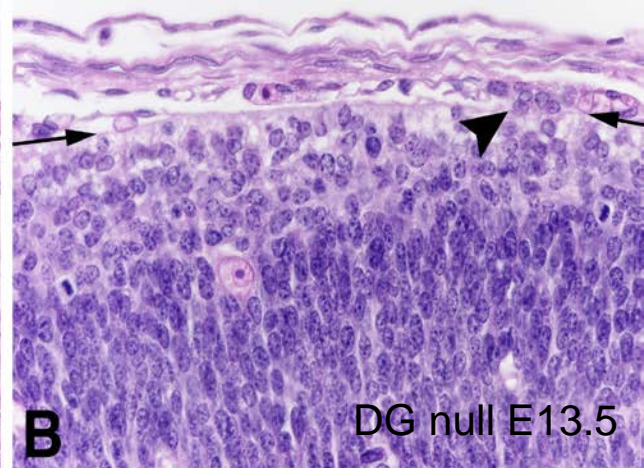
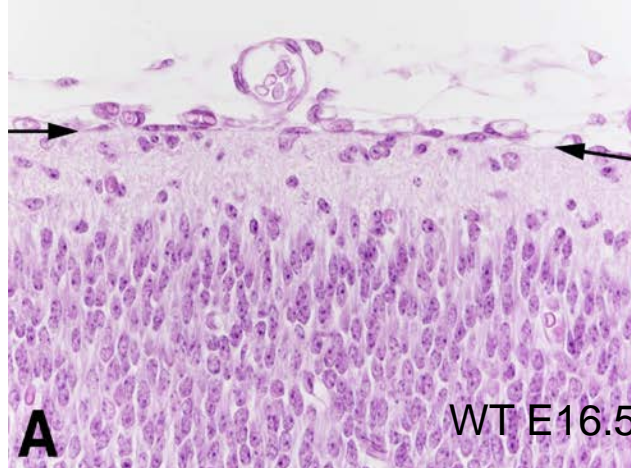
DG-null E13.5 cerebrum



dystroglycan/DA  
PI



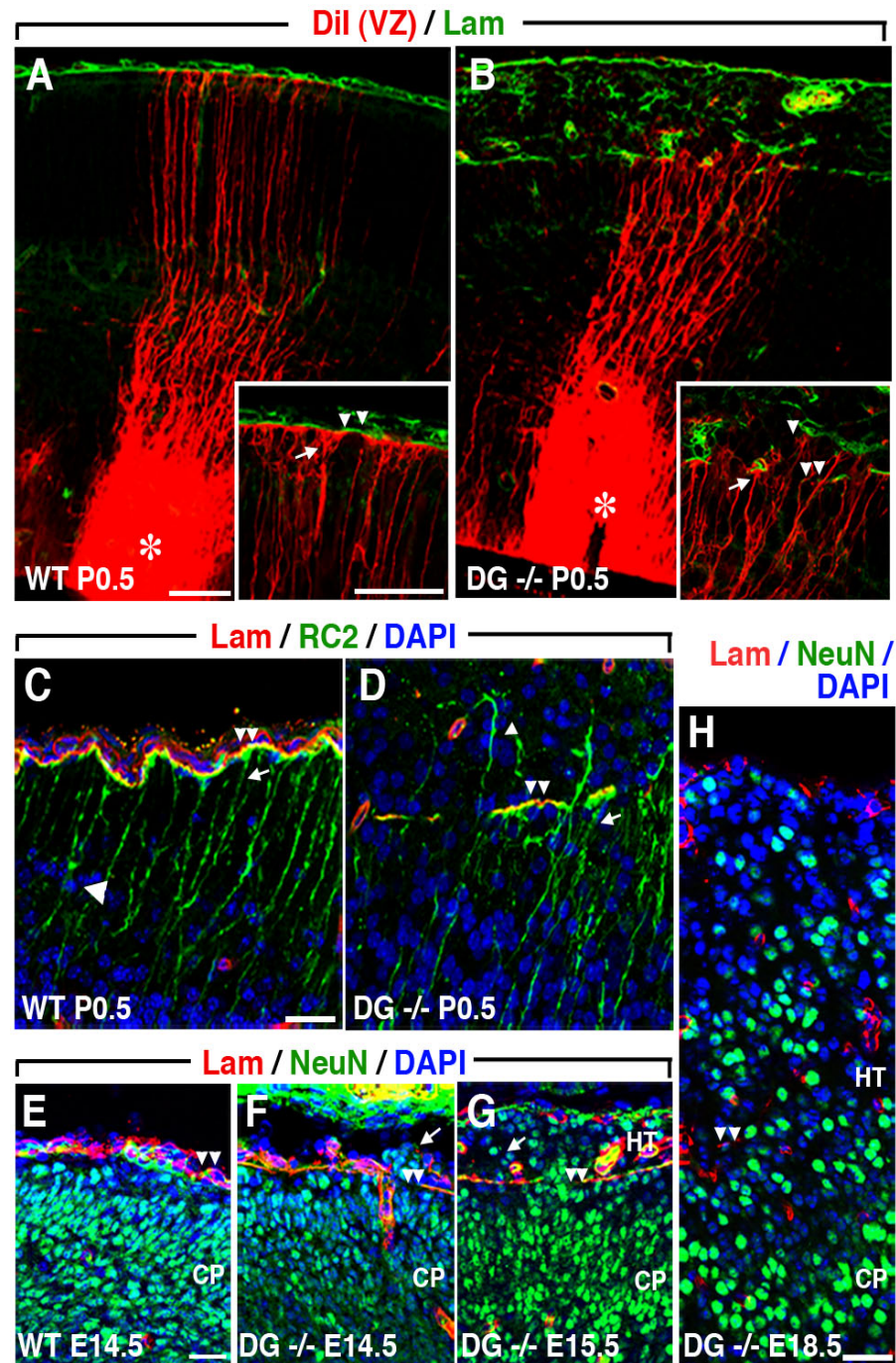
Glial-neuronal  
heterotopia  
begin to form  
at the same  
time  
dystroglycan  
is lost.



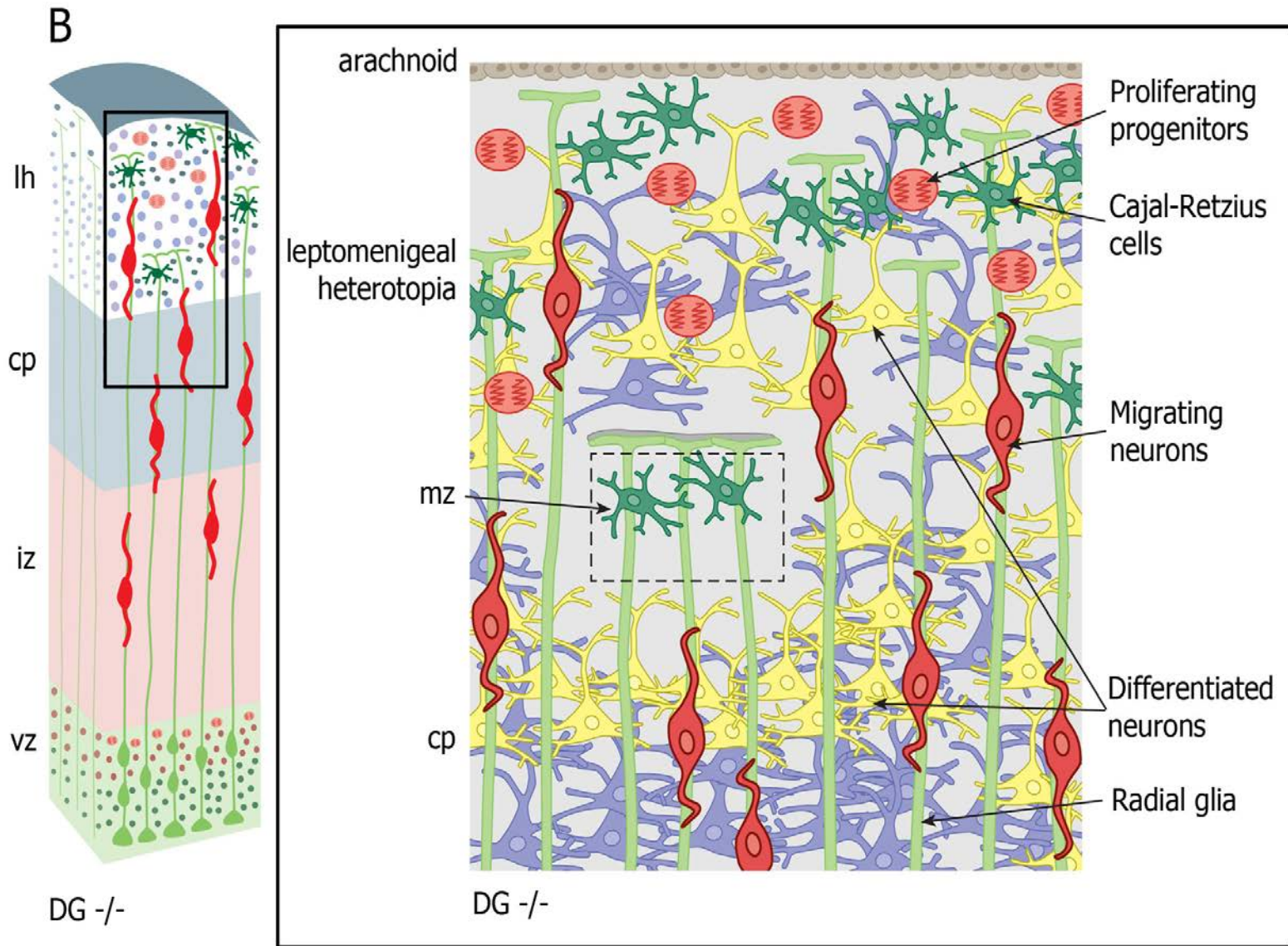
Satz et al., J Neurosci  
30:14560-14572, 2010.



Breaches of the basement membrane, disruptions of the positioning of radial glia endfeet, and migration of differentiating neurons into the leptomeningeal heterotopia

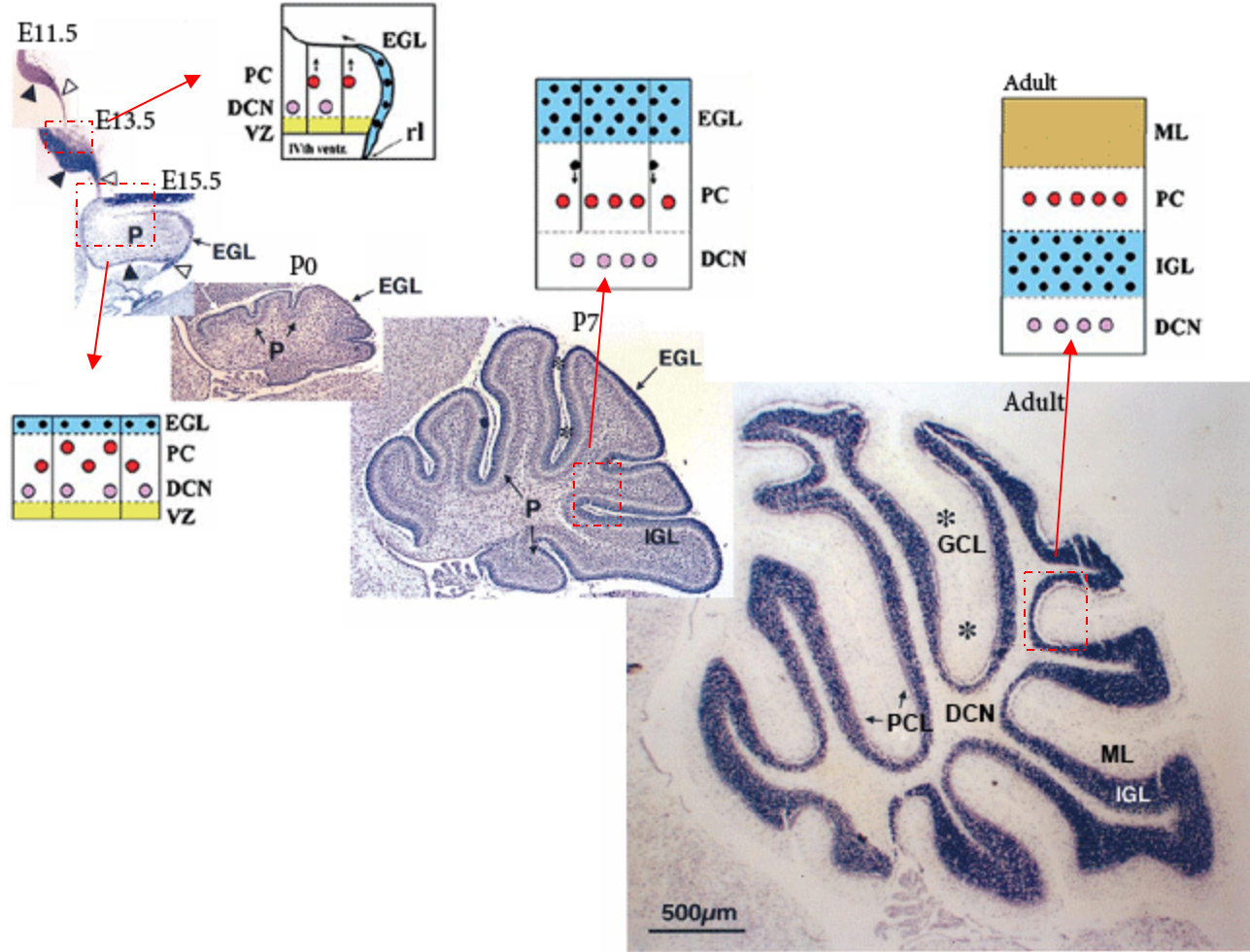


# cobblestone lissencephaly

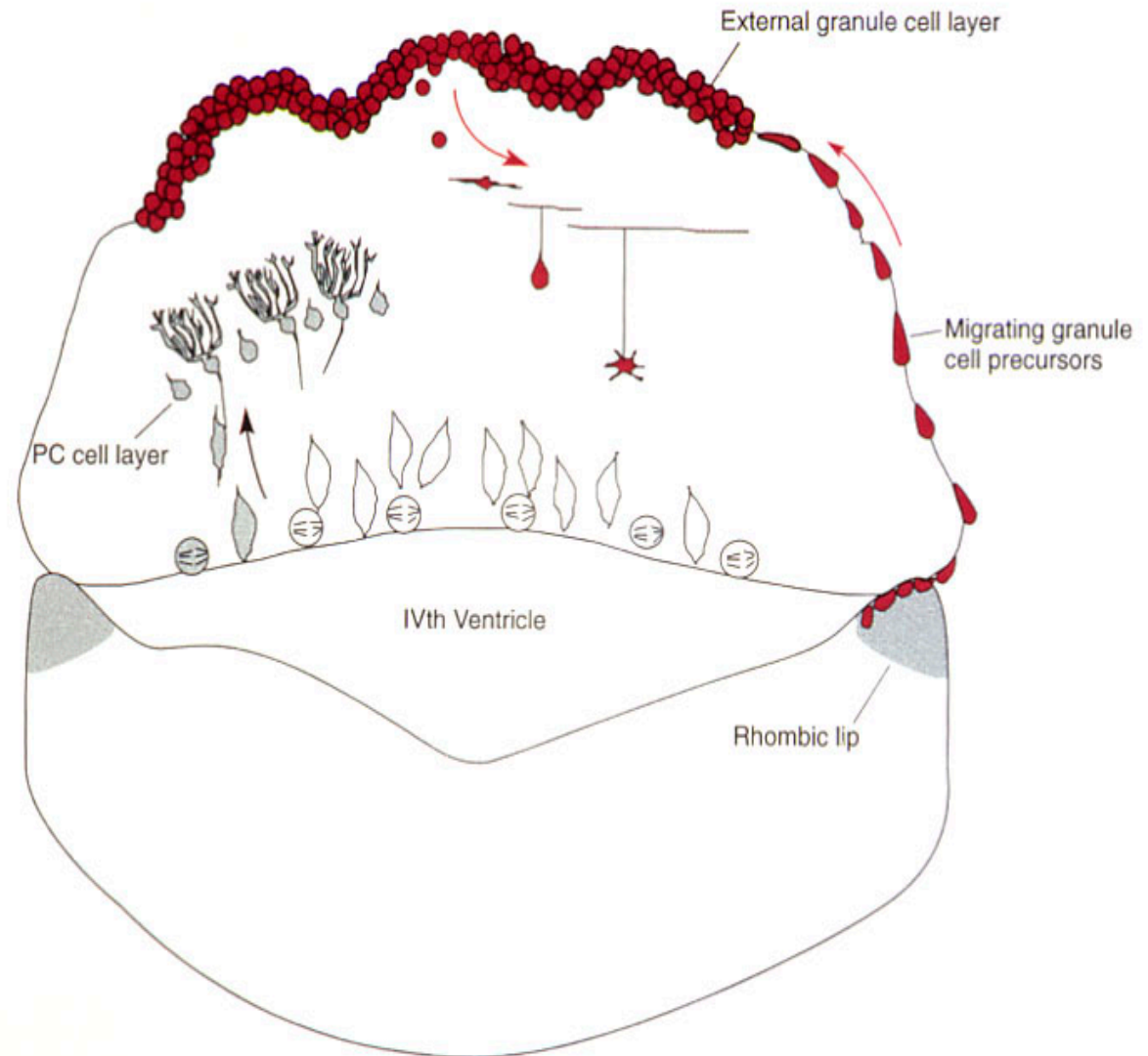




# cerebellar structure and development

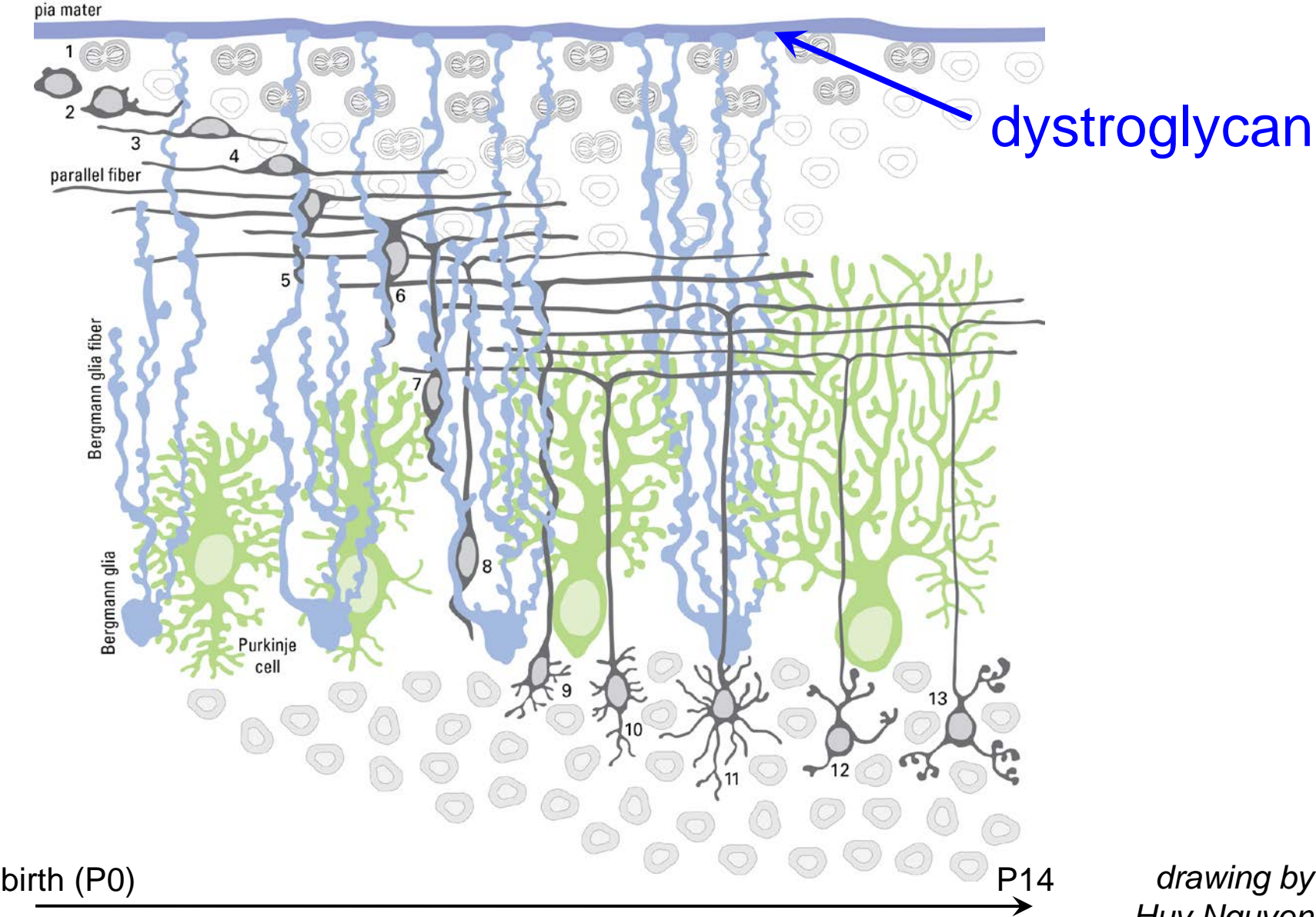


# histogenesis of cerebellar cortex





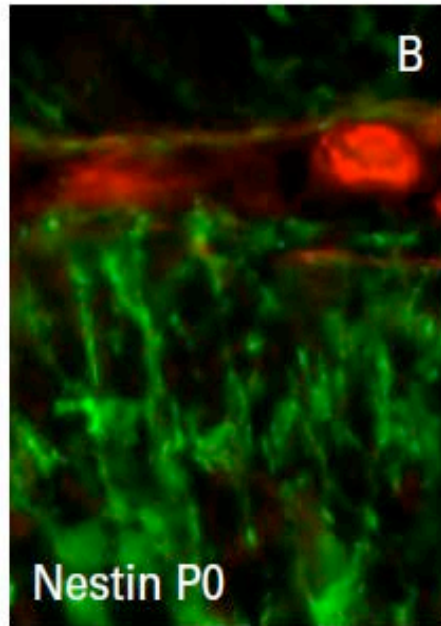
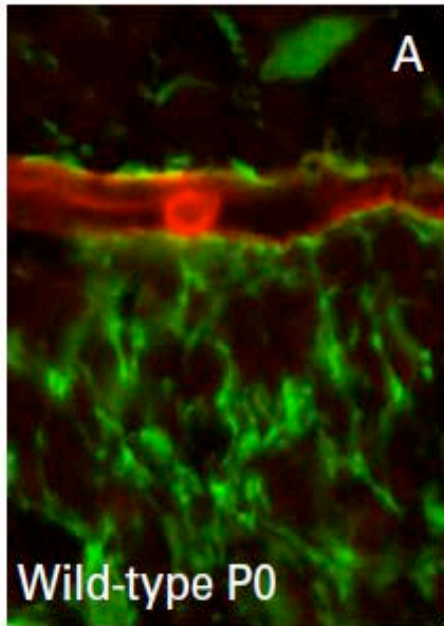
# normal postnatal cerebellar development



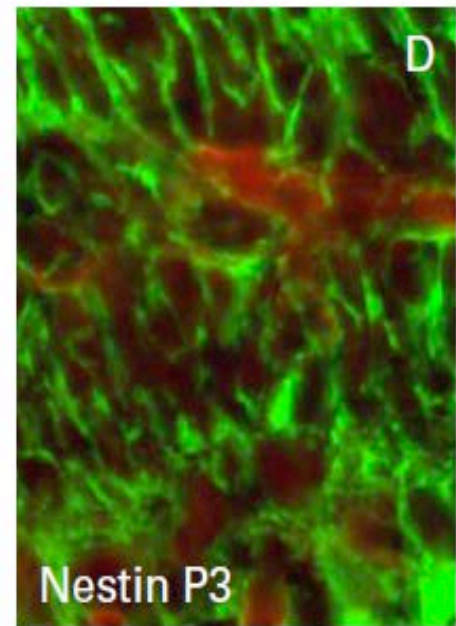
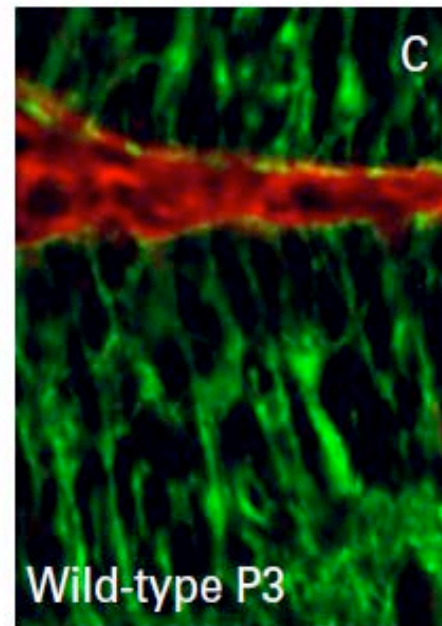
*drawing by  
Huy Nguyen*

# coincident glia limitans disruption and abnormalities of Bergmann glia processes in the absence of dystroglycan

Perl/BLBP



Perl/BLBP

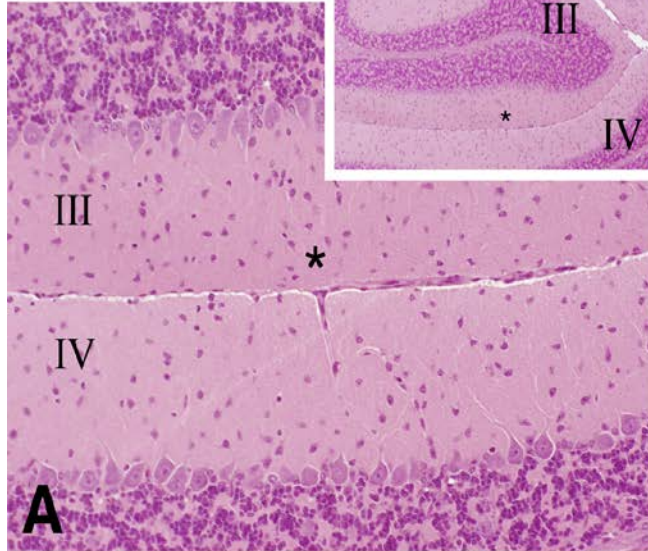


perlecan  
BLBP

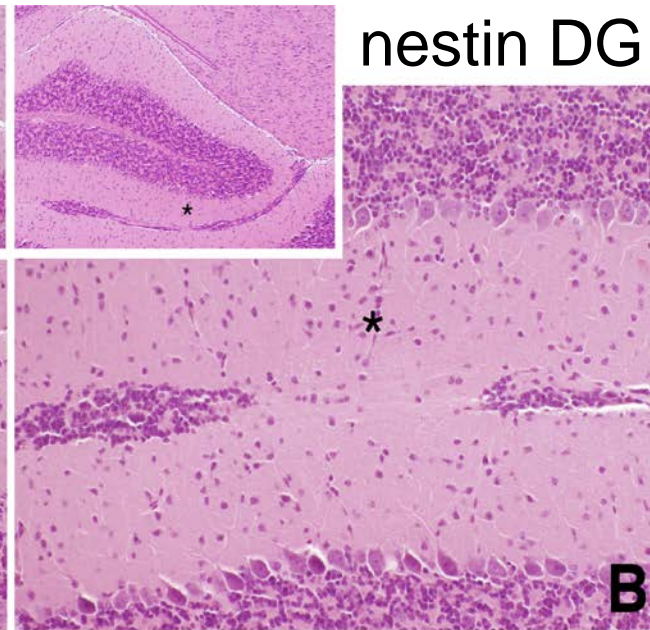


P16

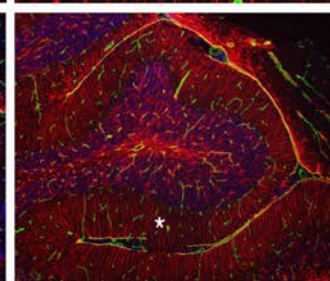
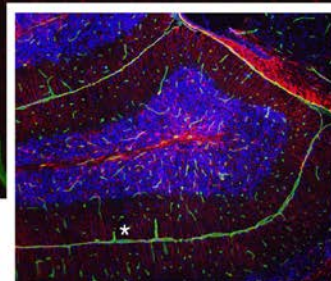
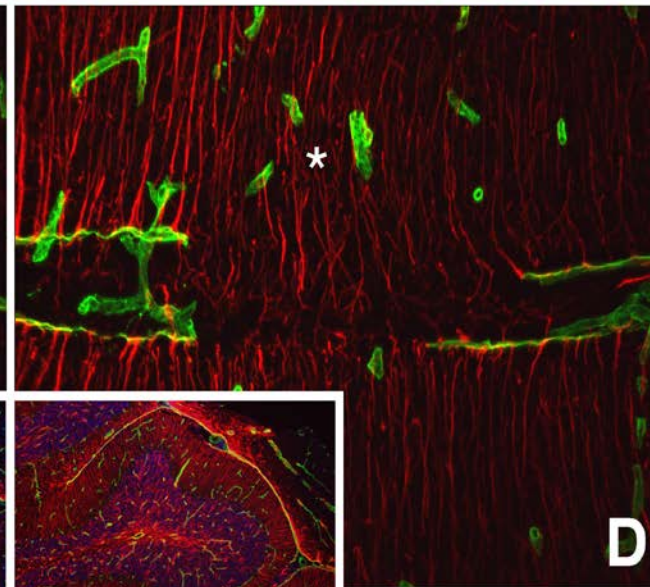
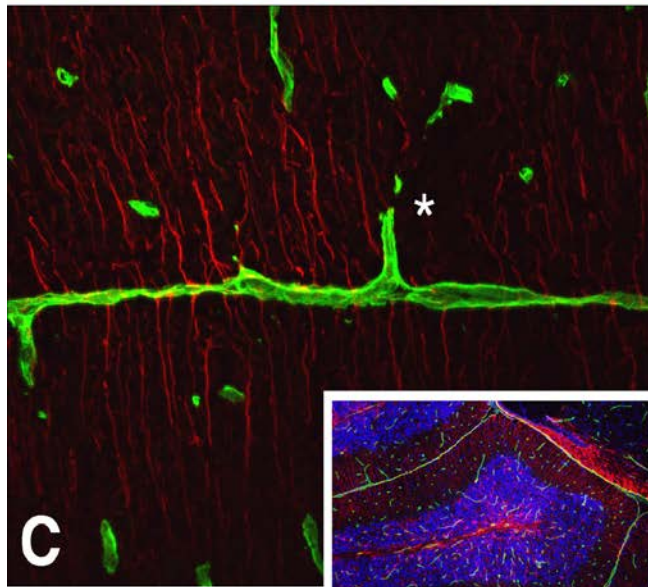
control



nestin DG null



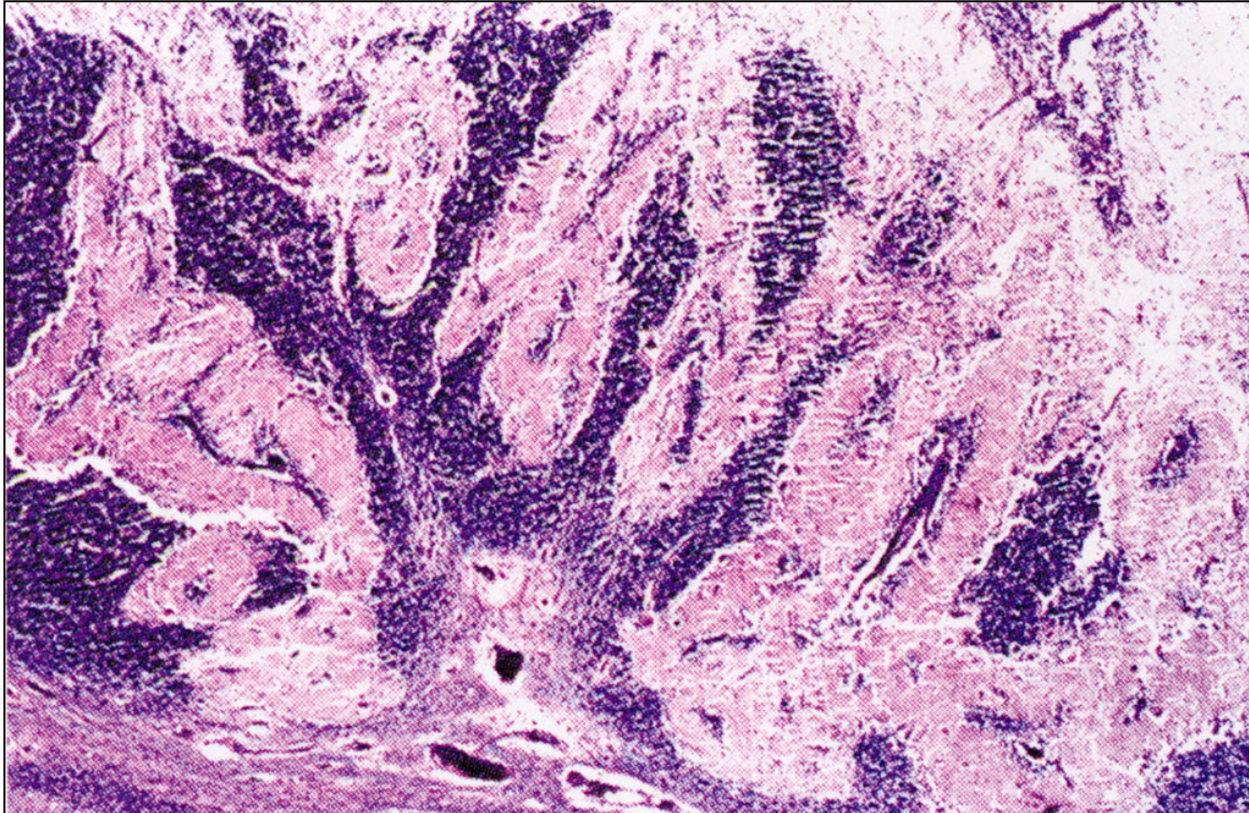
- failure of granule cell migration
- bridging across fissures



GFAP  
laminin  
DAPI



# cerebellar pathology in dystroglycanopathies

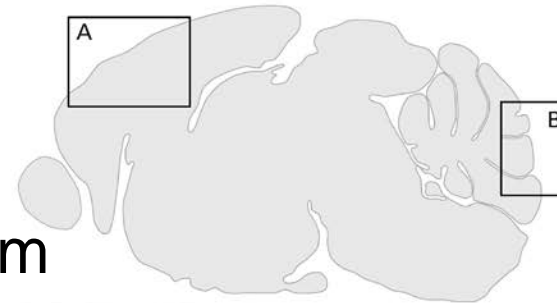
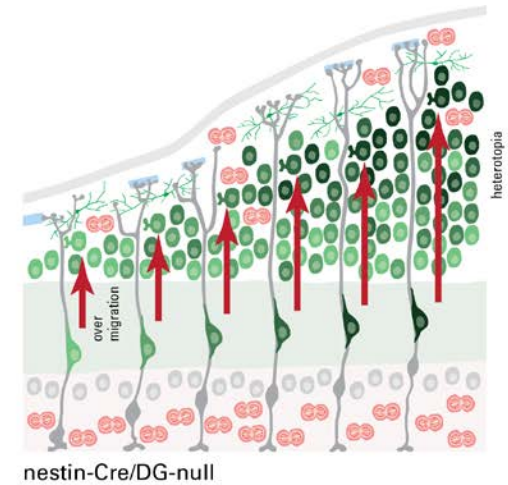
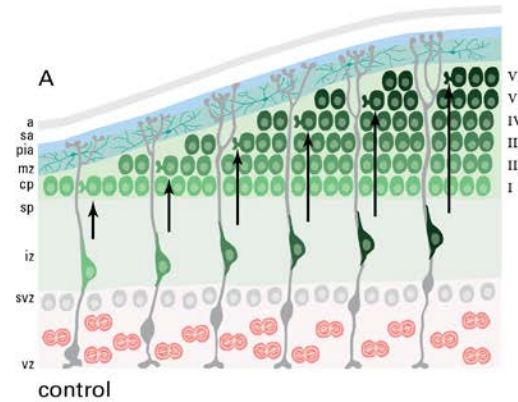


Walker-Warburg syndrome cerebellum

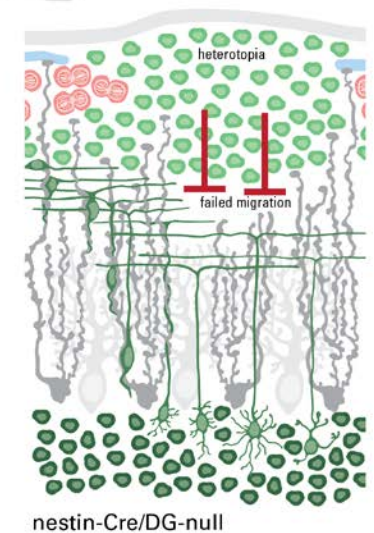
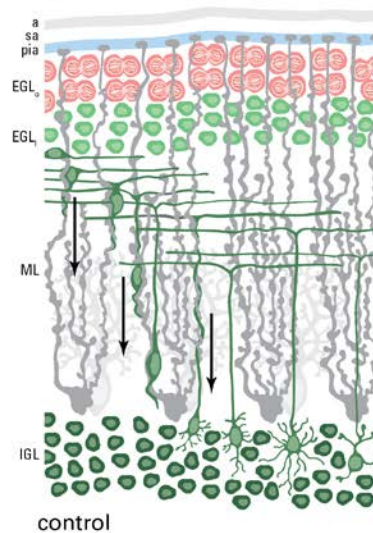


- Basement membrane disruption occurs in both cerebrum and cerebellum.
- Abnormal inside-out migration results in glial neuronal heterotopia filling the cerebral subarachnoid space.
- Abnormal outside-in migration results in cerebellar granule cell heterotopia.

## cerebrum

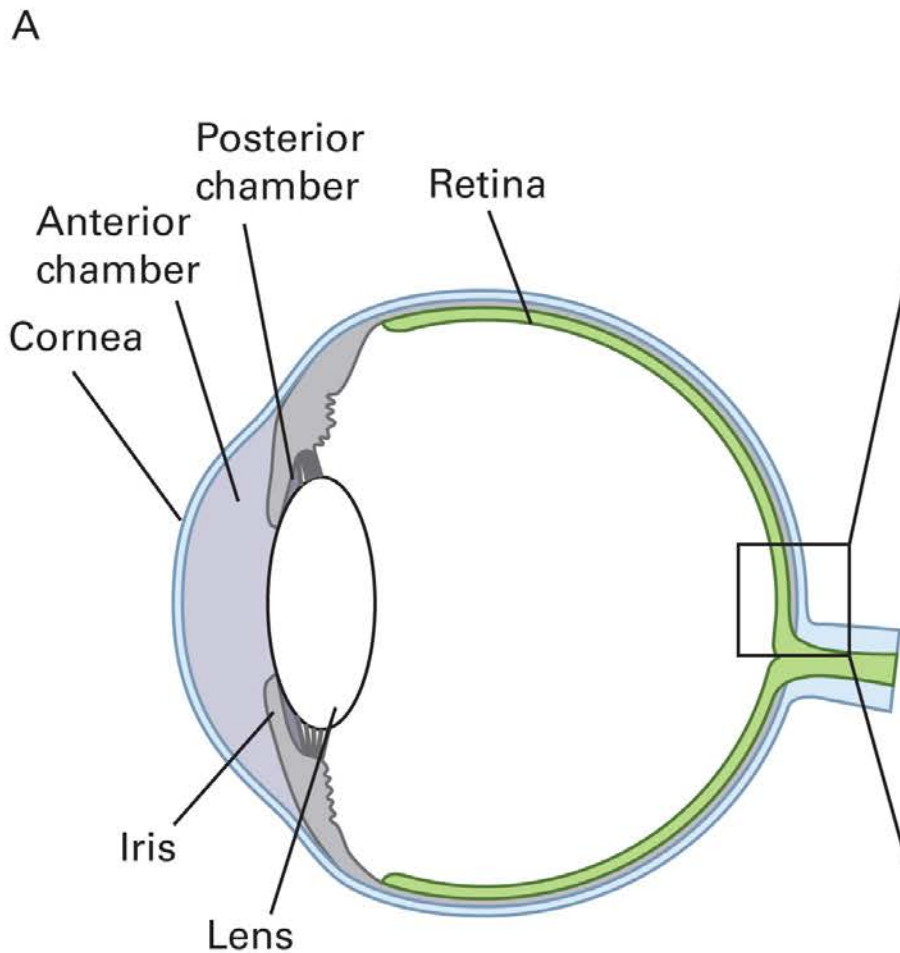


## cerebellum

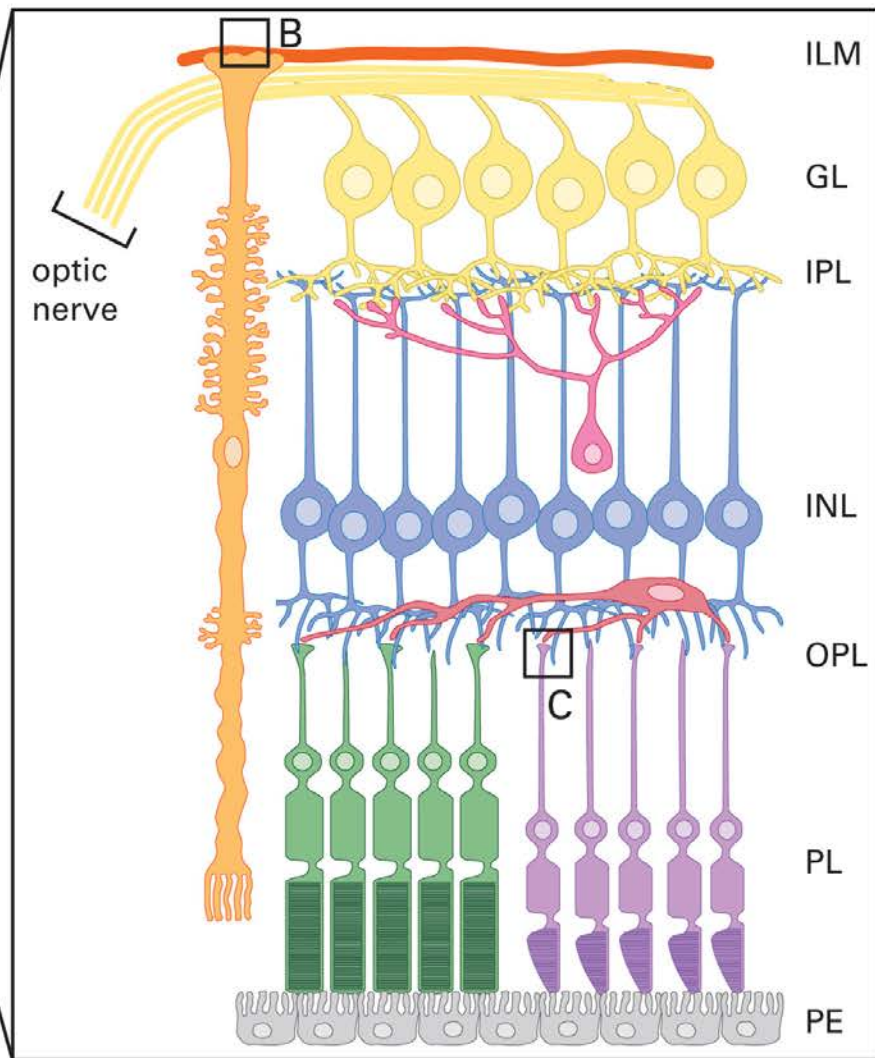


*drawing by Huy Nguyen*

# eye

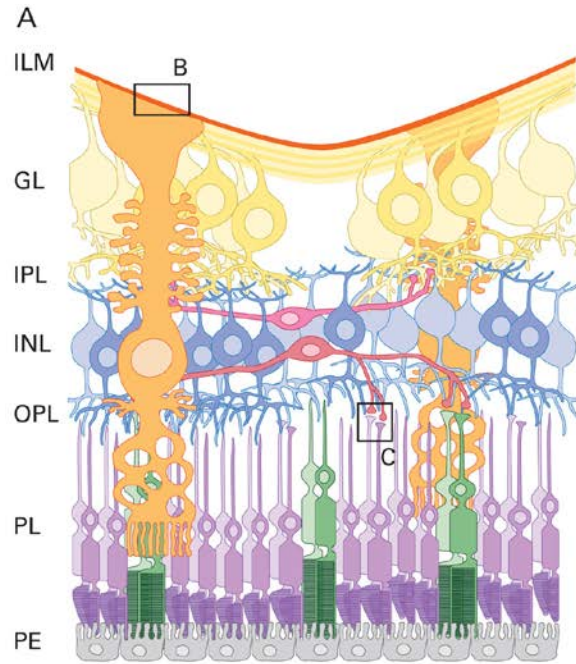


# retina

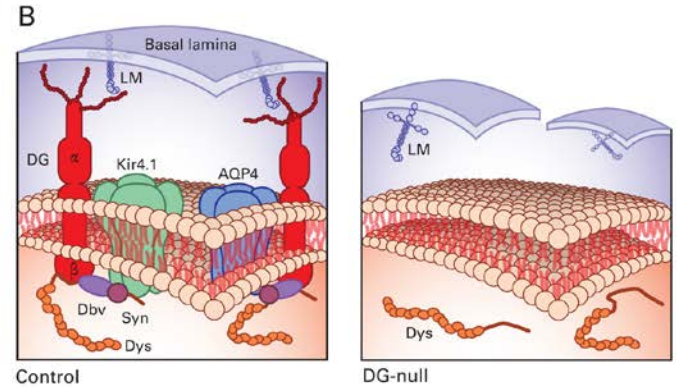




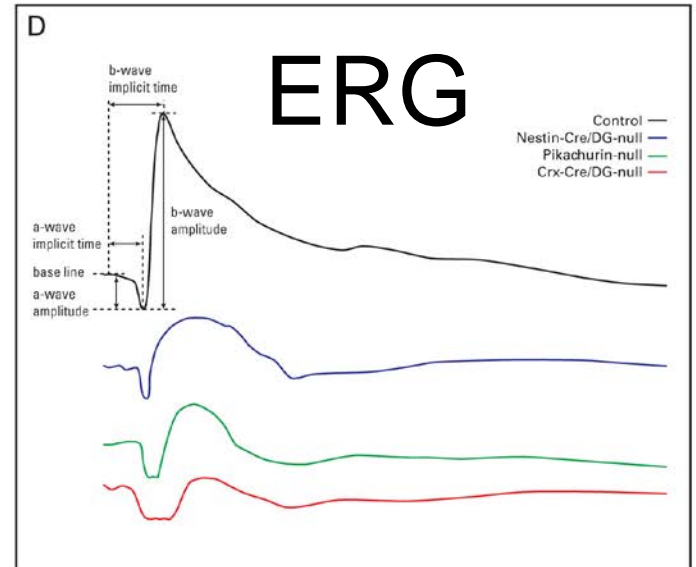
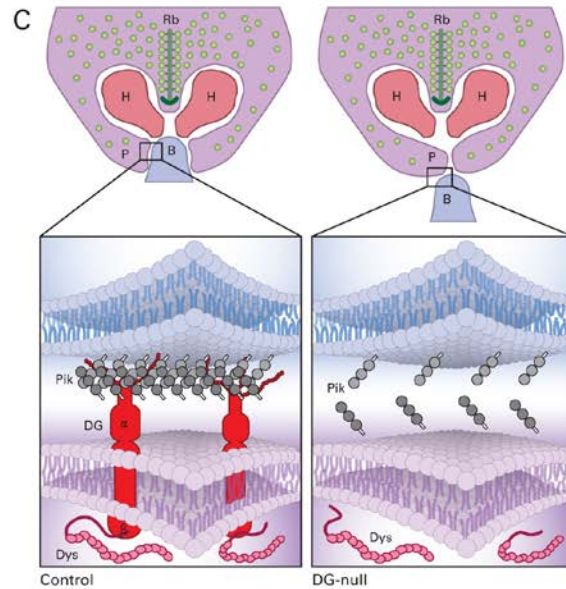
retina



Muller glia

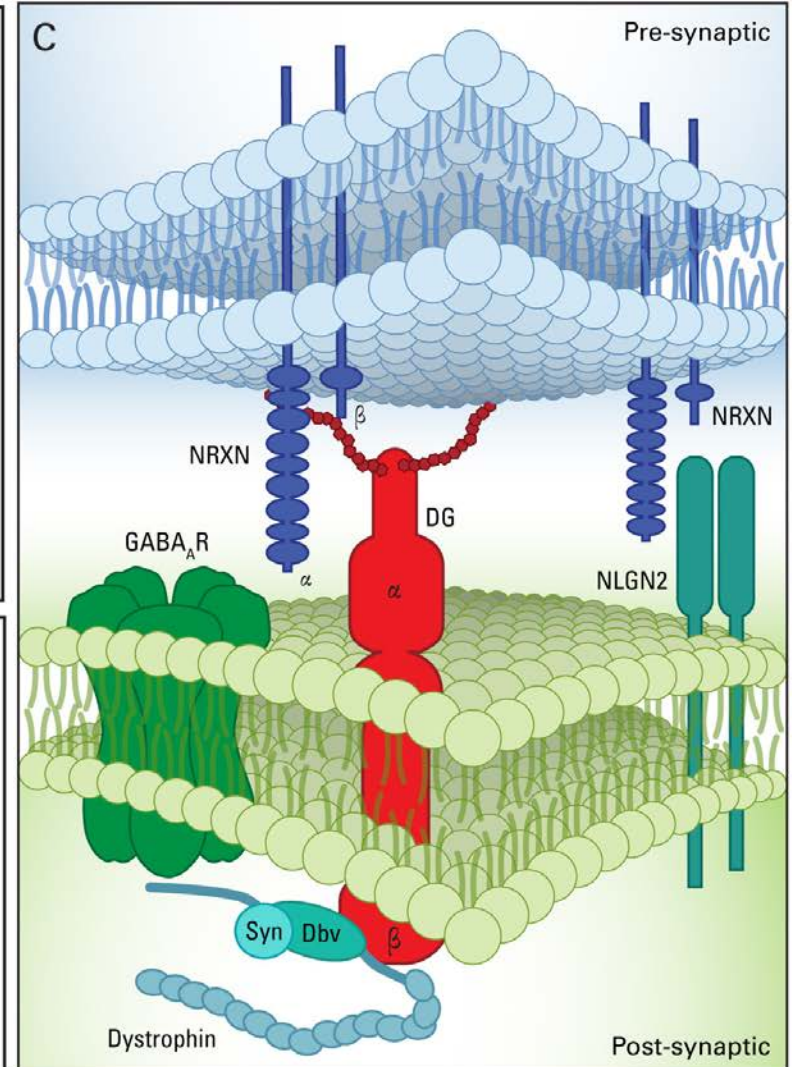
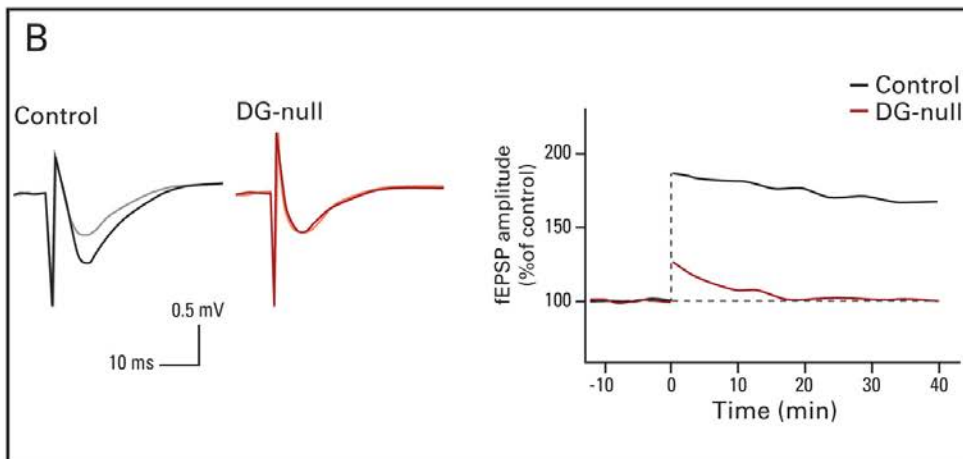
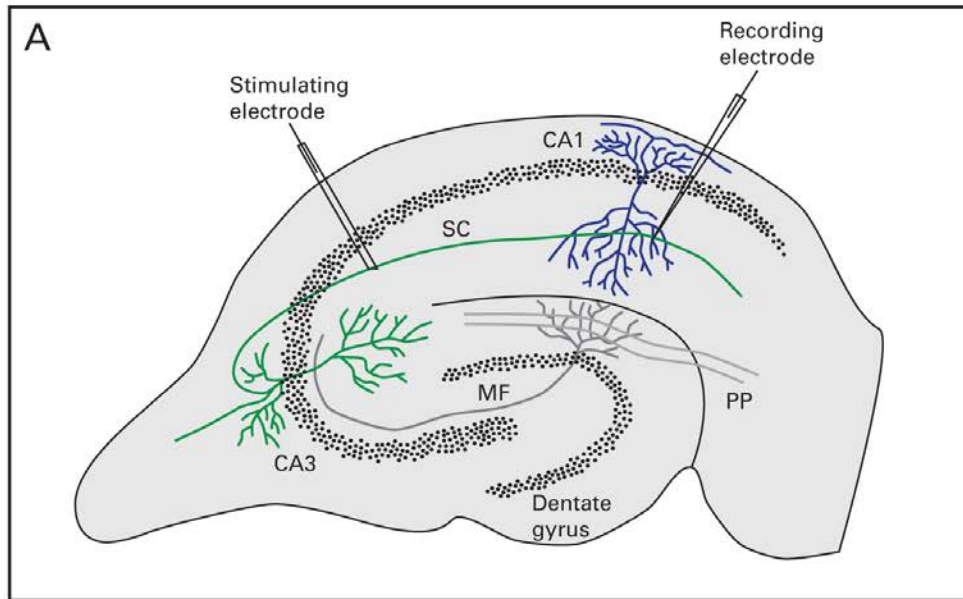


ribbon synapse



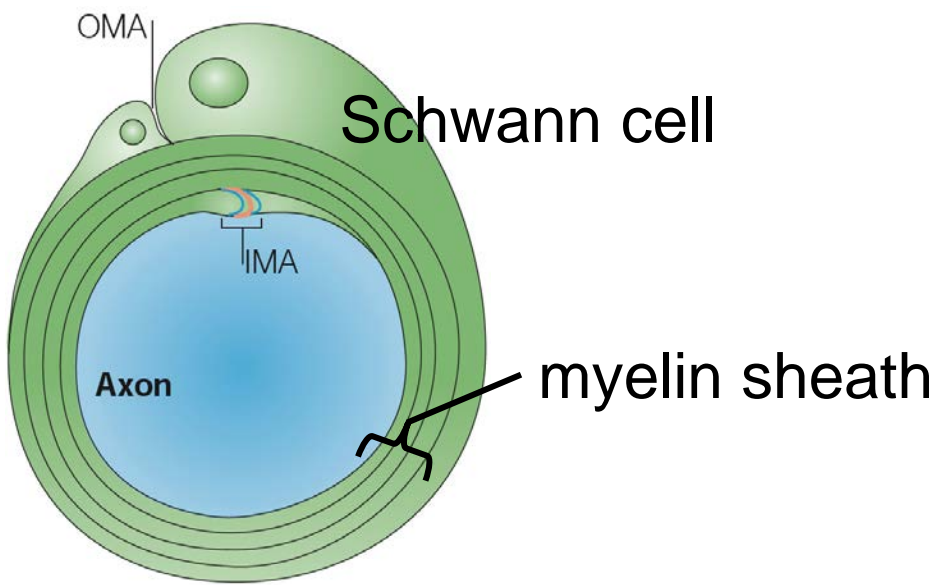
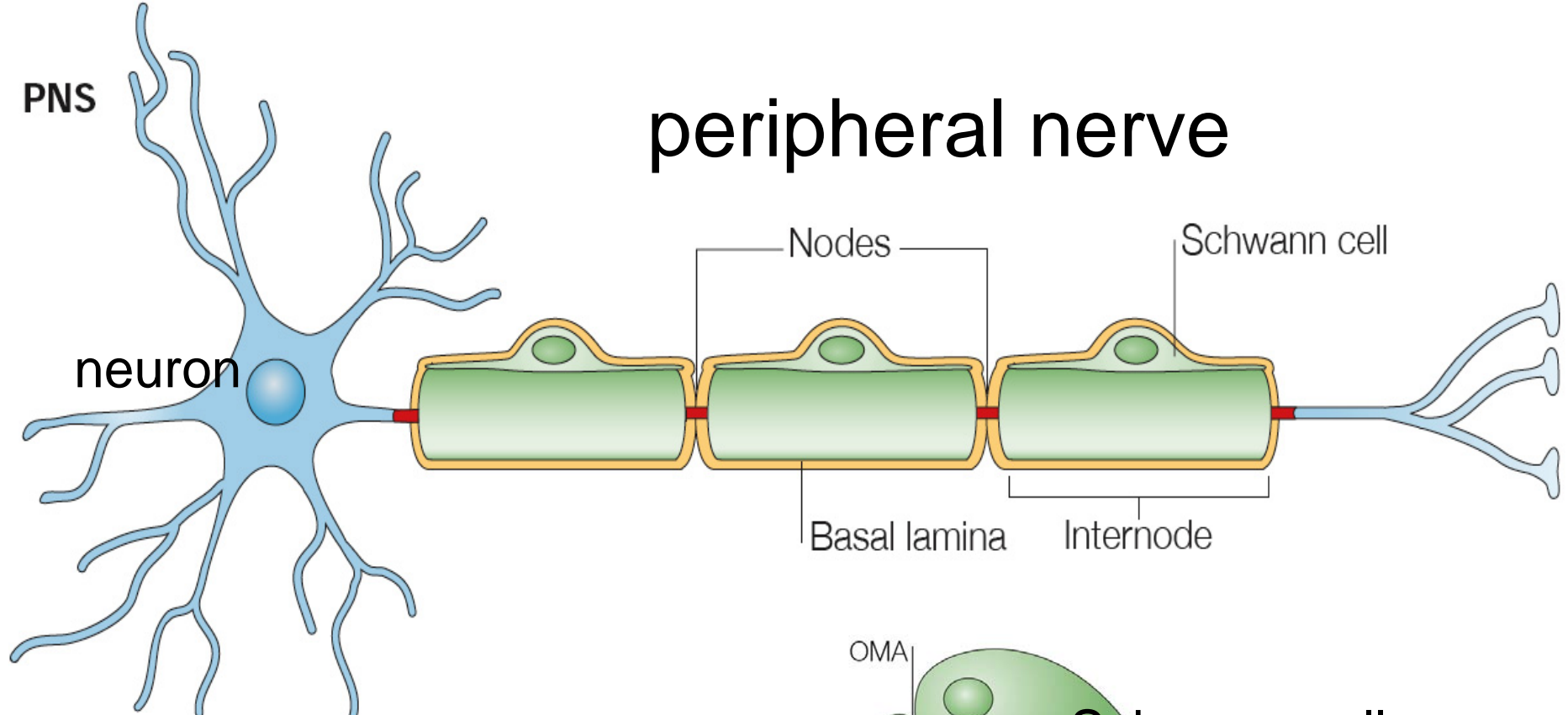
*drawing by Huy Nguyen*

# neuronal dystroglycan and LTP



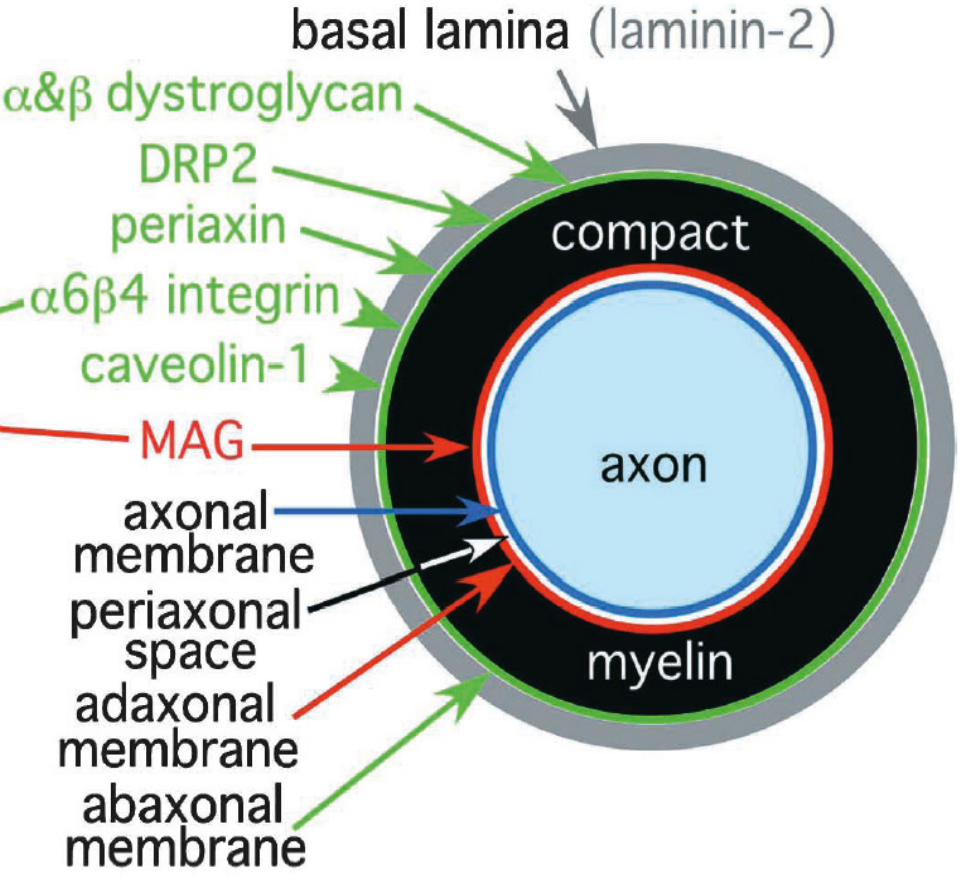
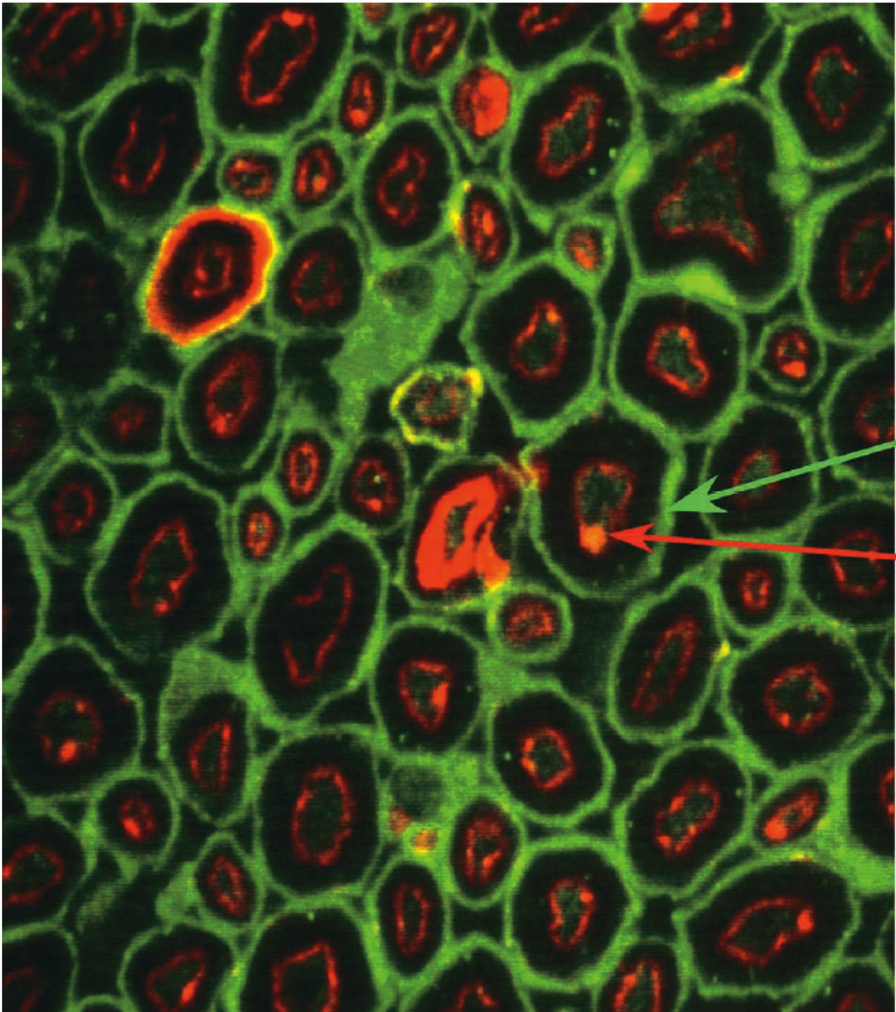
*drawing by Huy Nguyen*





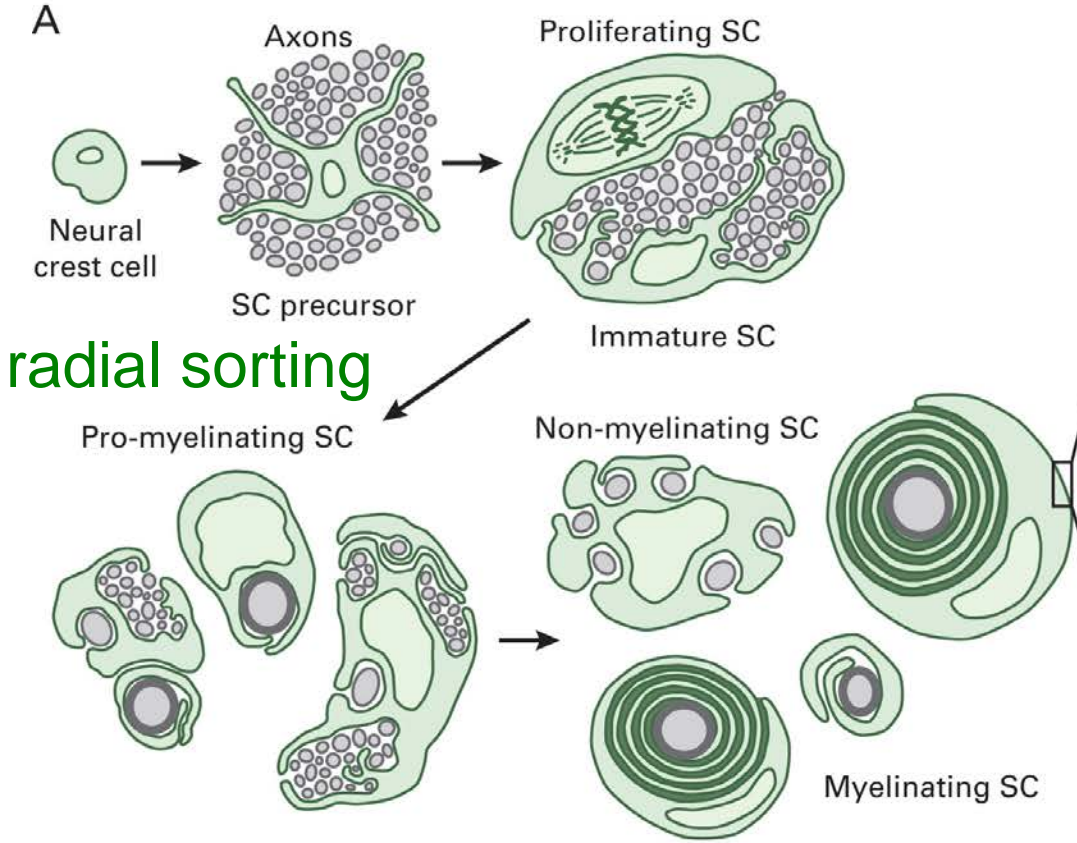
modified from Nature  
Reviews Neuroscience  
4:969, 2003

# peripheral nerve



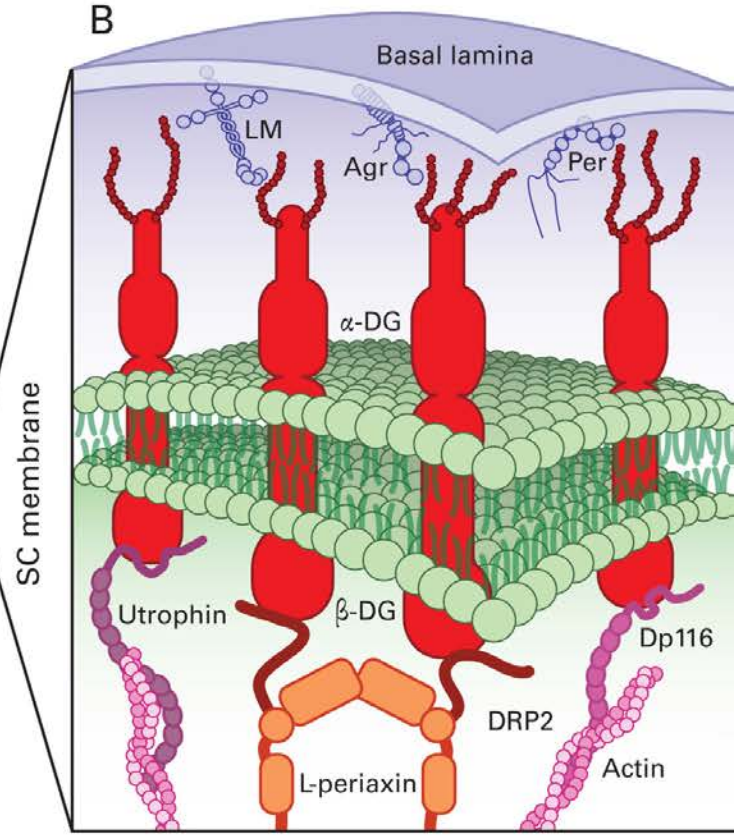


# peripheral nerve development



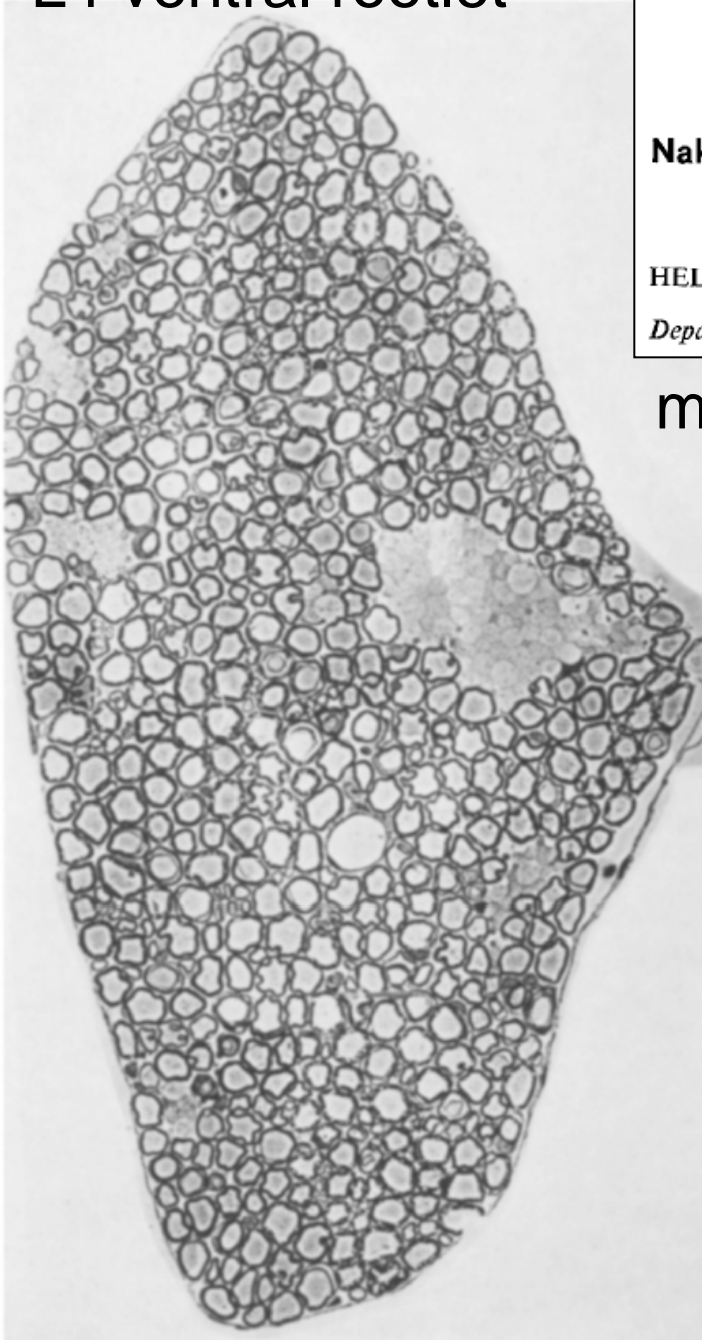
myelination

# Schwann cell dystroglycan



drawing by Huy Nguyen

# L4 ventral rootlet

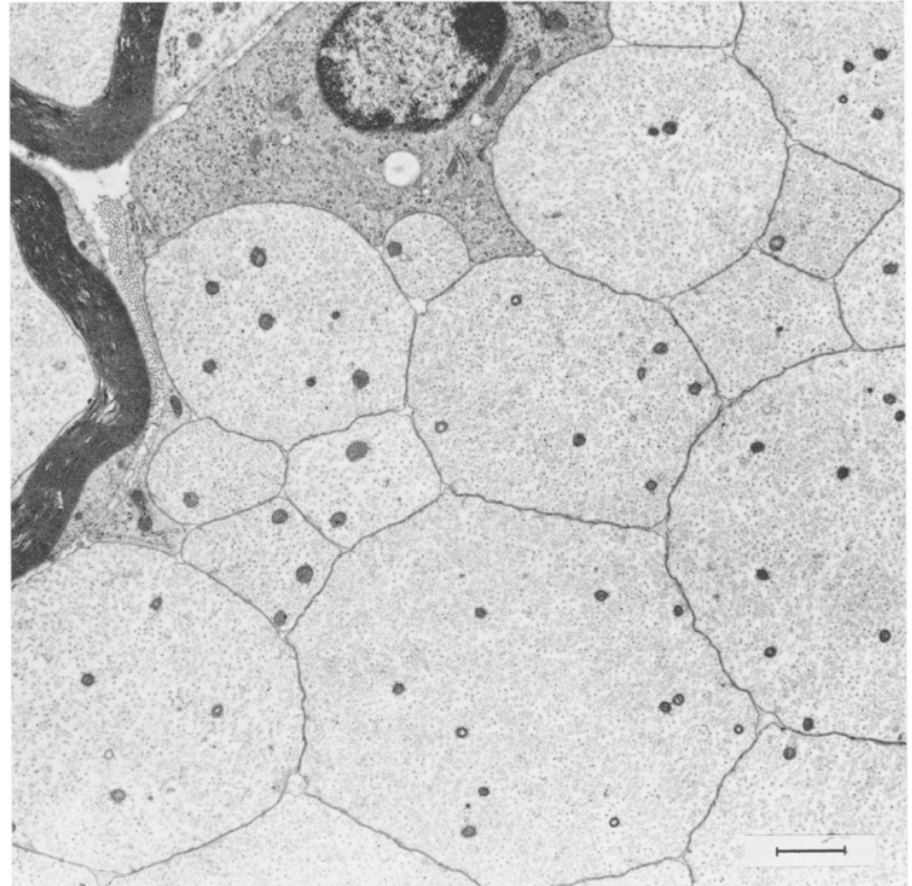


## Naked axons in myodystrophic mice

HELEN BERYL RAYBURN and ALAN CLARKE PETERSON

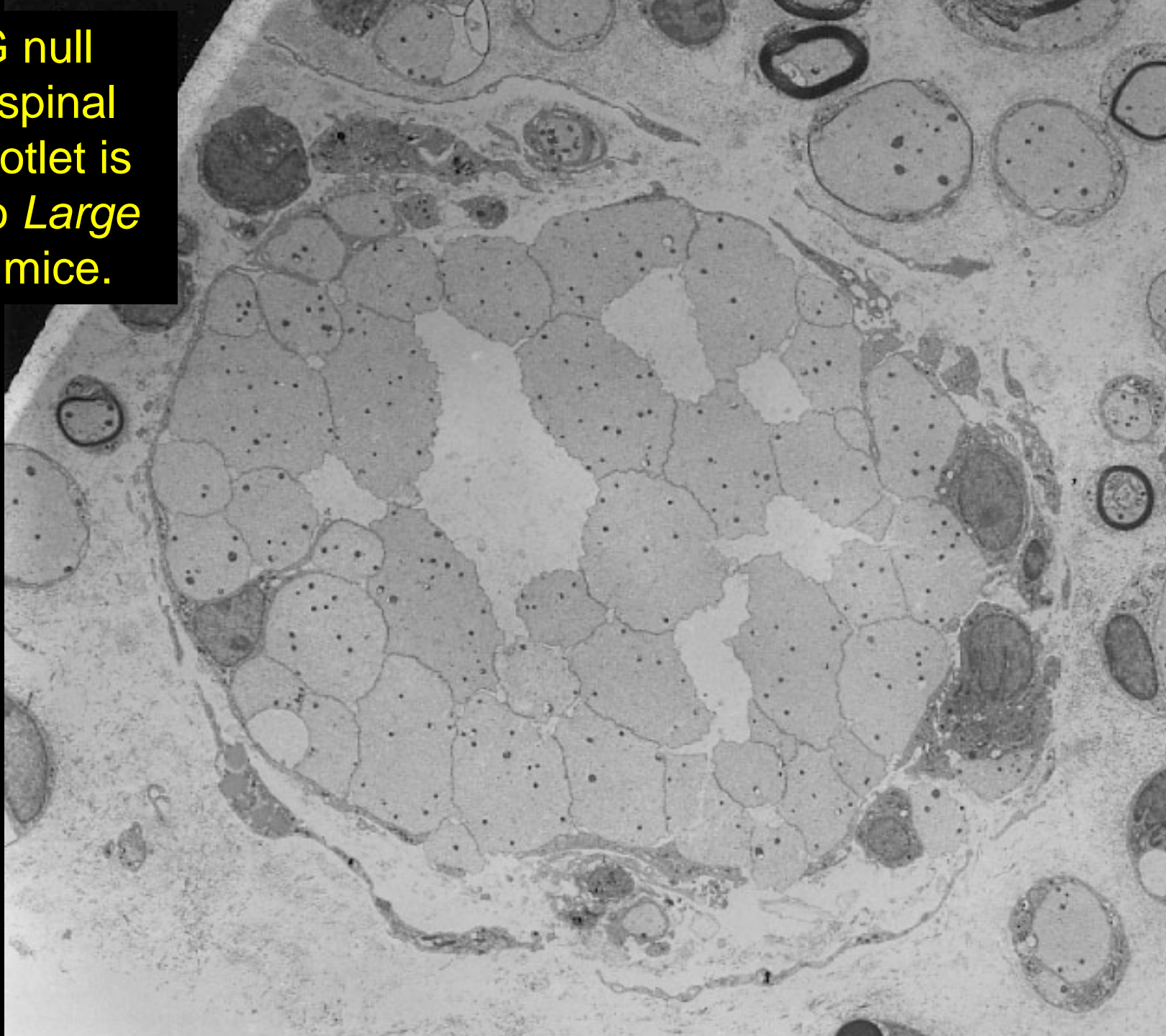
*Department of Neurosciences, McMaster University, Hamilton, Ontario (Canada)*

myodystrophic mouse = Large<sup>myd</sup> mouse

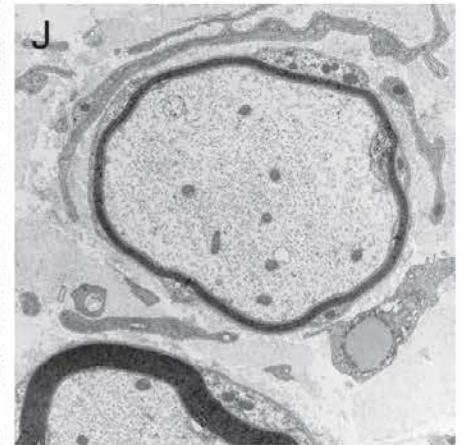
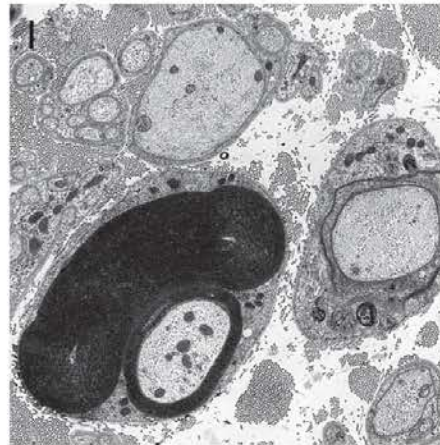
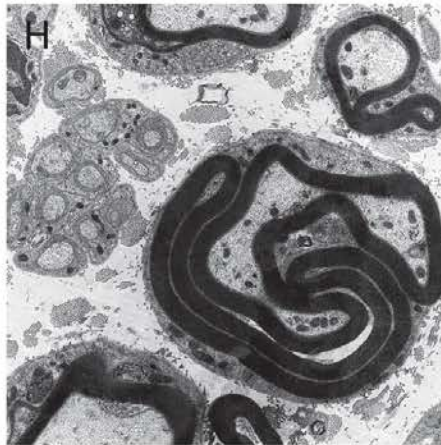
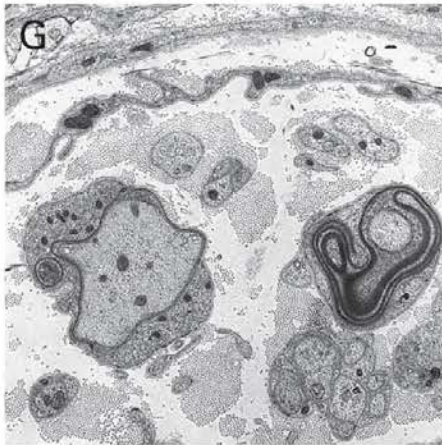
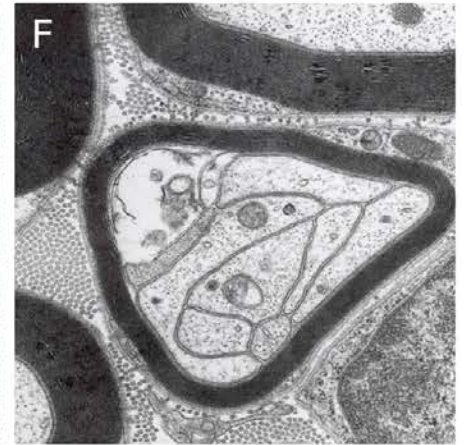
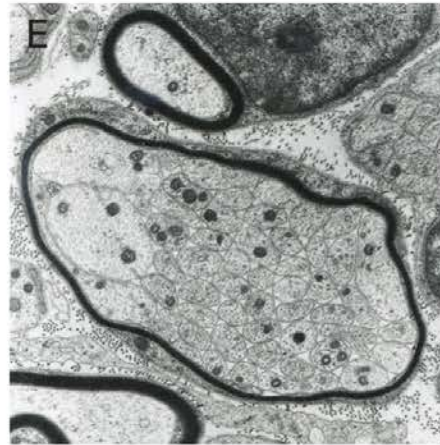
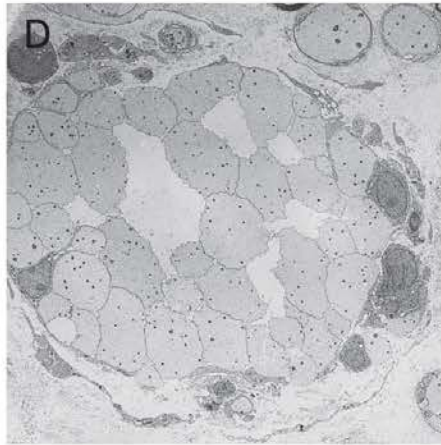
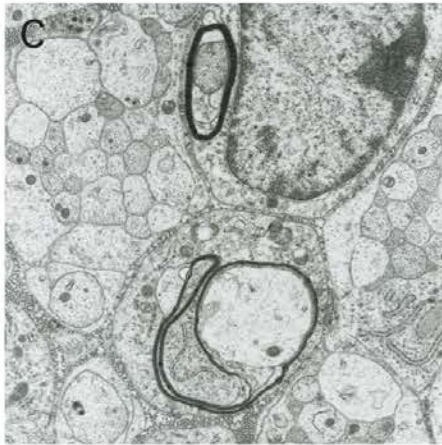




P0-DG null  
ventral spinal  
nerve rootlet is  
similar to *Large*  
mutant mice.

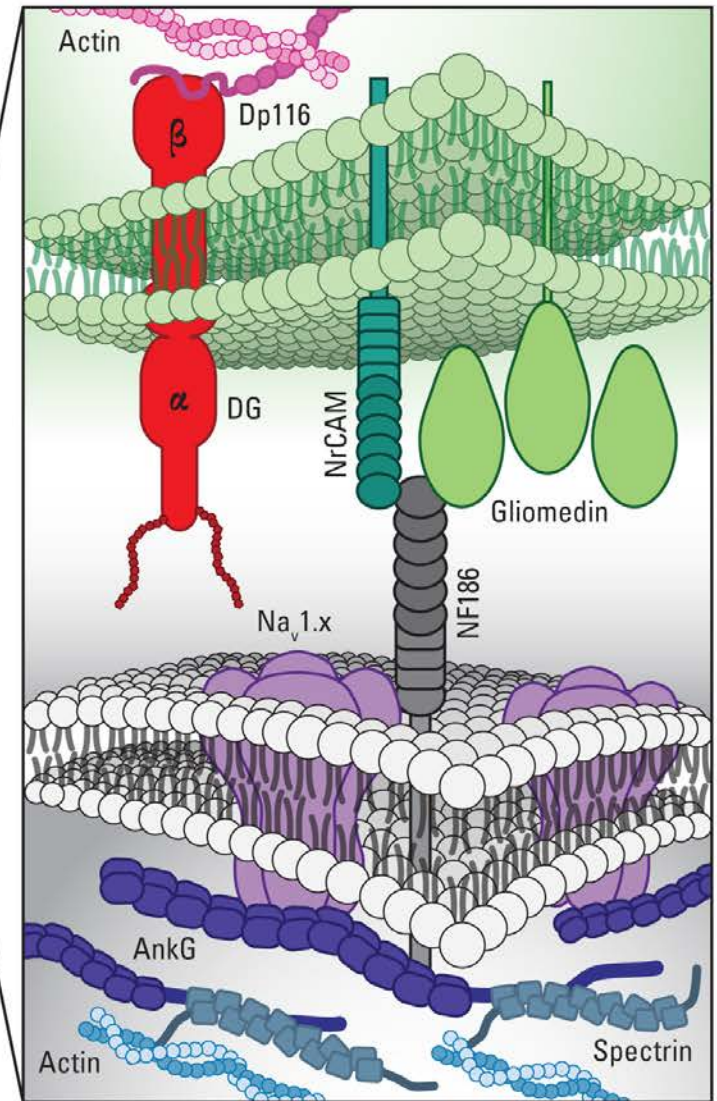
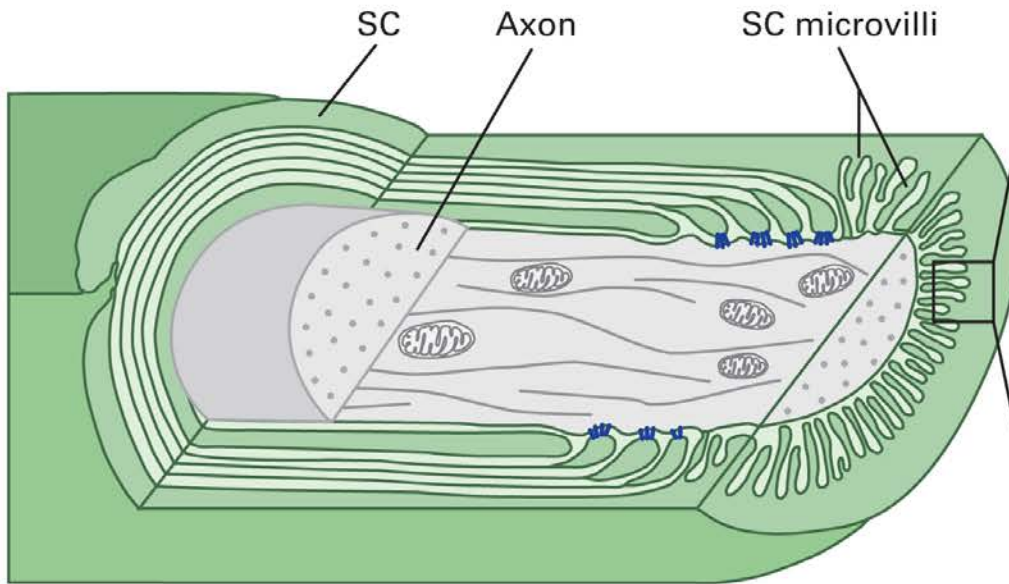


# peripheral nerve pathology in the absence of dystroglycan





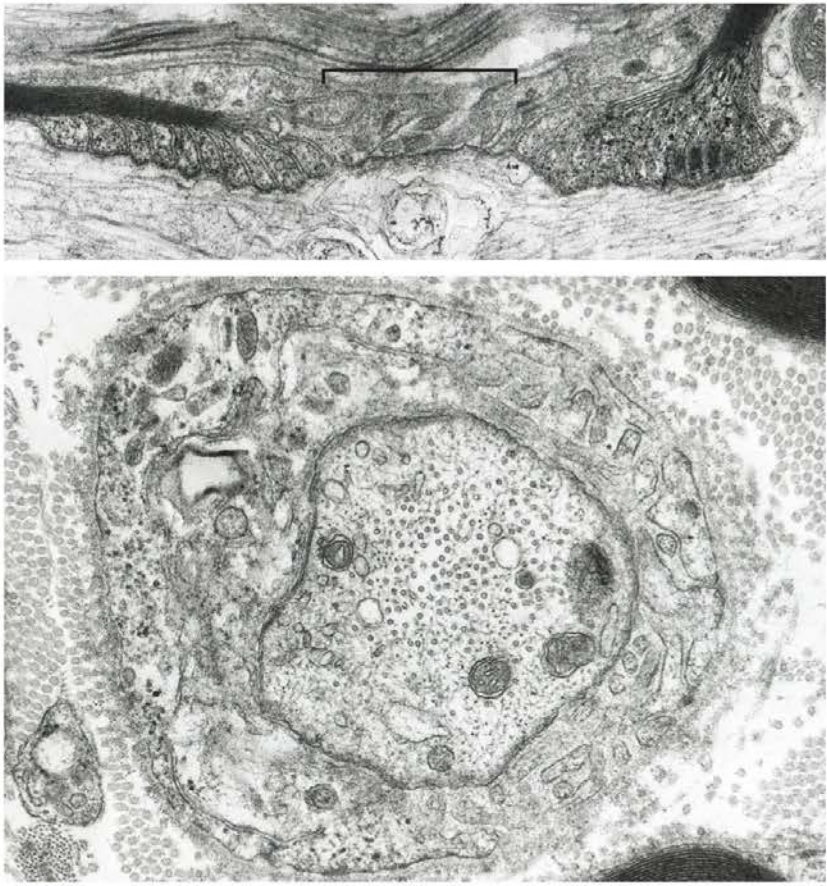
# dystroglycan at nodes of Ranvier



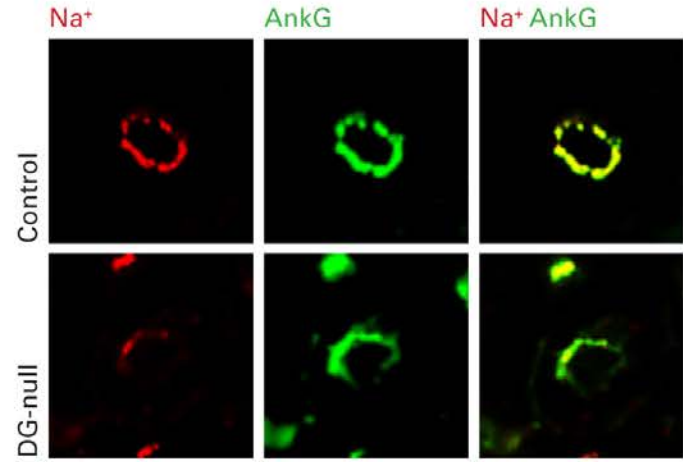
*drawing by Huy Nguyen*

# pathology at nodes of Ranvier in the absence of dystroglycan

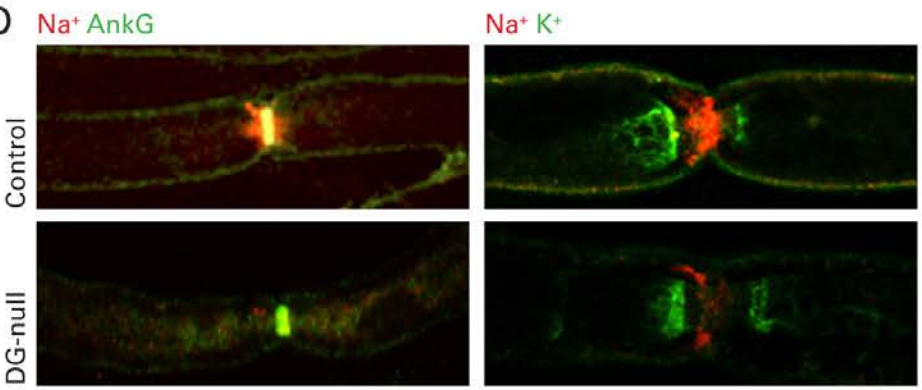
B



C



D



*immunostains by Rita Barresi*



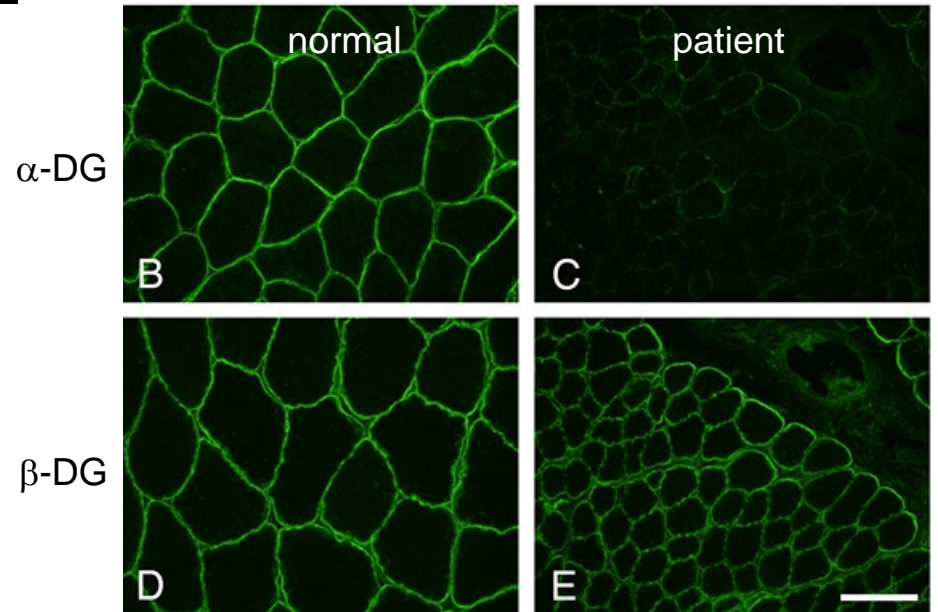
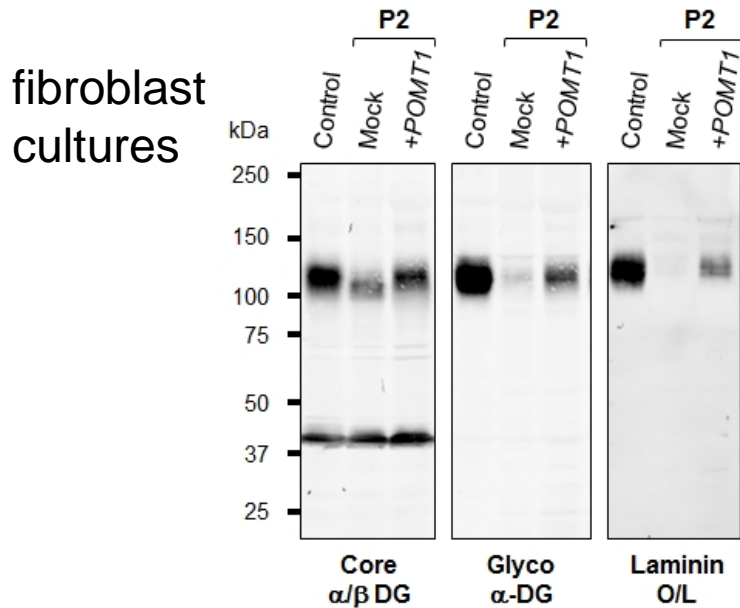
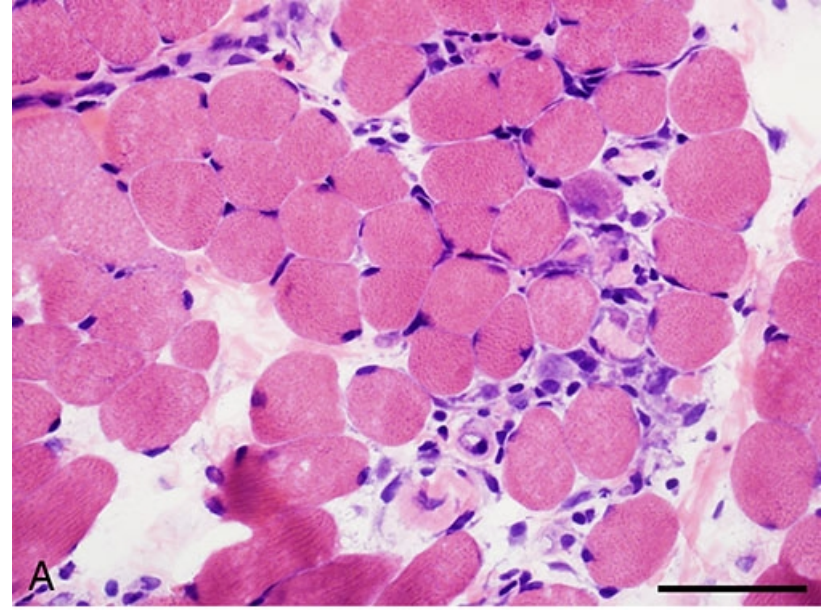
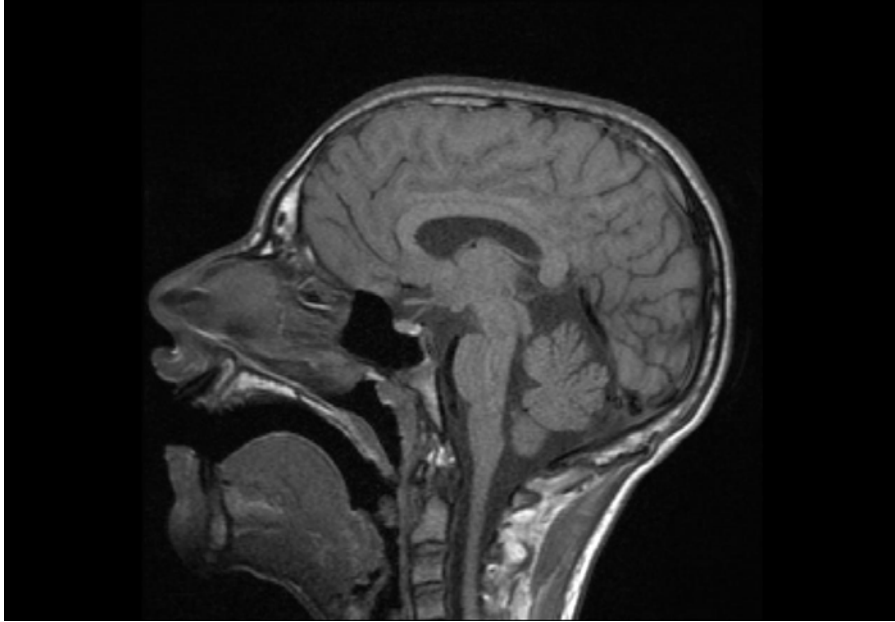
# Summary

- Dystroglycanopathies are heterogeneous: varying degrees of muscle, brain, eye, and nerve involvement.
- Pathology is largely due to reduced binding of  $\alpha$ -dystroglycan to basement membranes.
- In brain, eye, and nerve, many of the abnormalities are developmental.
- Additional abnormalities stem from the roles of  $\alpha$ -dystroglycan at synapses and nodes of Ranvier.





# CMD with cognitive impairment - *POMT1* mutations



# compound heterozygous *POMT1* mutations

- Asp723Glyfs\*8 (relatively common mutation)
- Pro653Leu (novel mutation)

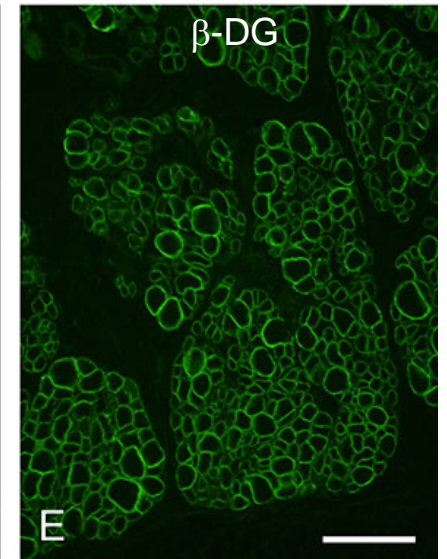
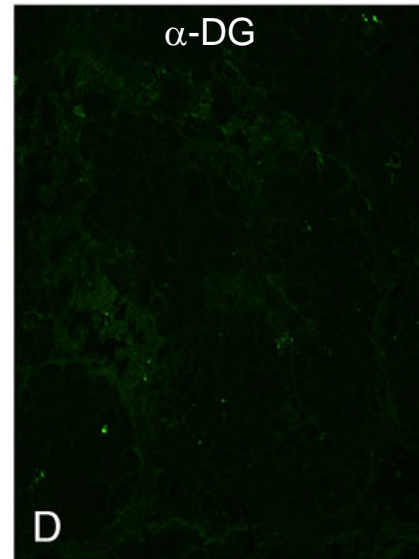
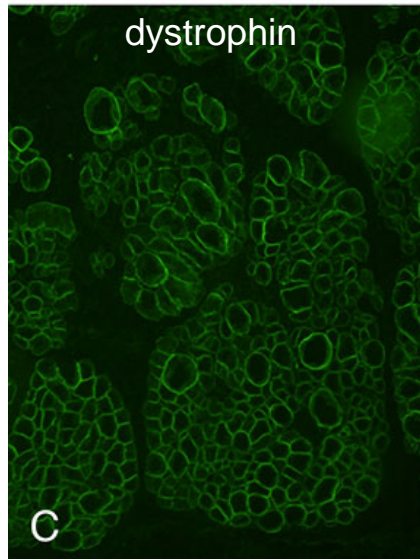
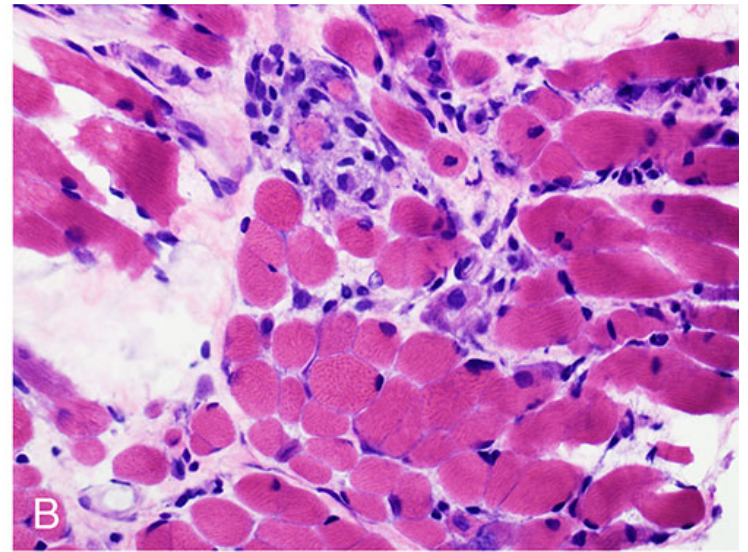
HsPOMT1	645	GGWAVNYLPFFLMEKTLFL
MmPOMT1	645	GGWAVNYLPFFLMEKTLFL
C1POMT1	623	GGWAVNYLPFFMMEKTLFL
GgPOMT1	623	GGWVNYLPFFLMEKTLFL
DrPOMT1	618	GGWAVNYLPFFLMEKTLFL
HsPOMT2	645	LGWTLHYFPFFLMGRVLYF
PtPOMT2	645	LGWTLHYFPFFLMGRVLYF

- Pro653 is highly conserved.
- Each parent is a carrier of one mutation.
- A third, unrelated patient was identified with the same two mutations. She also has CMD with cognitive impairment and dystroglycanopathy on muscle biopsy.



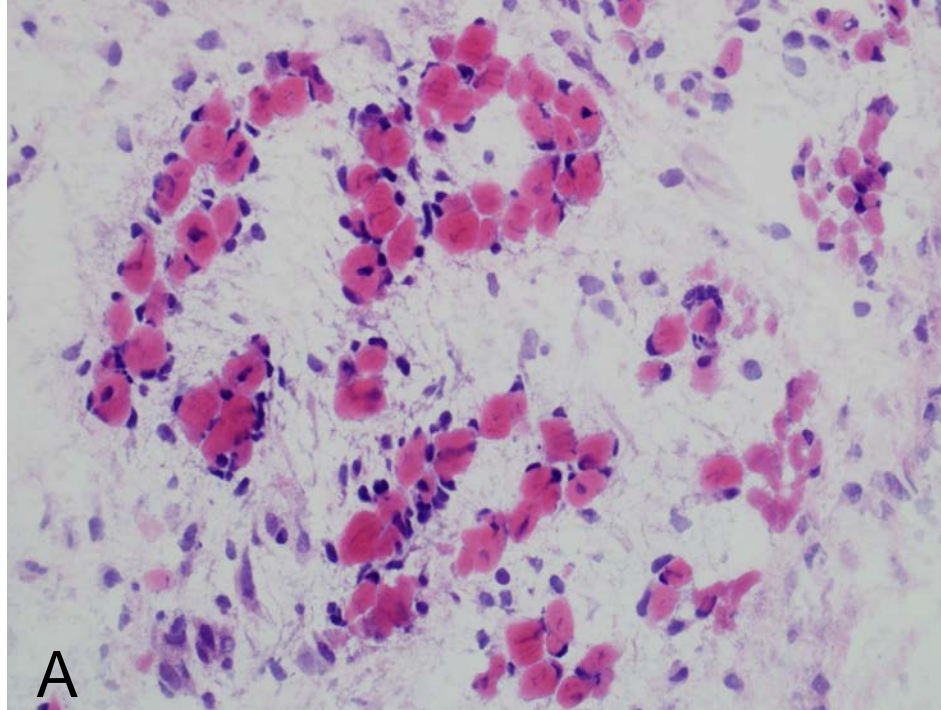
# homozygous Asp723Glyfs\*8 *POMT1* mutations

Walker-  
Warburg  
syndrome  
(WWS)



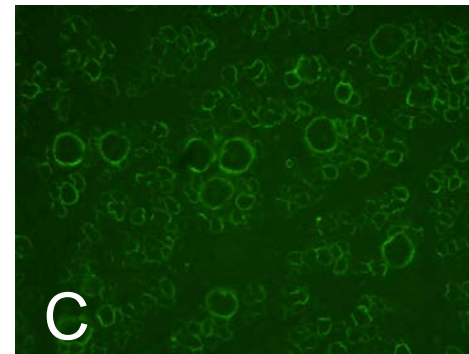
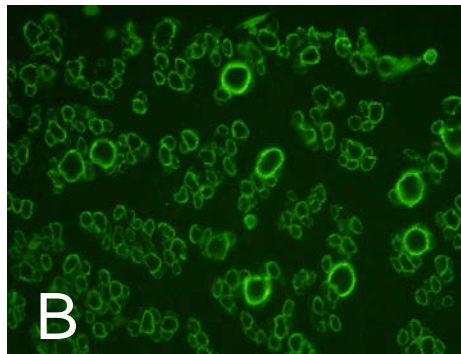
Ashkenazi Jewish  
founder mutation in  
*FKTN* causes WWS

exon 9 of *FKTN*  
homozygous 1-base pair  
insertion (c.1167insA,  
p.F390Ifs\*14)



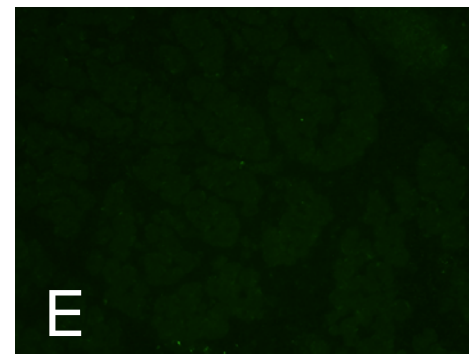
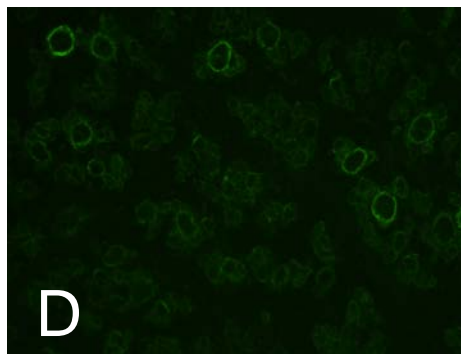
fetal  
muscle

dystrophin



$\alpha$ -DG  
(GT20ADG)

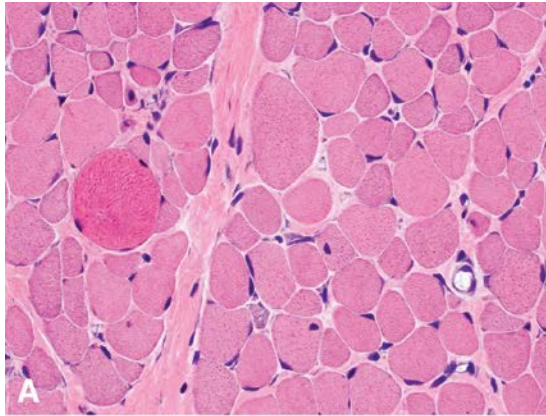
$\beta$ -DG



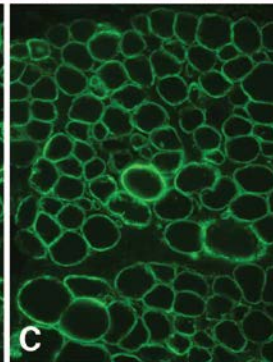
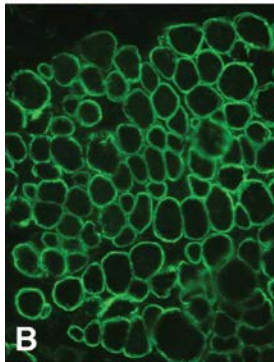
$\alpha$ -DG  
(IIH6)



# *FKTN* mutations can also cause mild childhood onset LGMD

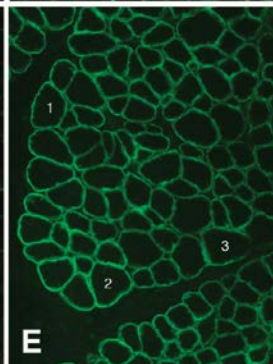
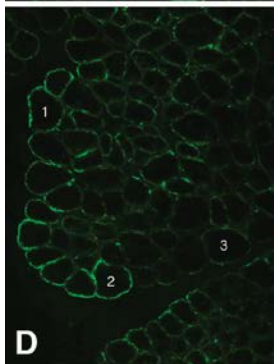


dystrophin

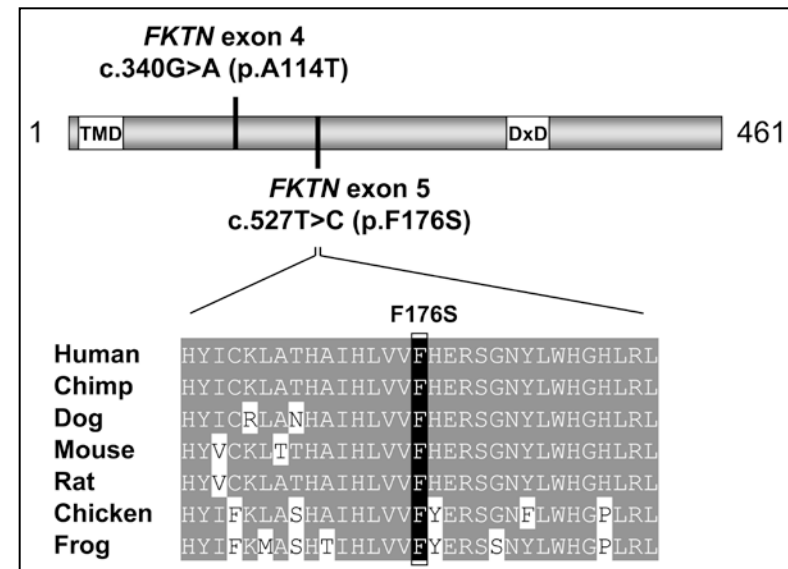
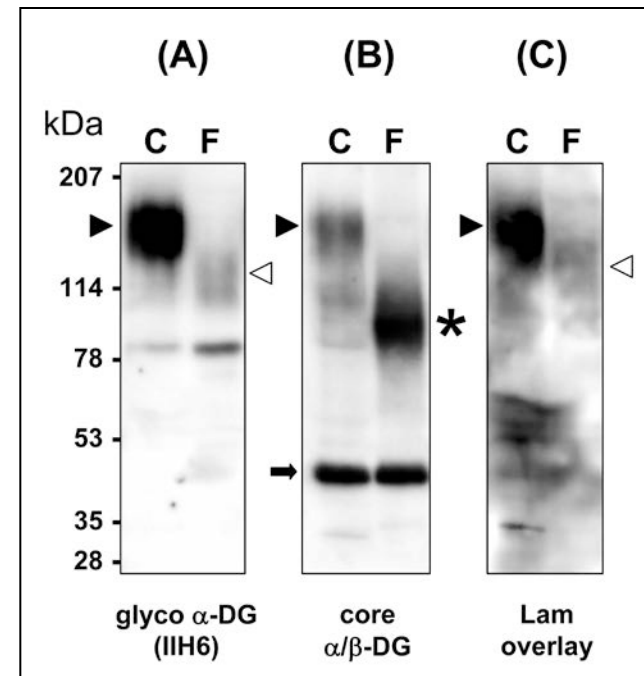


$\alpha$ -DG  
(GT20ADG)

$\alpha$ -DG  
(IIH6)

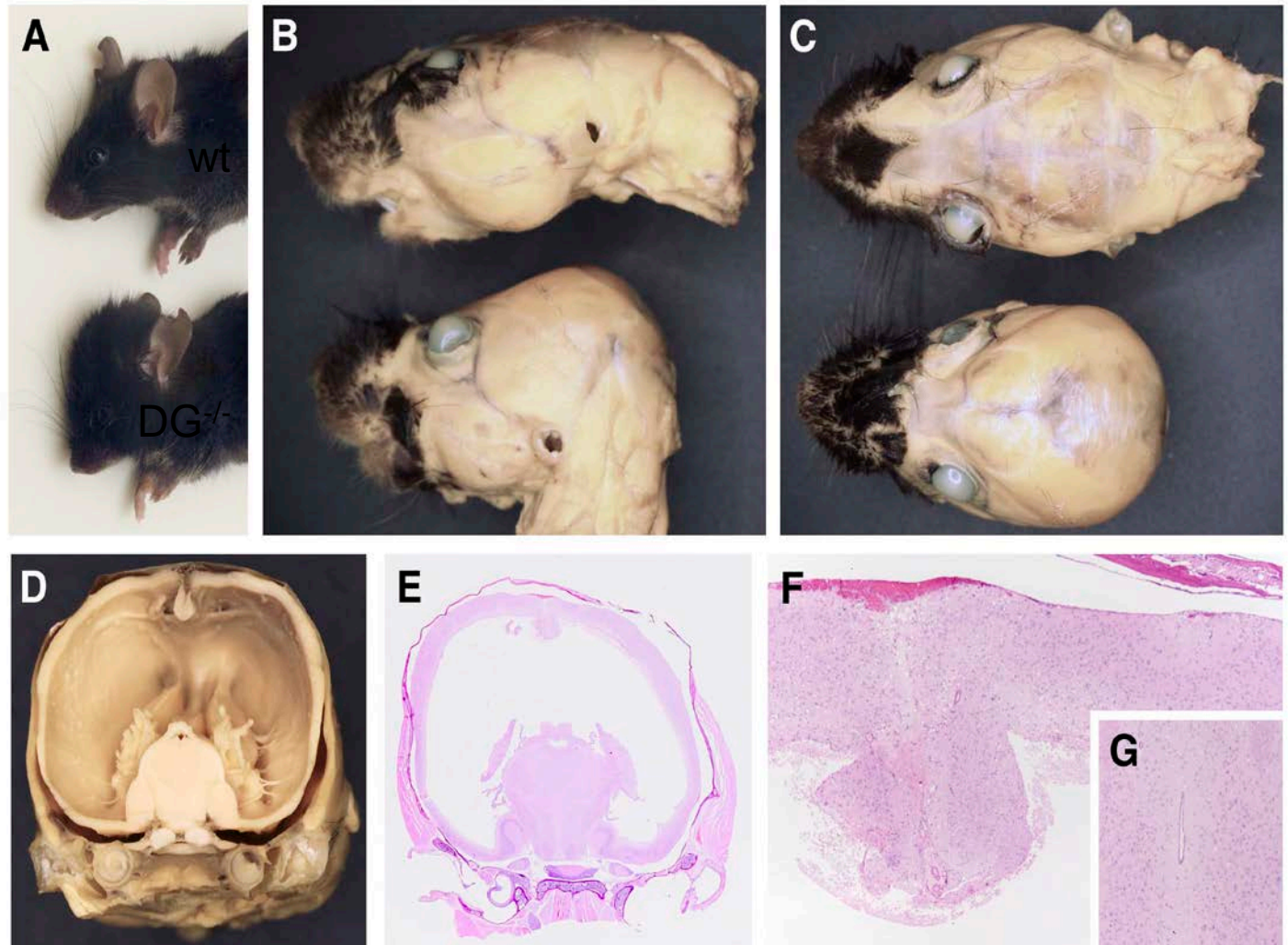


$\beta$ -DG



Severe hydrocephalus is common in nestin-Cre, but rare in GFAP-Cre/DG null mice possibly a result of an obliterated subarachnoid space in nestin-Cre.

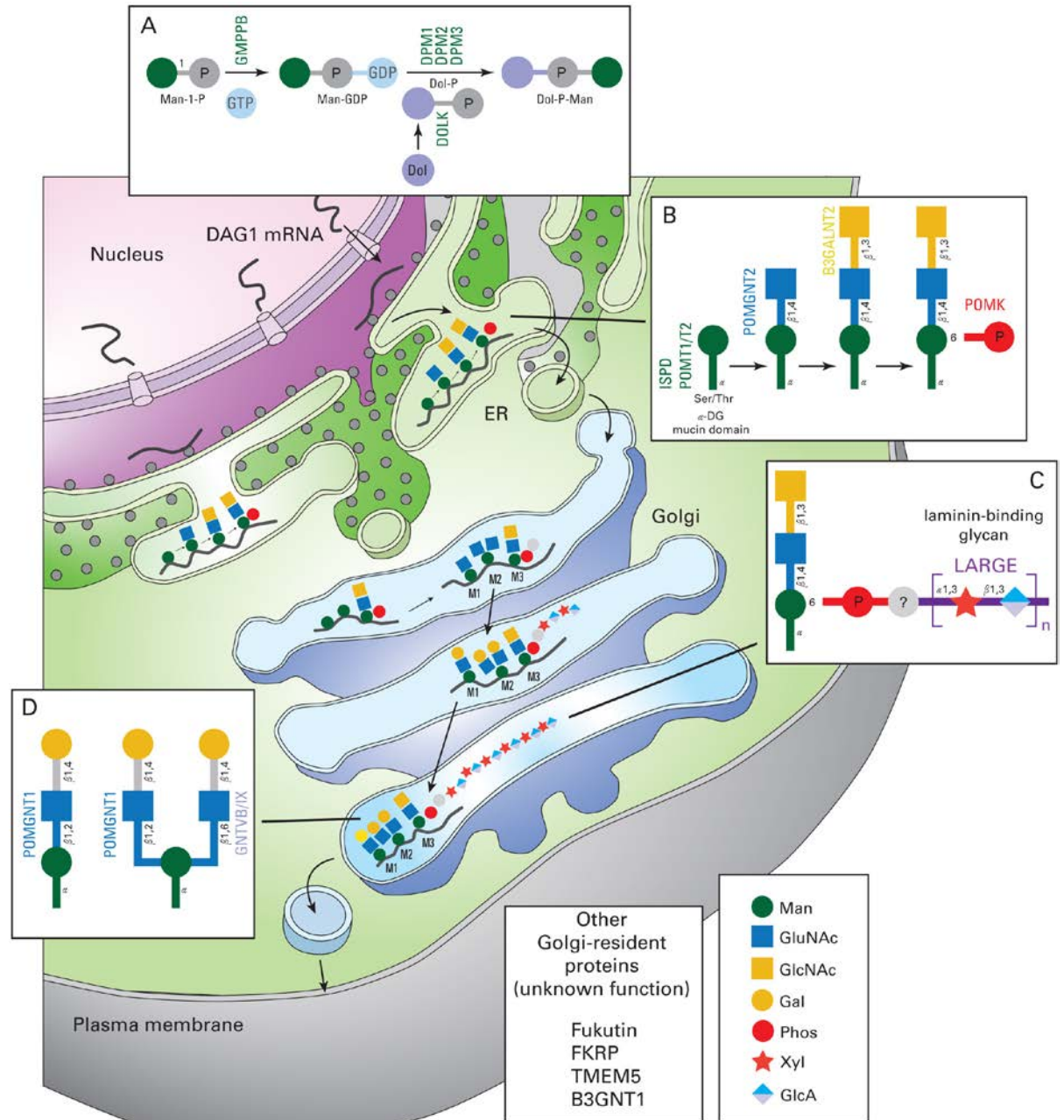
nestin-Cre  
littermates



Satz et al.,  
J Neurosci 30:14560-  
14572, 2010.

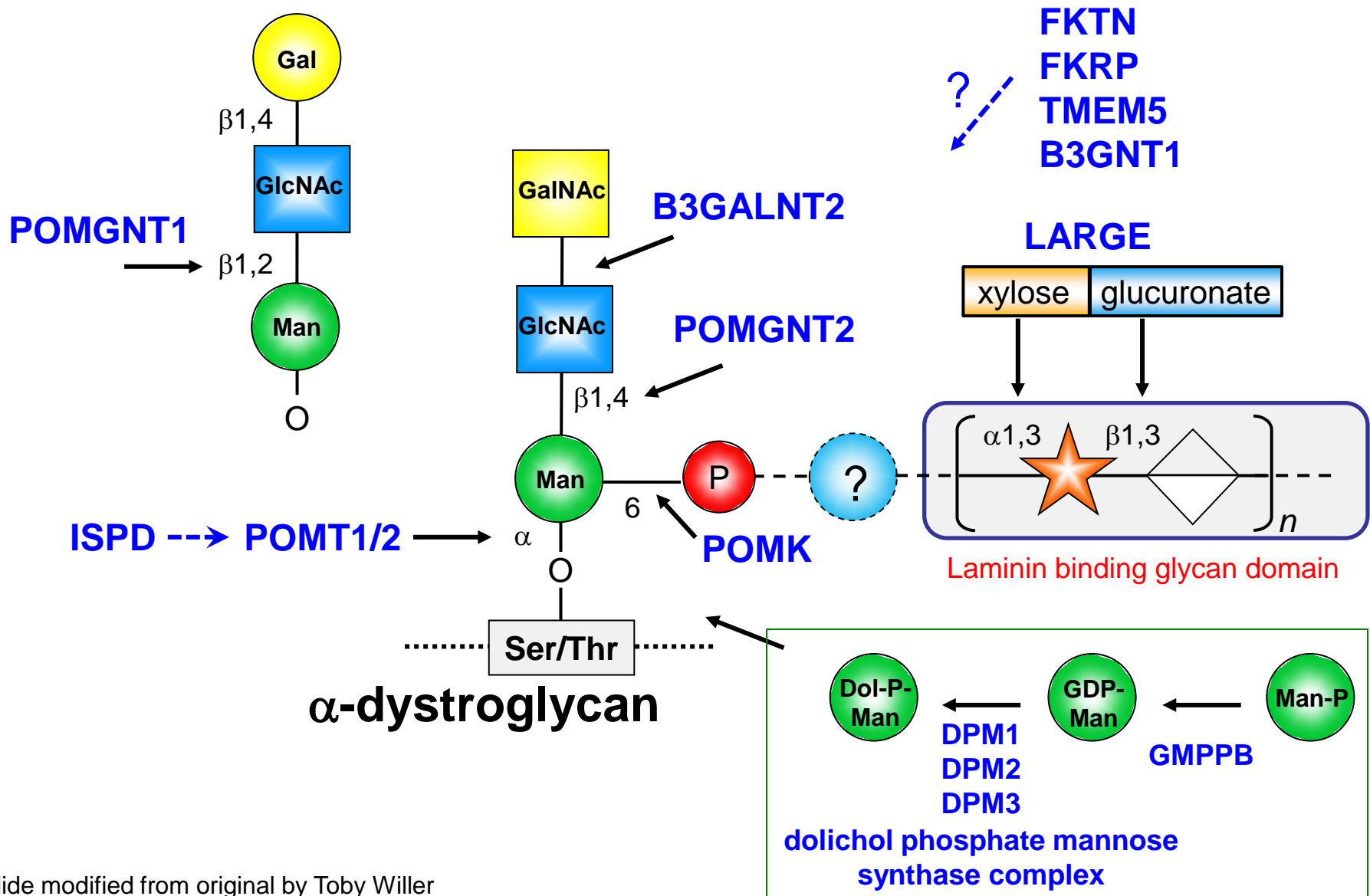


# dystroglycan glycobiology



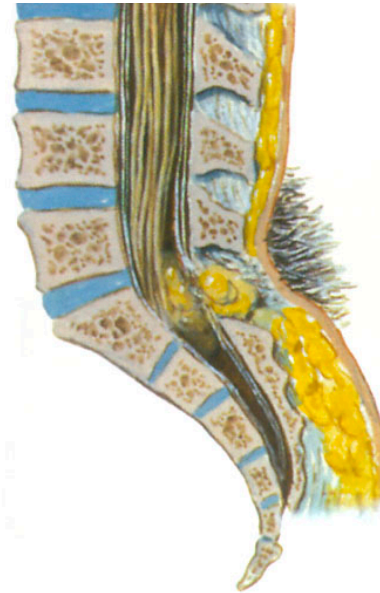
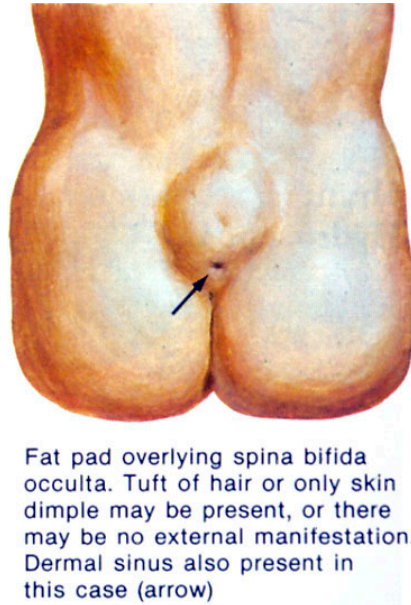
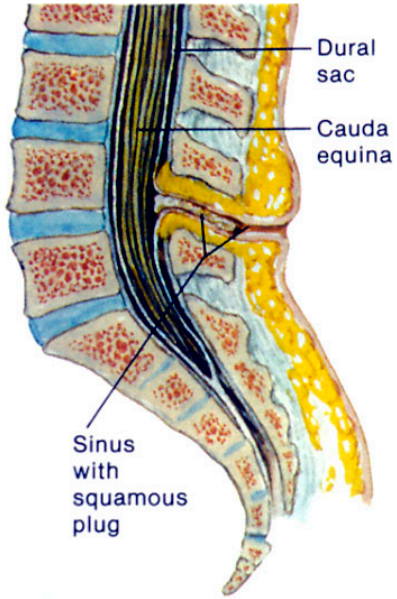
*drawing by Huy Nguyen*

# O-mannosylation of $\alpha$ -dystroglycan



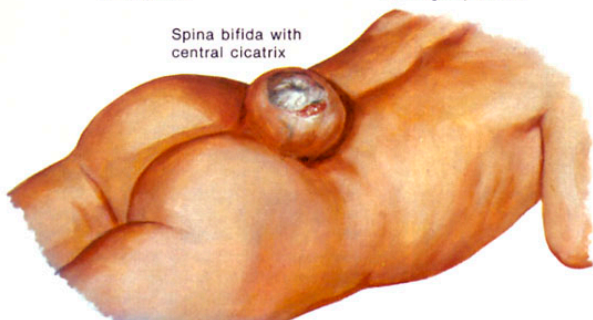
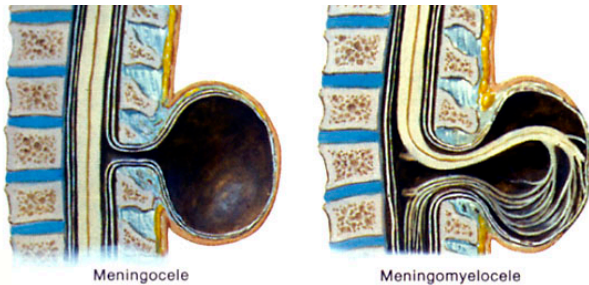


# neural tube closure defects



X-ray film showing deficit of lamina of sacrum (spina bifida occulta)

## meningocele (meningomyelocele)



## encephalocele

