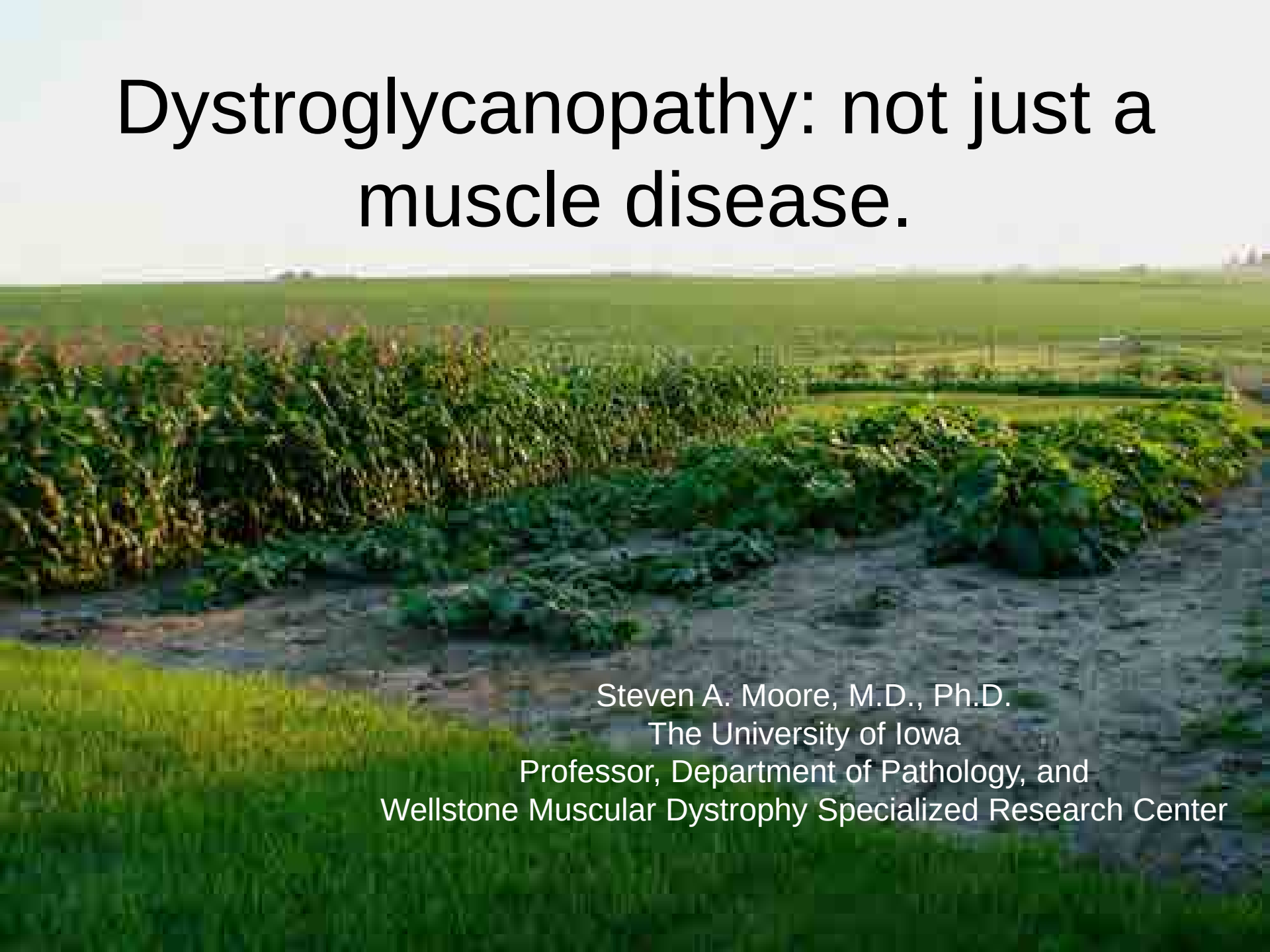
Dystroglycanopathy: not just a muscle disease.



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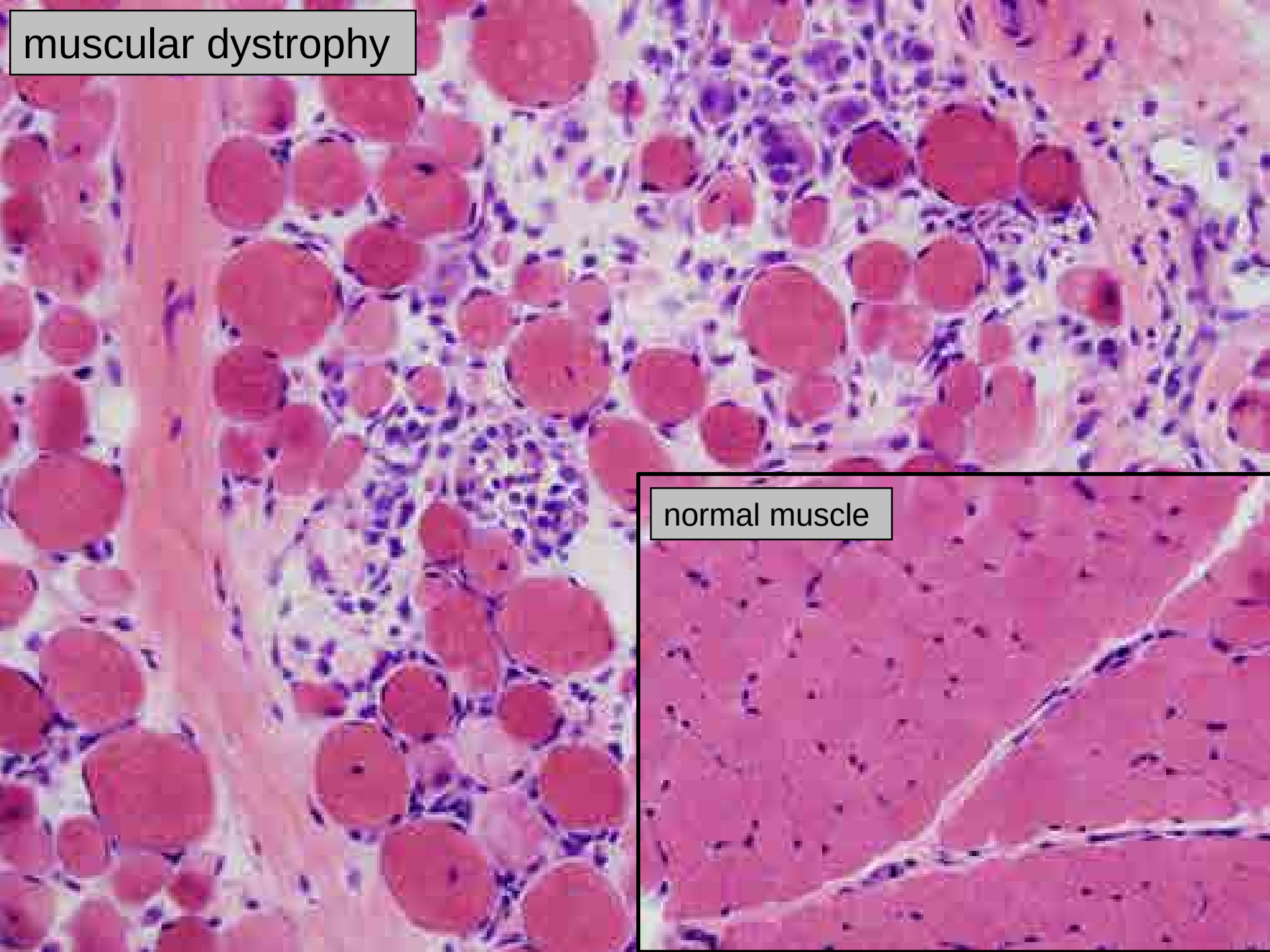
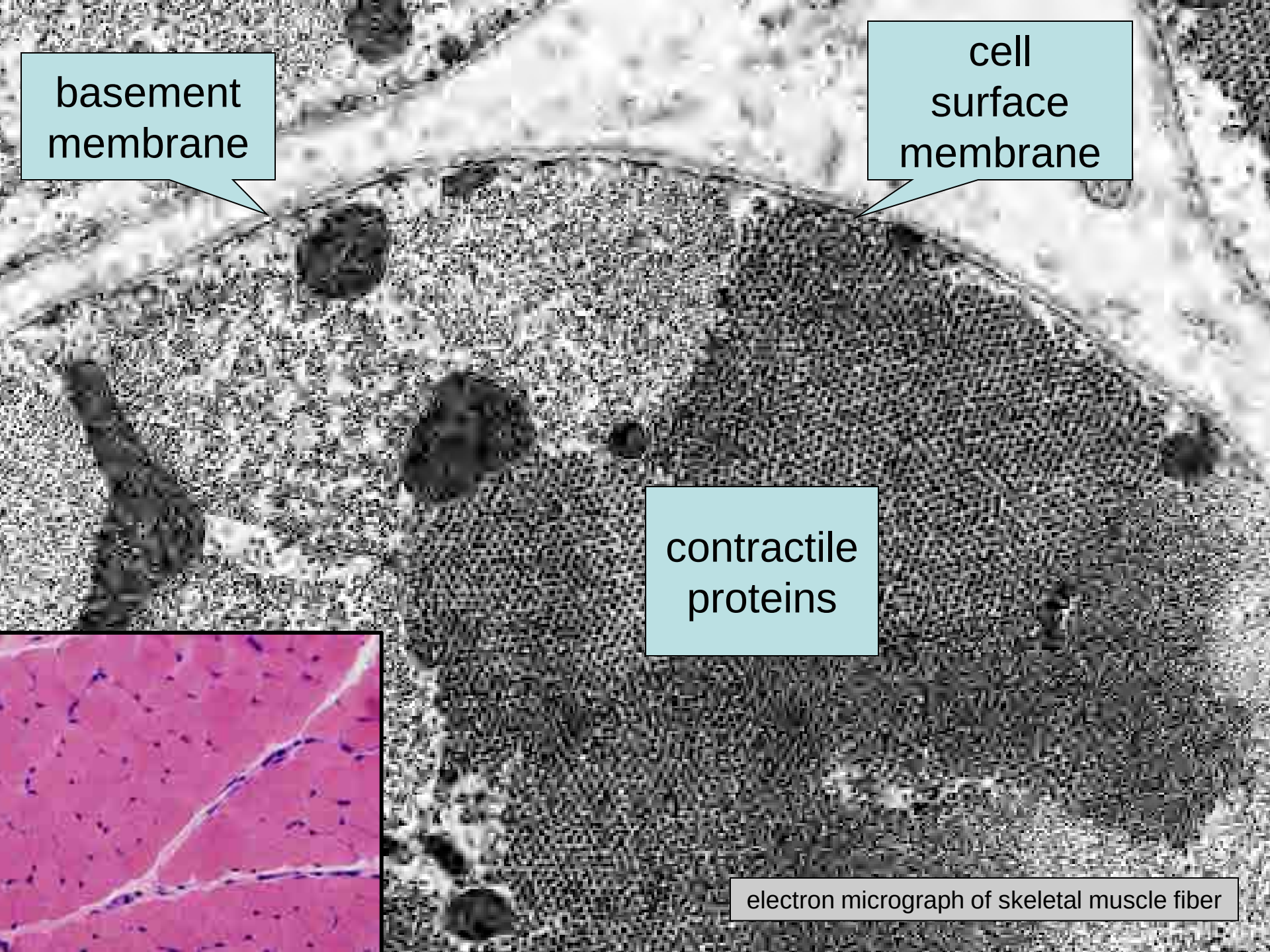
The University of Iowa
Professor, Department of Pathology, and
Wellstone Muscular Dystrophy Specialized Research Center

No financial conflicts of interest to disclose.

dystroglycanopathies

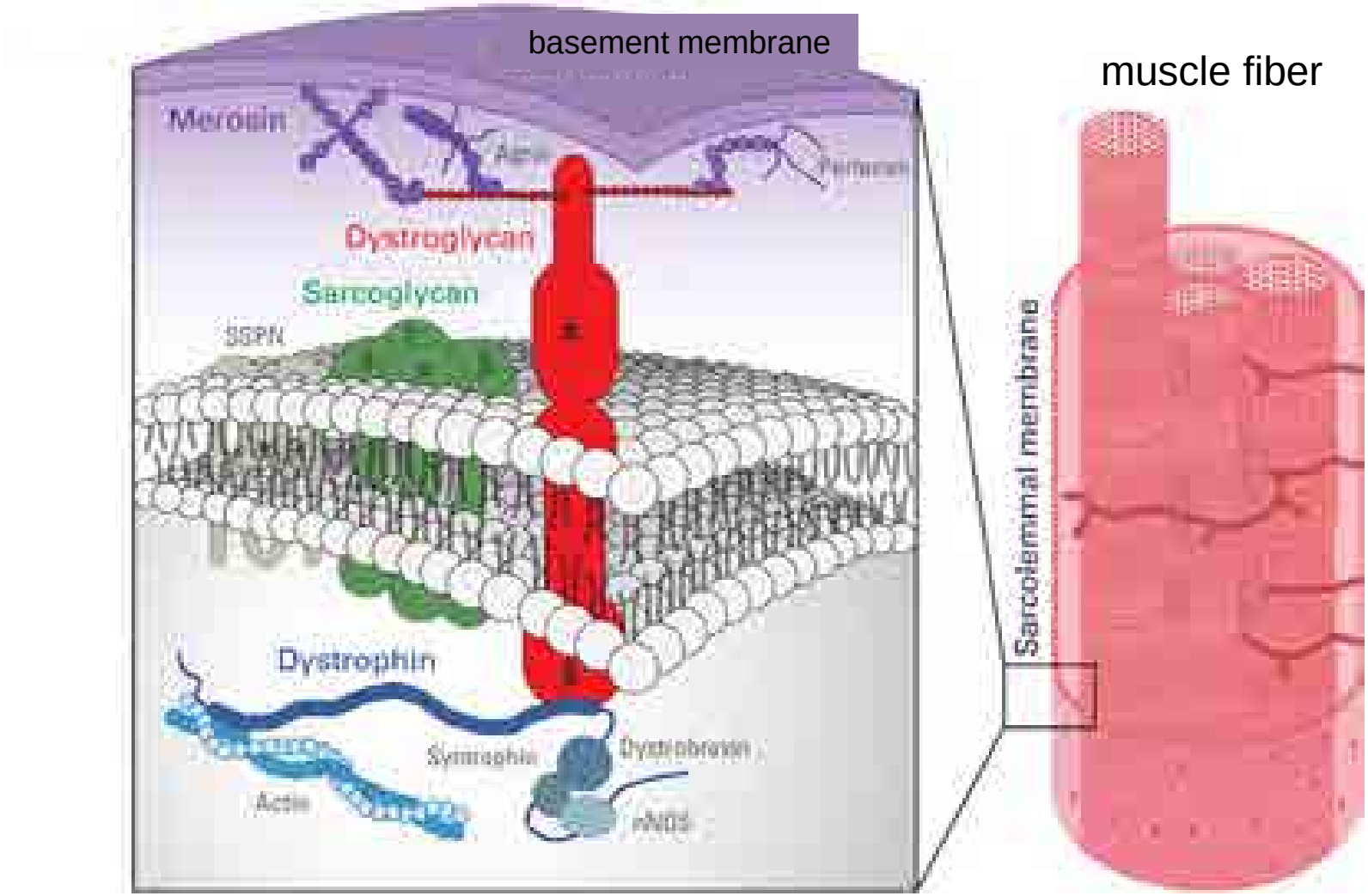
- muscle disease
  - muscular dystrophy
    - congenital muscular dystrophy (CMD)
    - limb-girdle muscular dystrophy (LGMD)
  - cardiomyopathy


muscular dystrophy
normal muscle



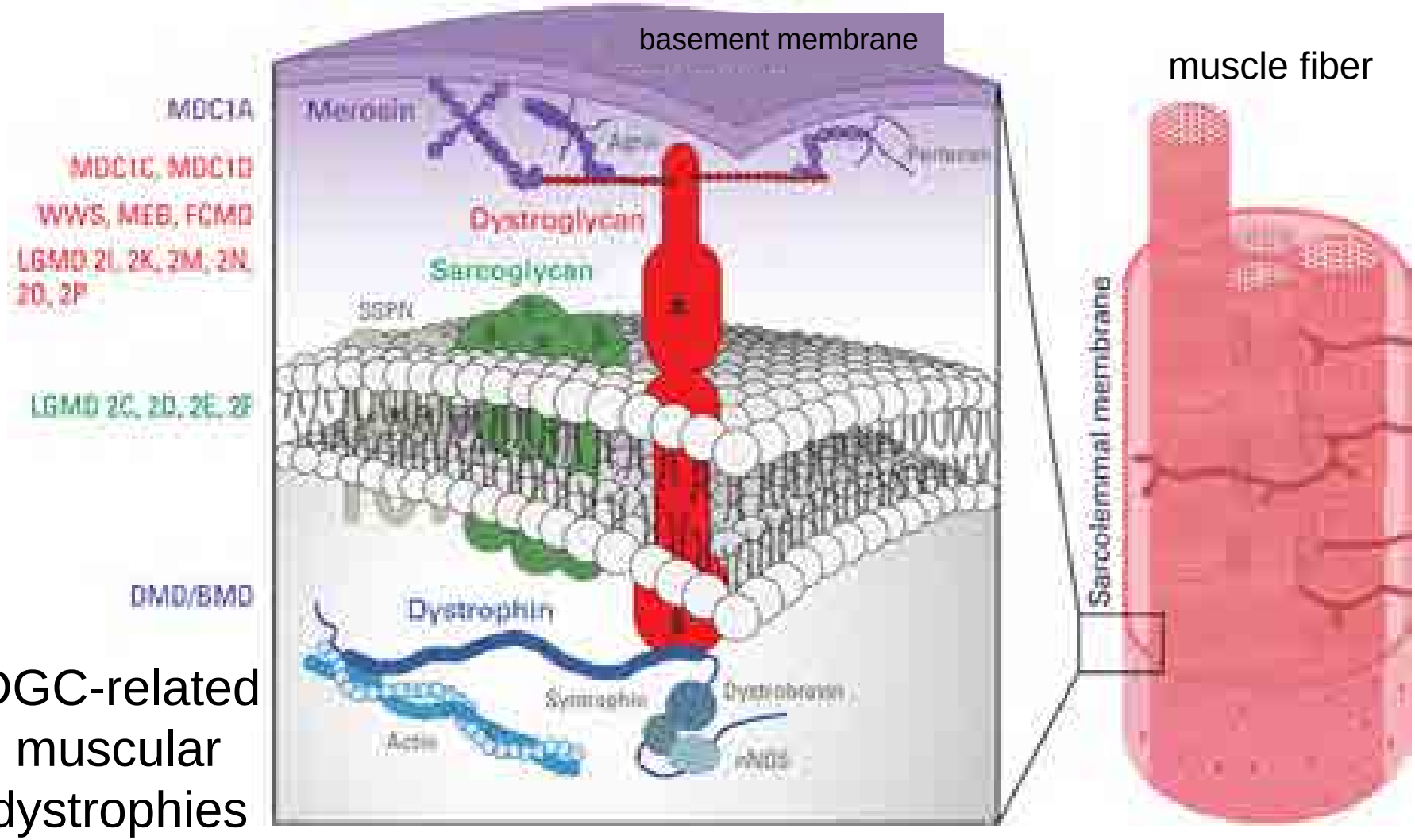
electron micrograph of skeletal muscle fiber

dystrophin-glycoprotein complex (DGC)



drawing by Huy Nguyen

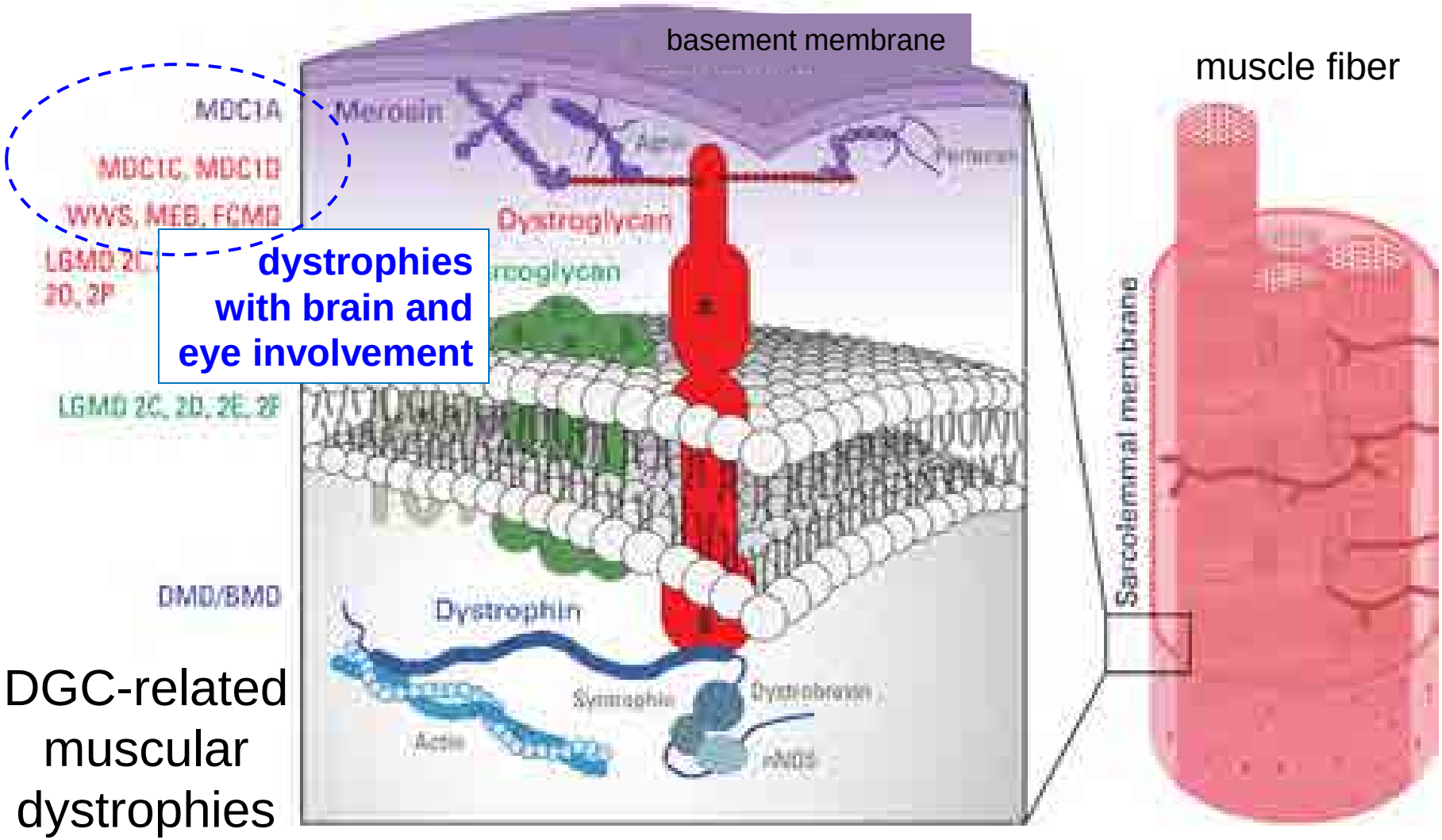
dystrophin-glycoprotein complex (DGC)



DGC-related muscular dystrophies

drawing by Huy Nguyen

dystrophin-glycoprotein complex (DGC)



DGC-related muscular dystrophies

drawing by Huy Nguyen

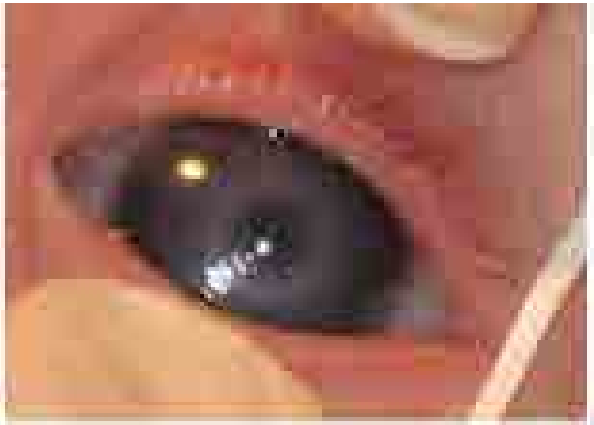
dystroglycanopathies

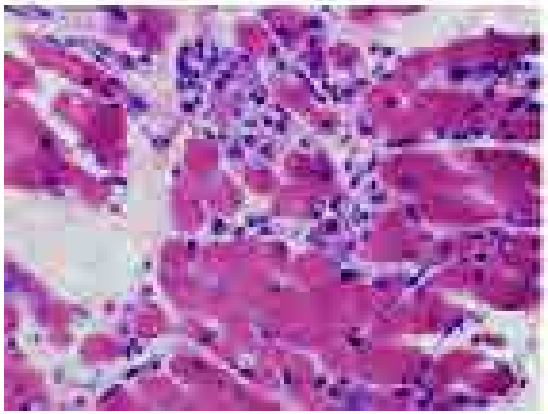
- muscle disease
  - CMD and LGMD
  - cardiomyopathy
- brain disease
- eye disease
- peripheral nerve disease (at least in mouse models)

dystroglycanopathies with brain and eye involvement

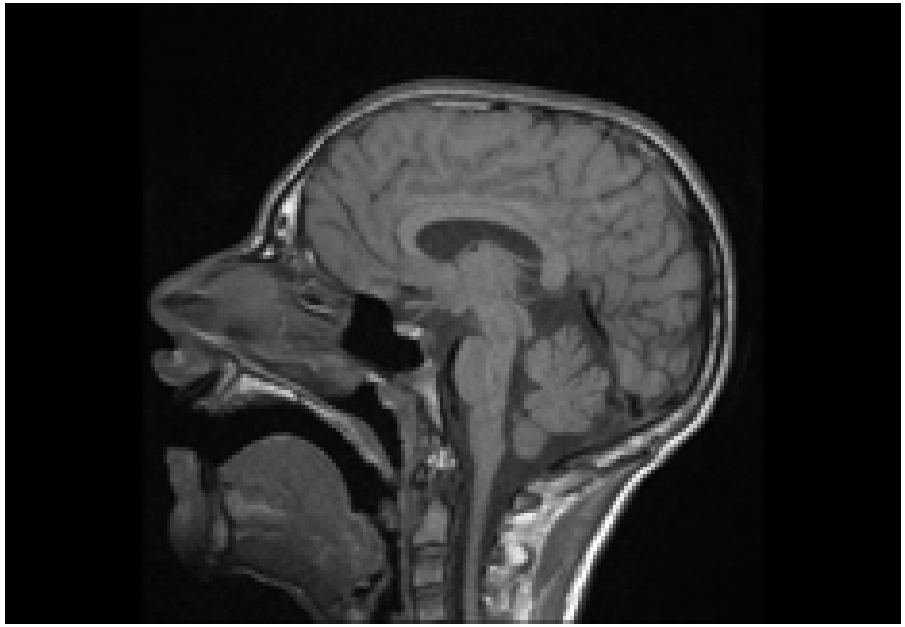
- Walker-Warburg syndrome – WWS
- muscle-eye-brain disease – MEB
- Fukuyama congenital muscular dystrophy – FCMD
- cerebellar hypoplasia / cerebellar cysts
- congenital muscular dystrophy (CMD) or limb-girdle muscular dystrophy (LGMD) with cognitive impairment (brain may appear to be structurally normal)

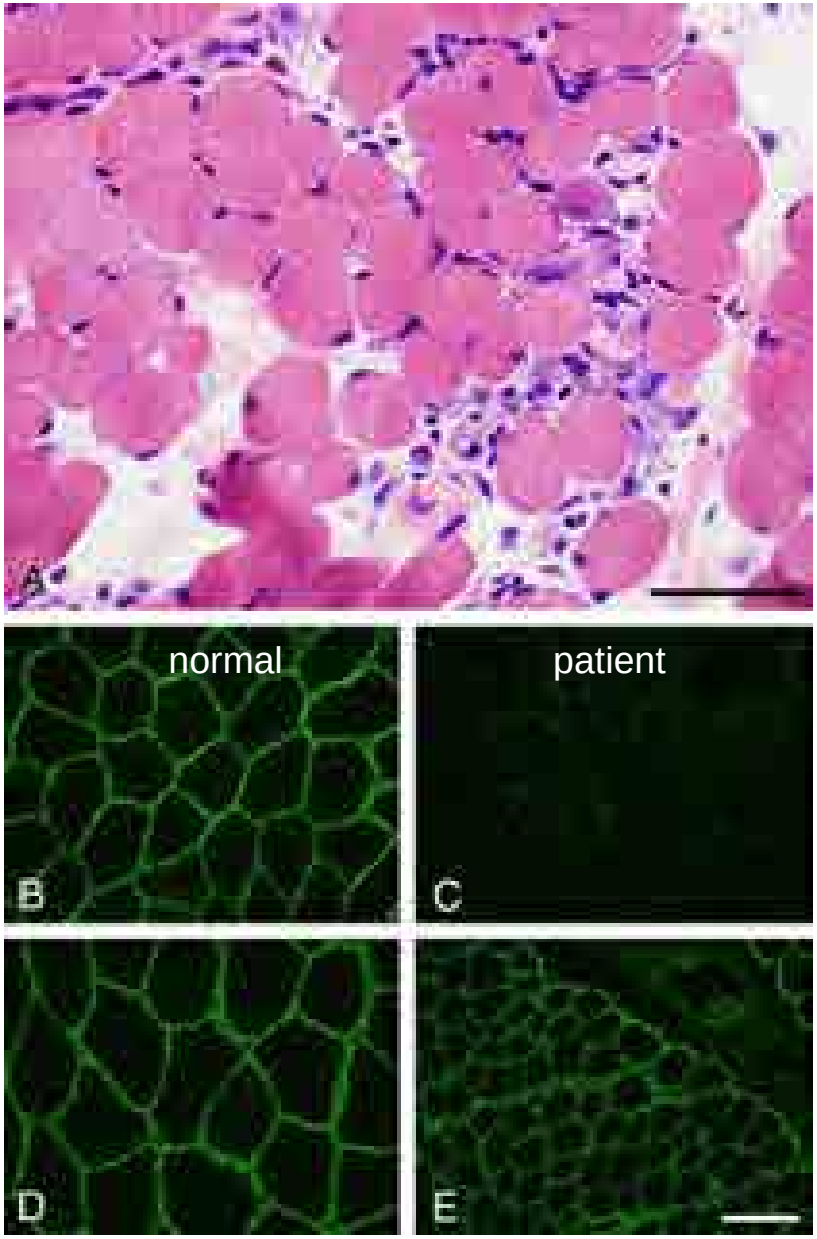
WWS





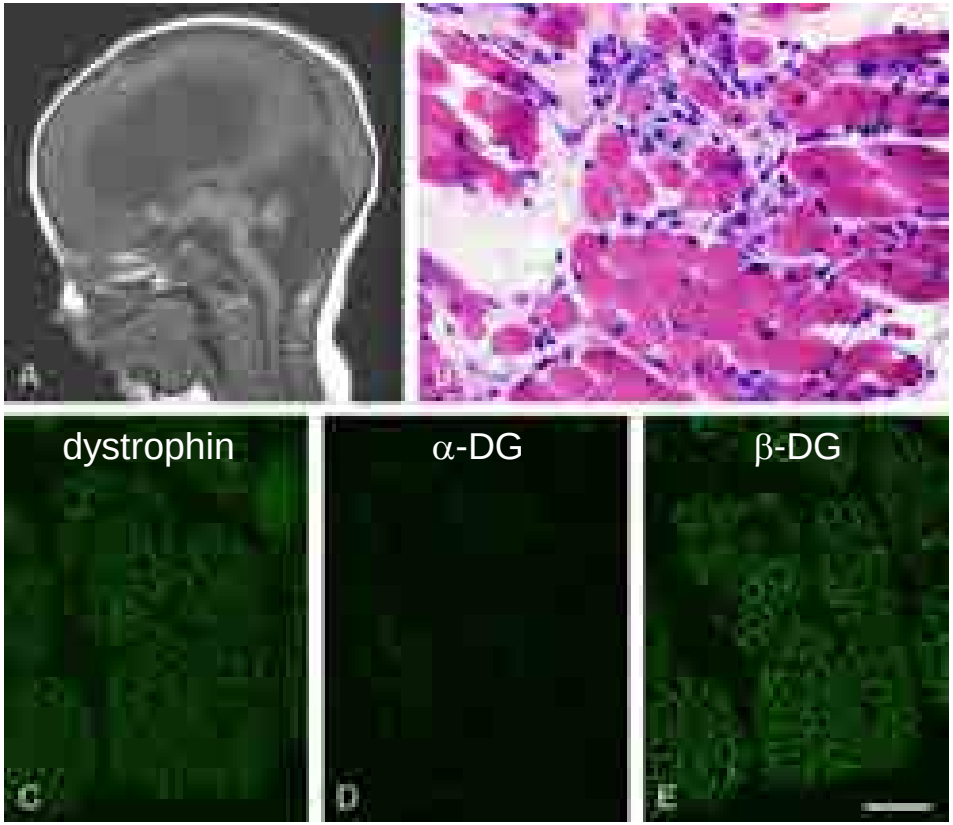
CMD with cognitive impairment



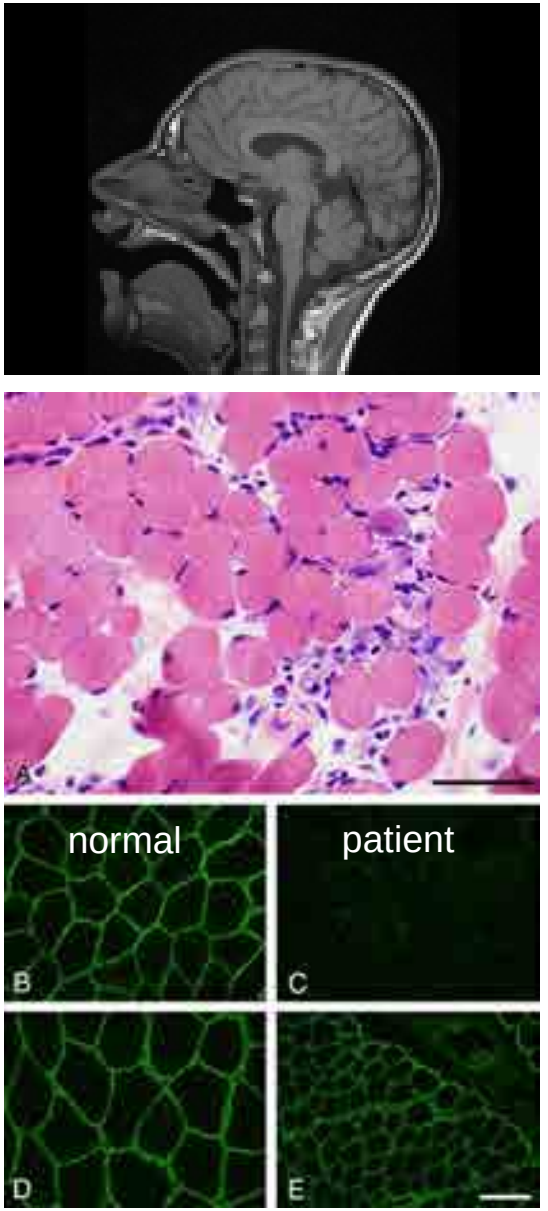


Wallace *et al., Neuromuscular Disorders* 24:312–320, 2014

Walker-Warburg syndrome (WWS)



CMD with cognitive impairment



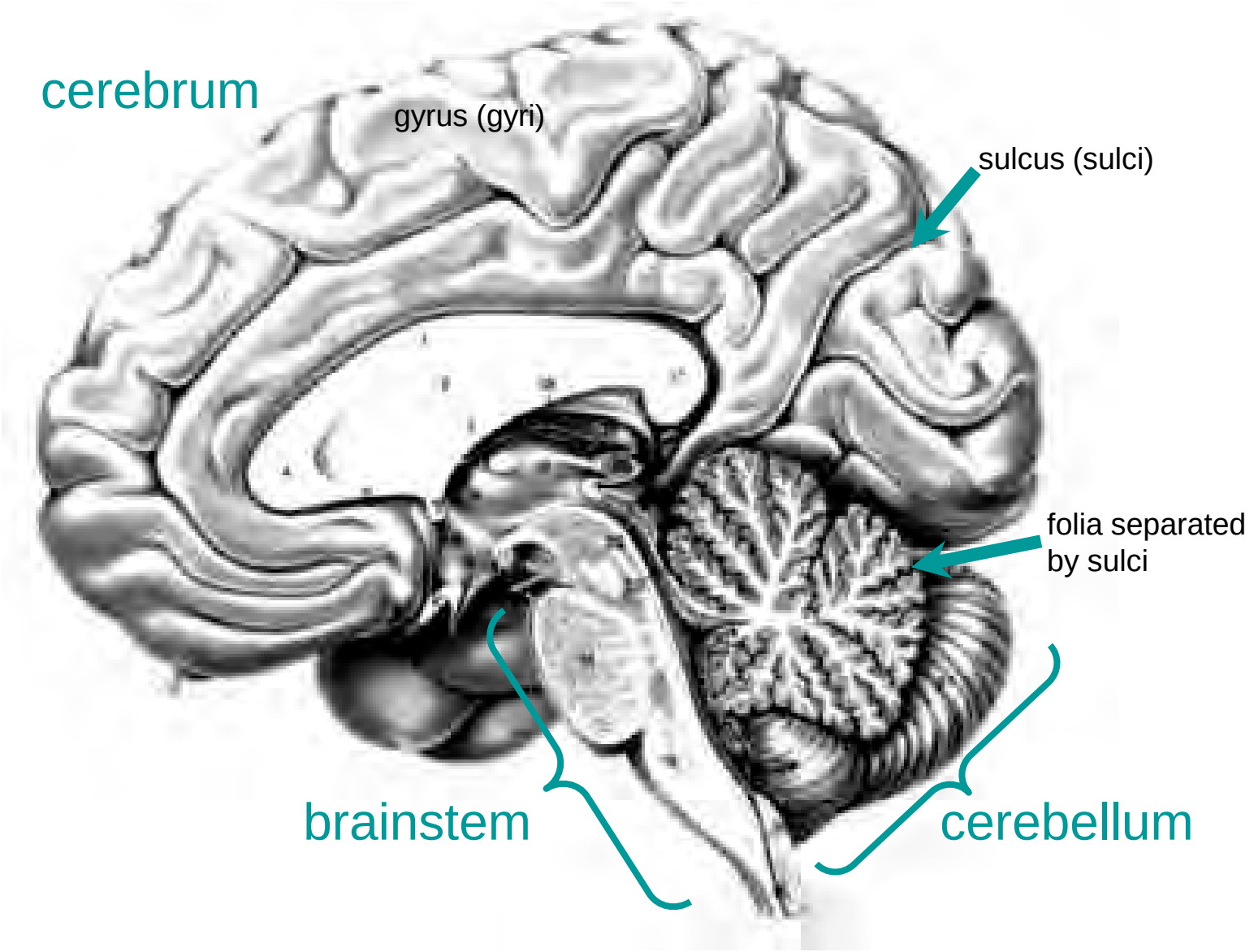
both cases have *POMT1* mutations

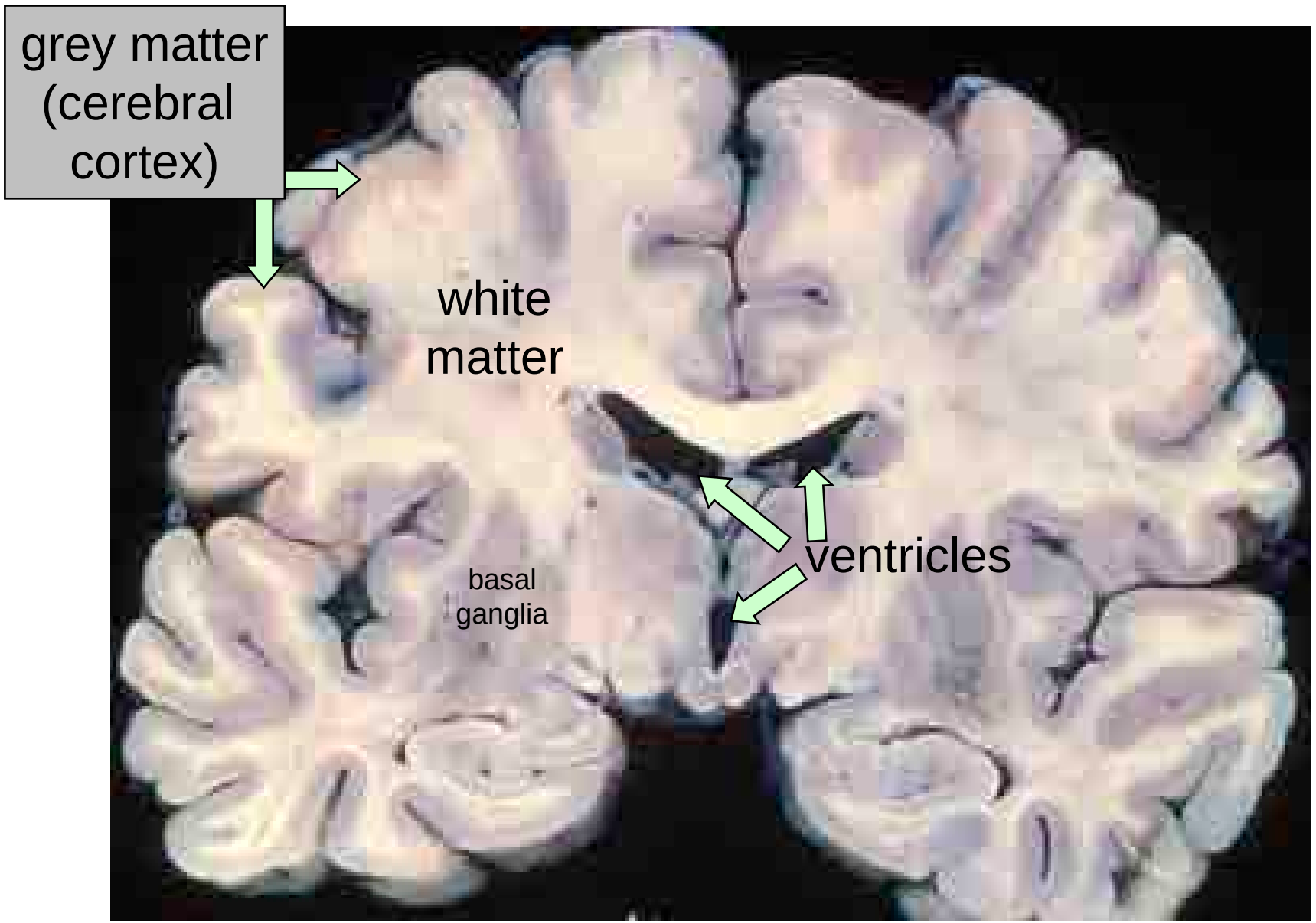
Wallace *et al., Neuromuscular Disorders* 24:312–320, 2014

neuroanatomy

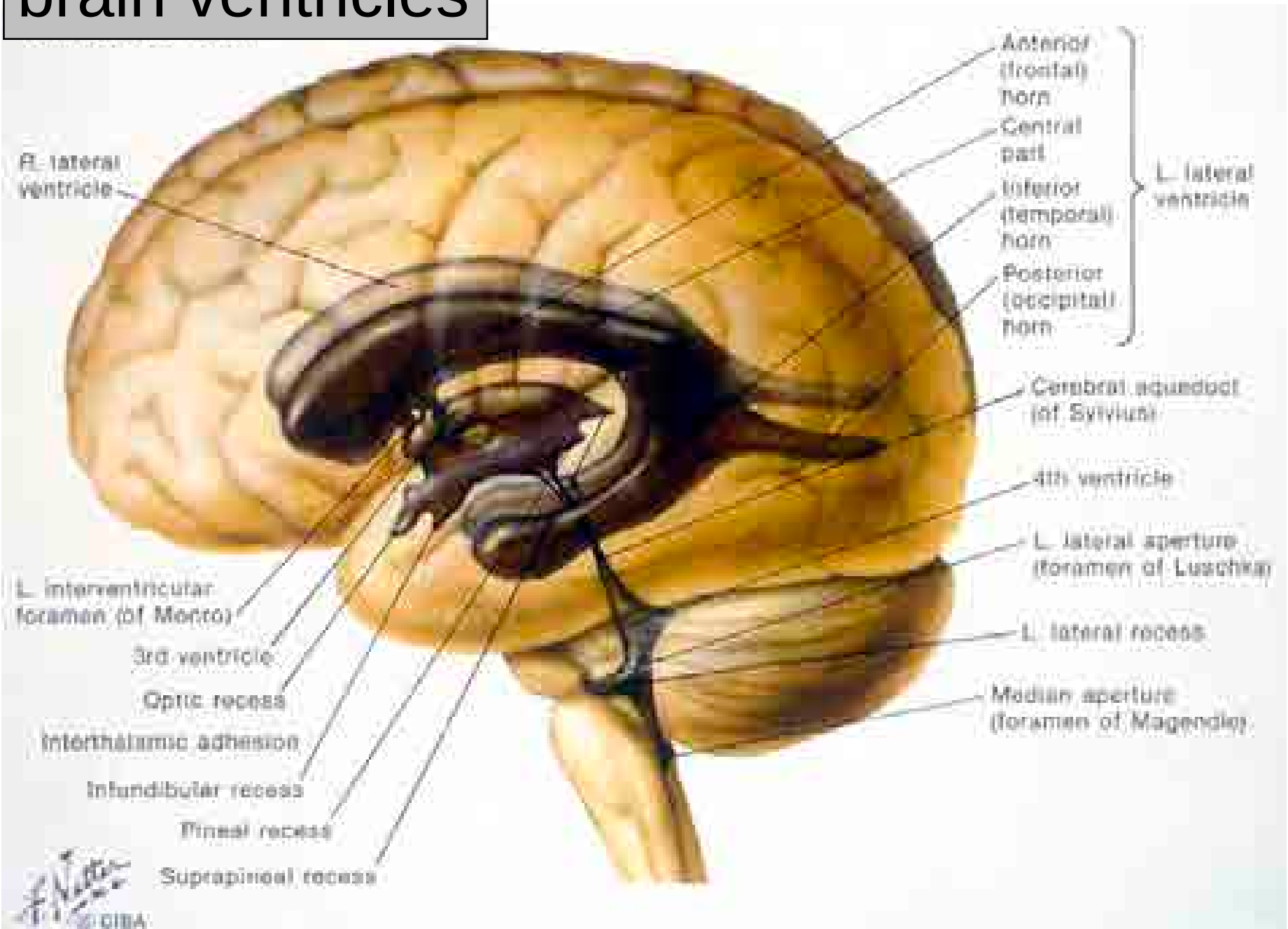
- a few key concepts -

brain

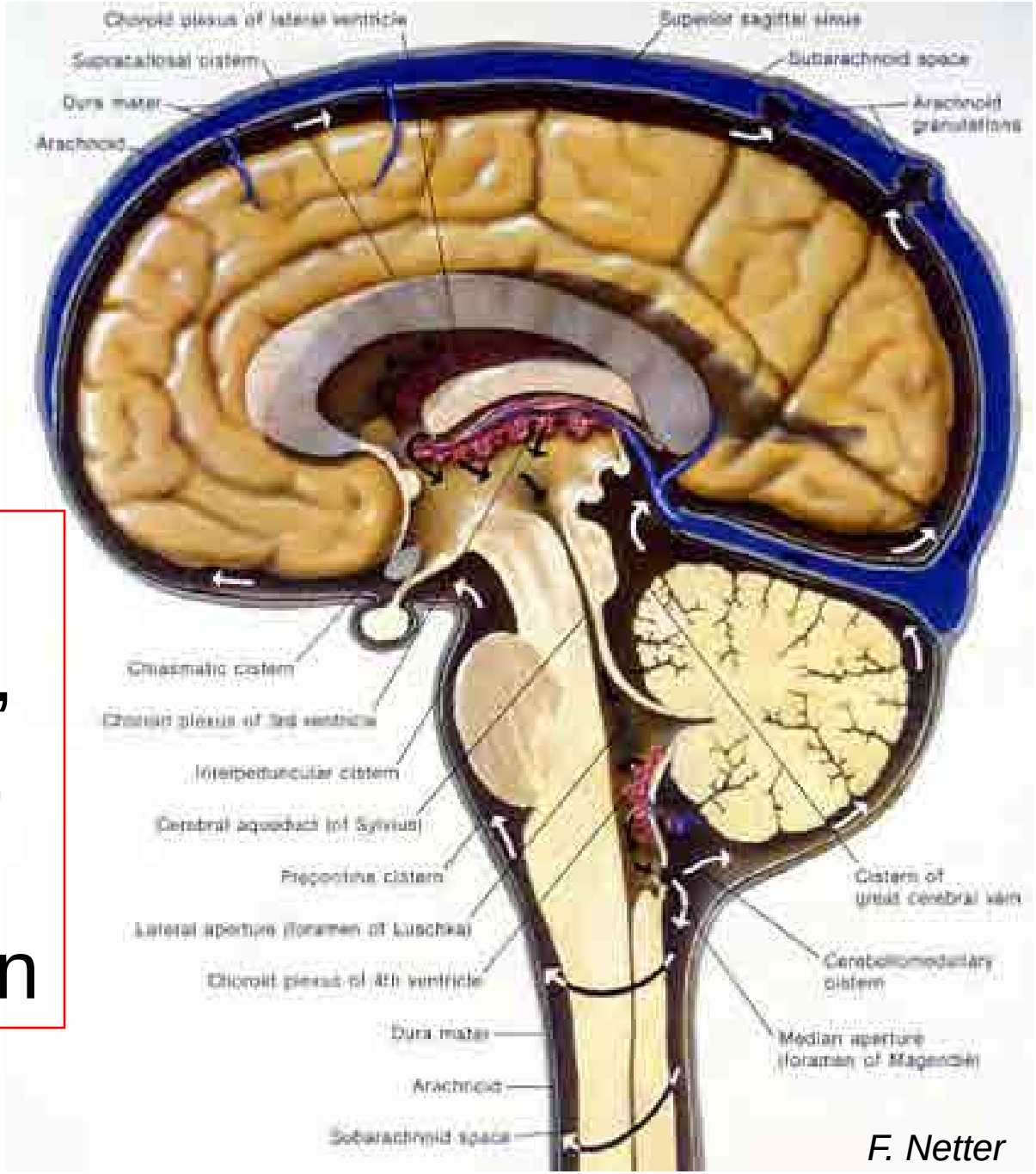

cerebrum
gyrus (gyri)
sulcus (sulci)
folia separated by sulci
brainstem
cerebellum


grey matter (cerebral cortex)
white matter
ventricles
basal ganglia

brain ventricles



CSF production, circulation, and reabsorption

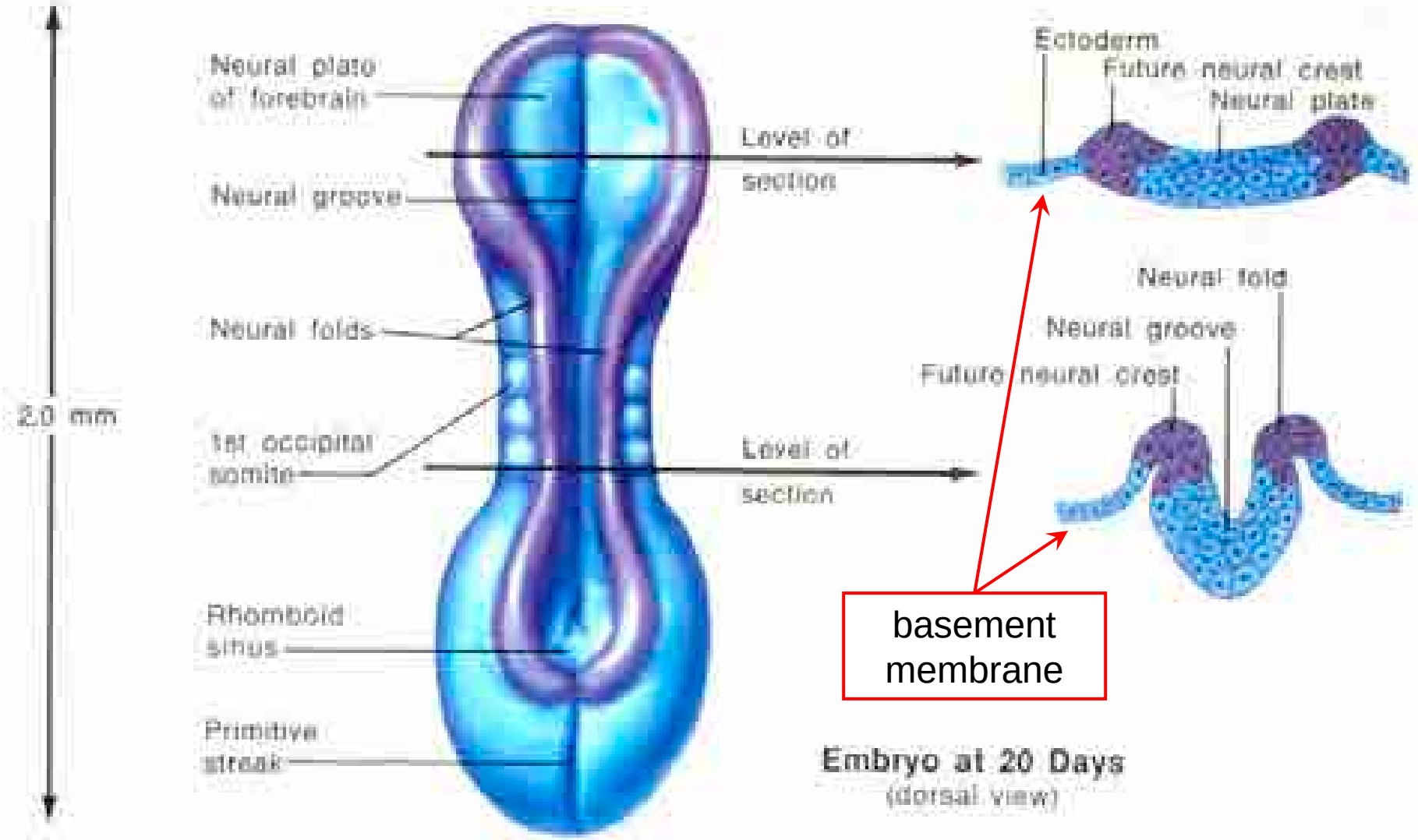


F. Netter

developmental neurobiology

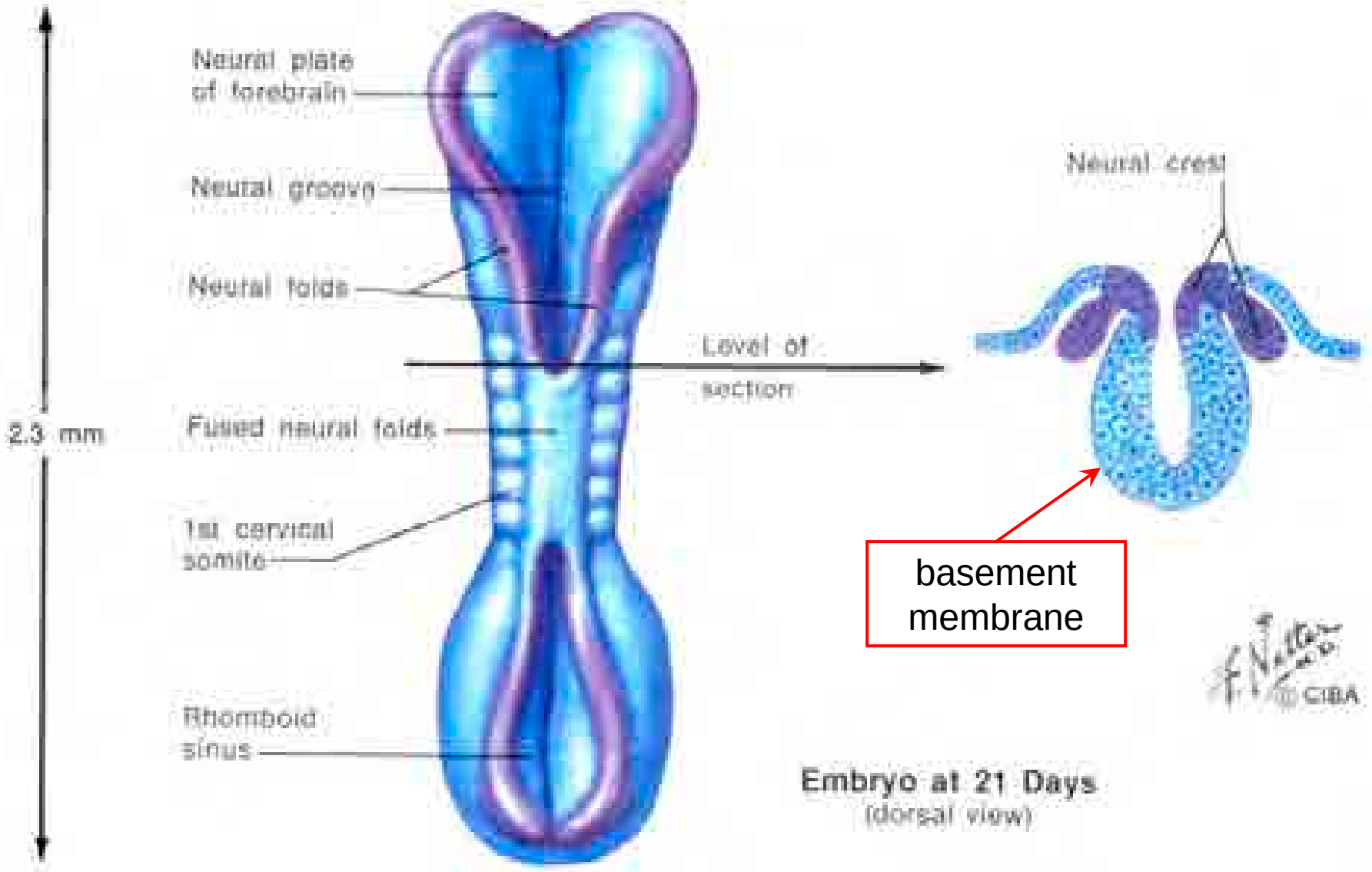
- normal brain development in five slides -

normal neural tube closure

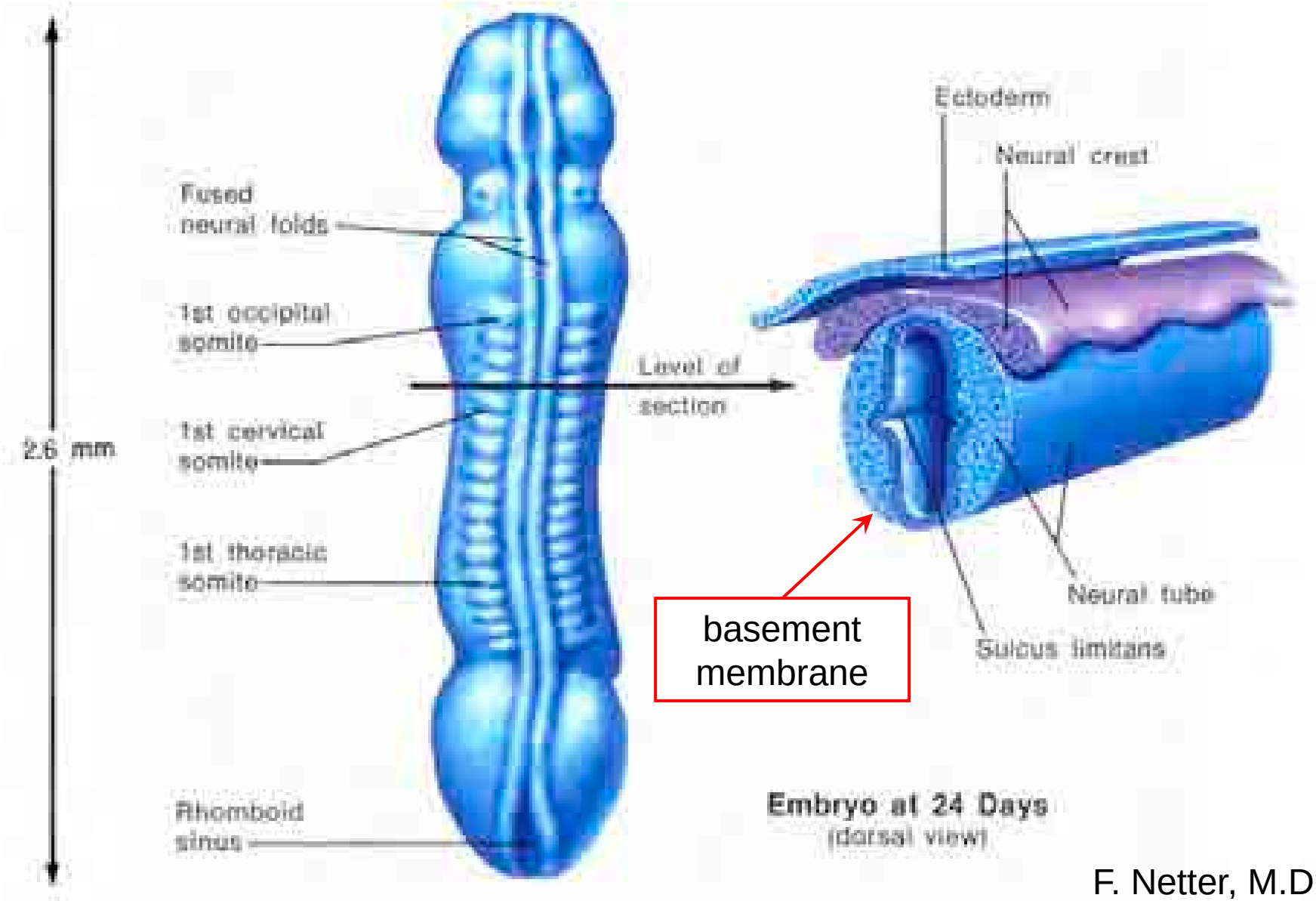


F. Netter, M.D.

normal neural tube closure



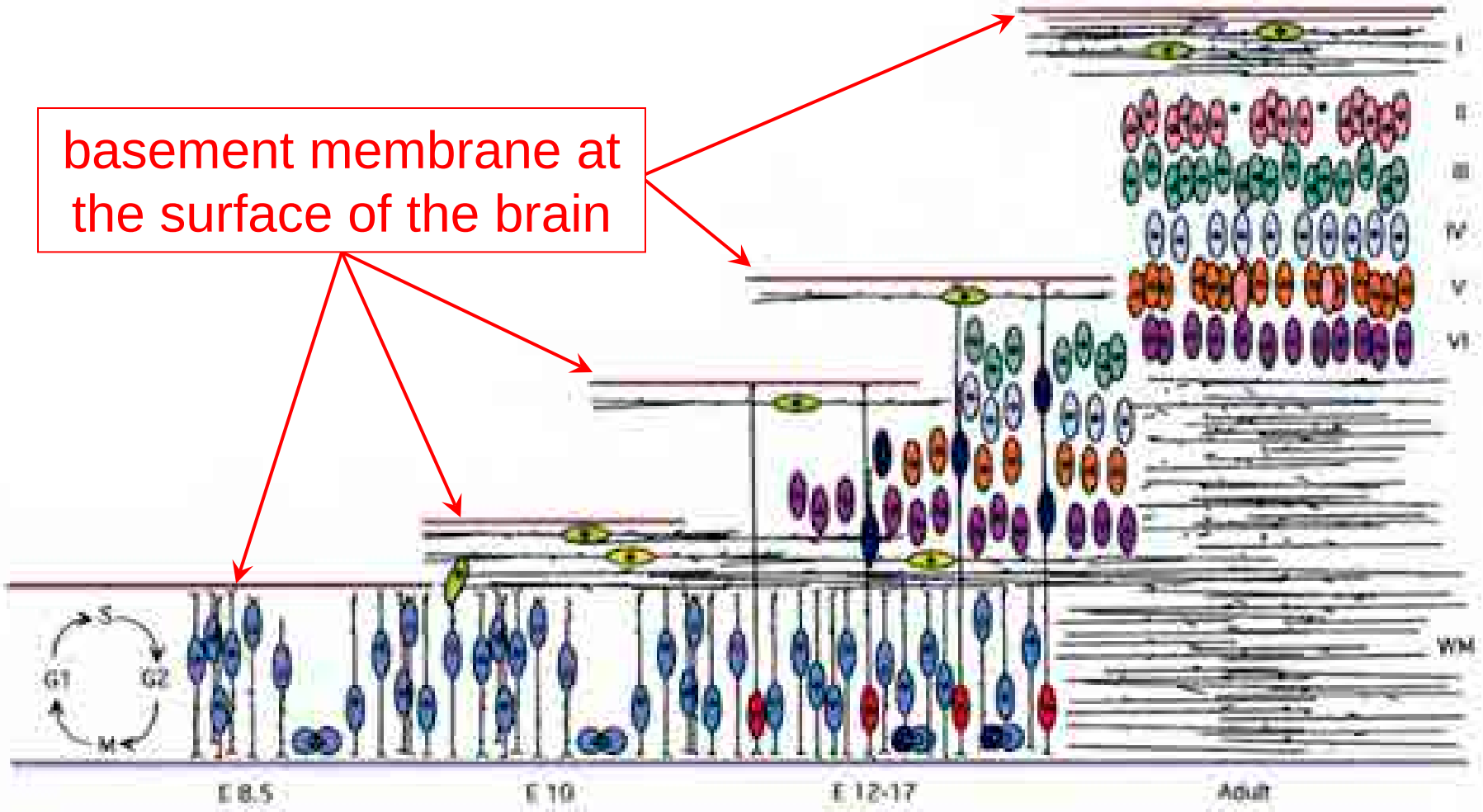
normal neural tube closure



F. Netter, M.D.

normal cerebral cortex development

basement membrane at the surface of the brain



inside of neural tube → ventricle

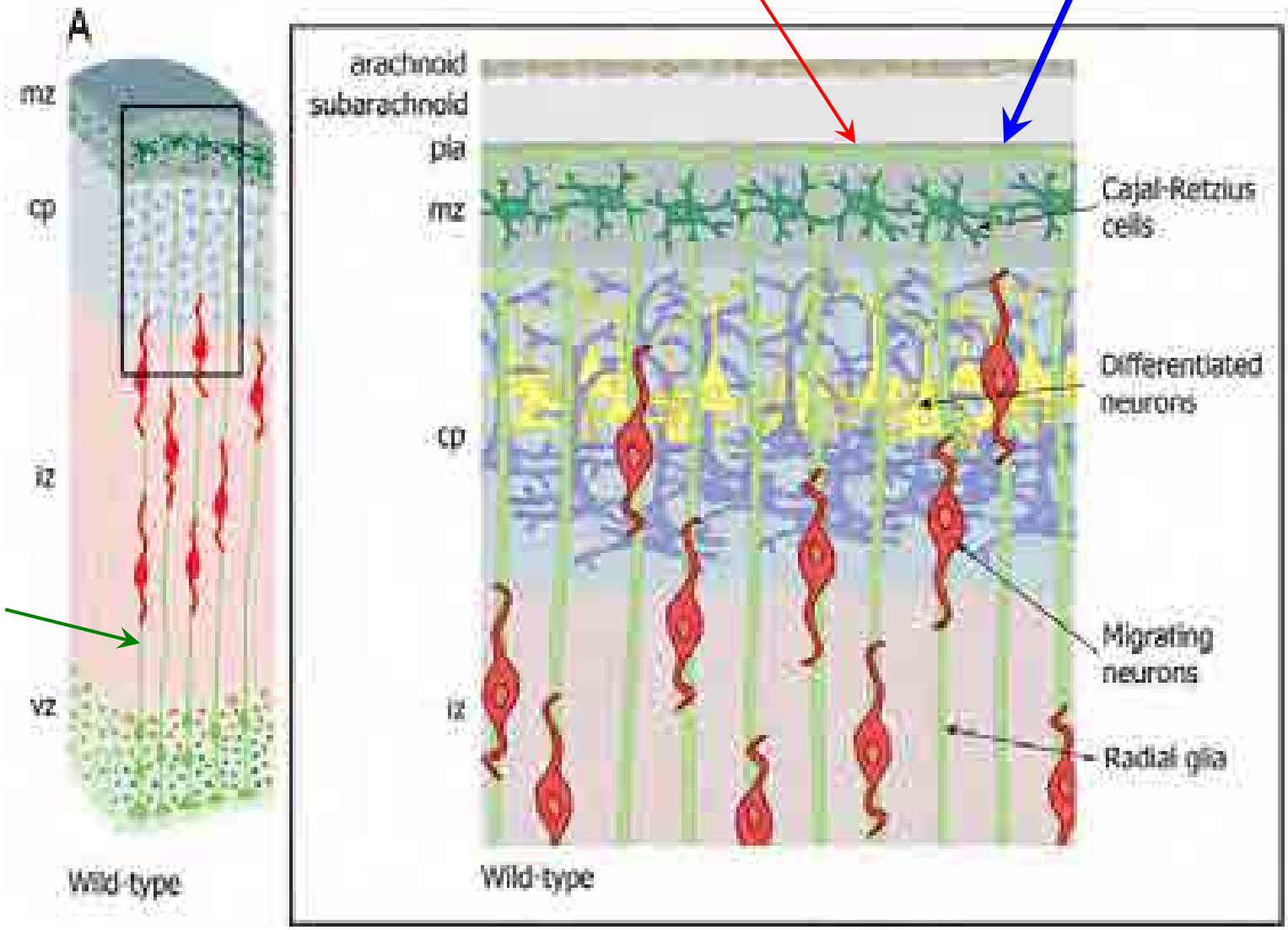
Developmental Neuropathology, ISN, 2004, p.35.

normal development

basement membrane

dystroglycan

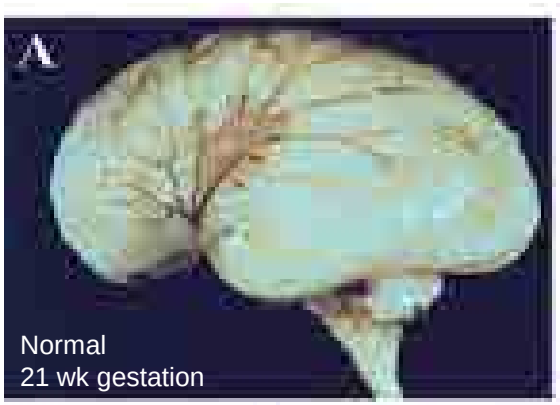
radial glia

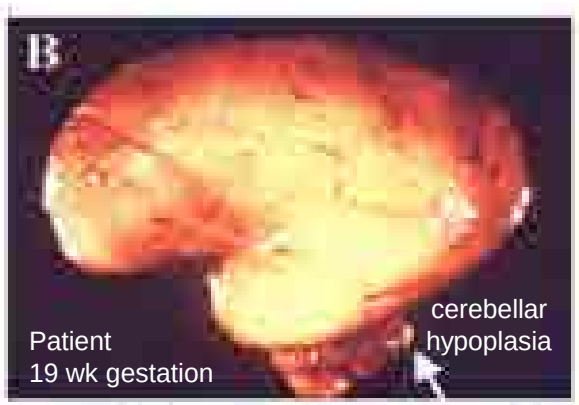


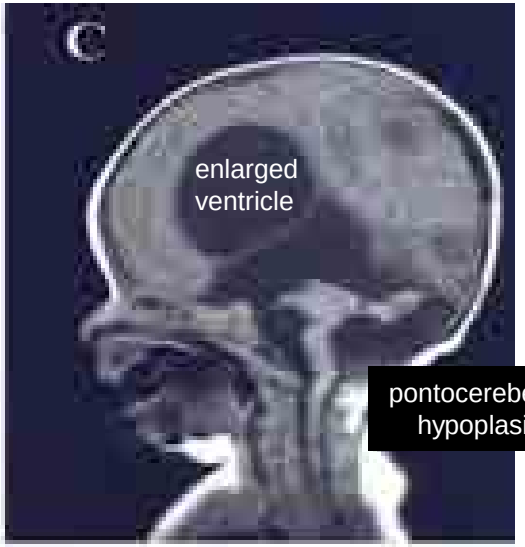
Myshrall et al., J Neuropathol Exp Neurol, 71:1047-1063 2012.

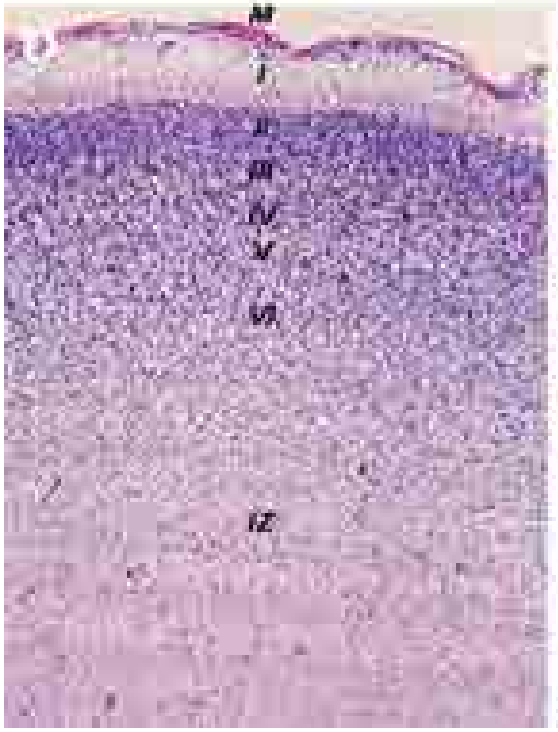
drawing by Huy Nguyen

Brain malformations in WWS patients with *POMT1* mutations

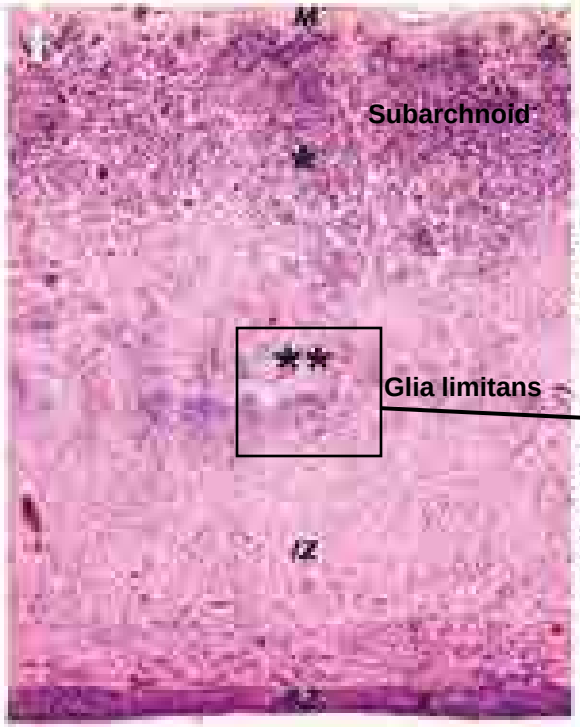




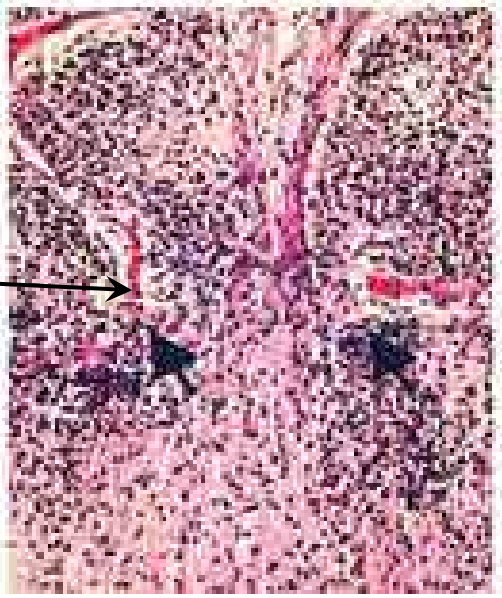




Normal



Patient

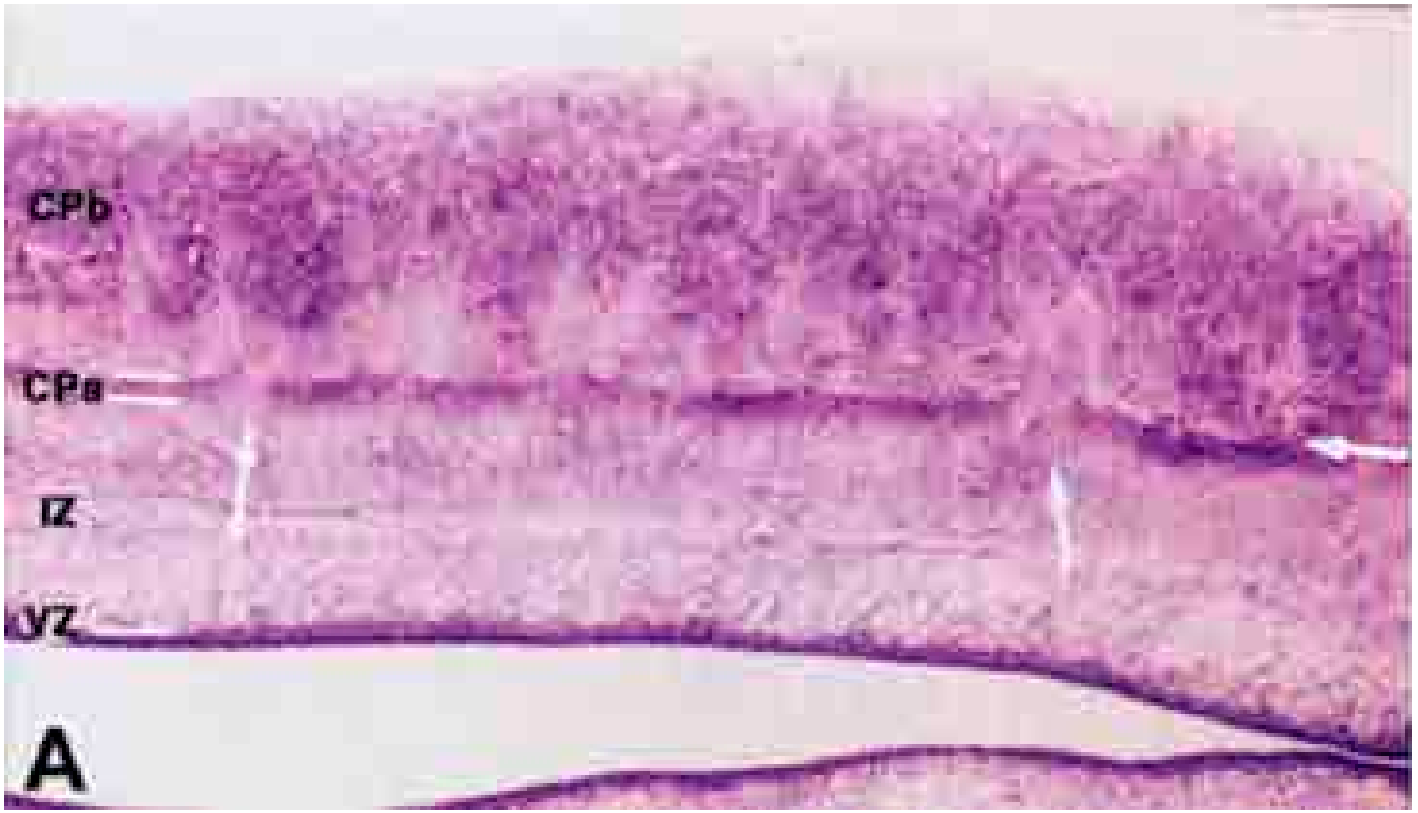


Glia limitans

Beltran-Valero de Bernabe et al., 2002

abnormal cerebral development

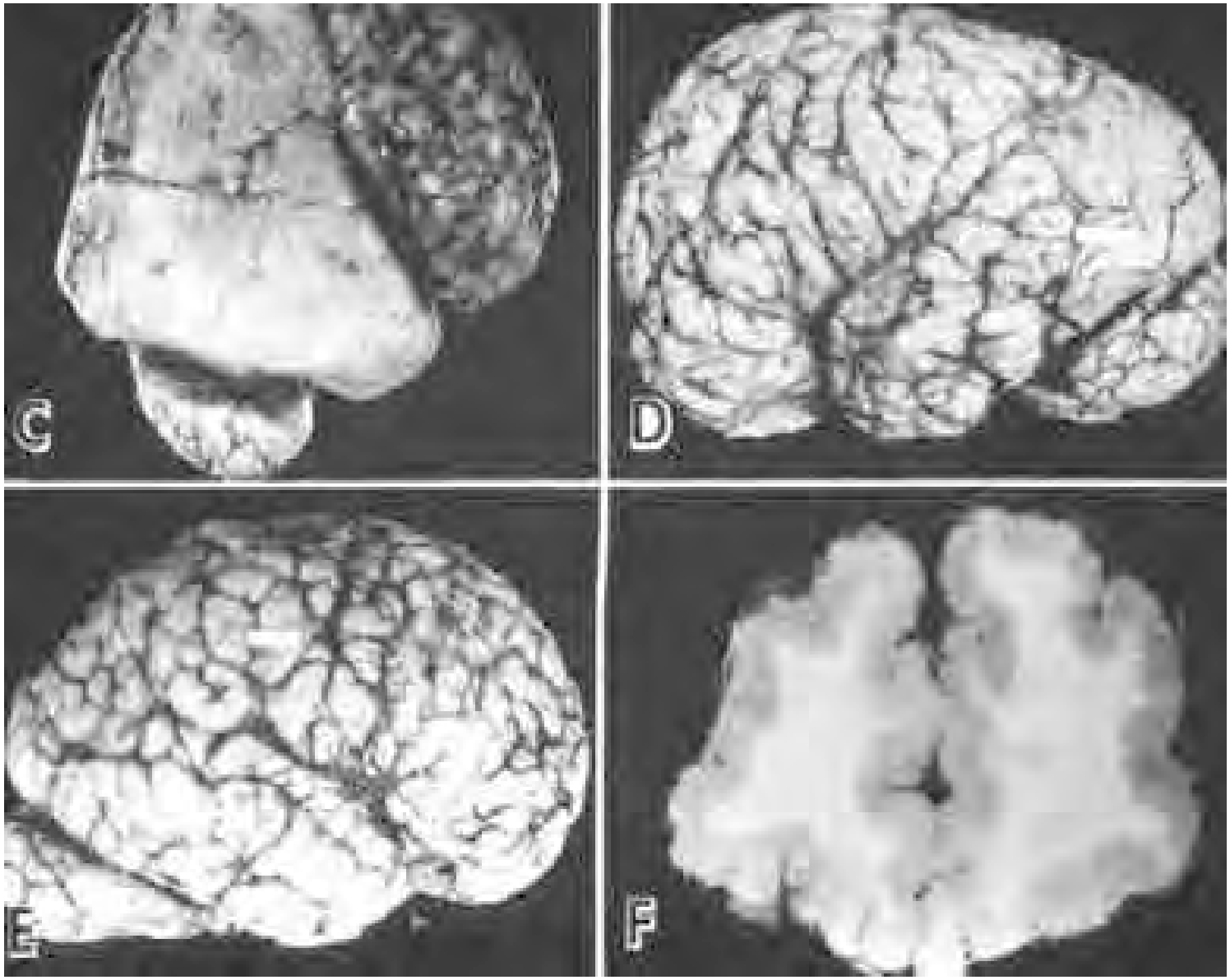
obliterating the subarachnoid space causes hydrocephalus



Walker-Warburg syndrome cerebrum - 21 week fetus

Developmental Neuropathology, ISN, 2004, p.45.

Fukuyama CMD - cobblestone lissencephaly



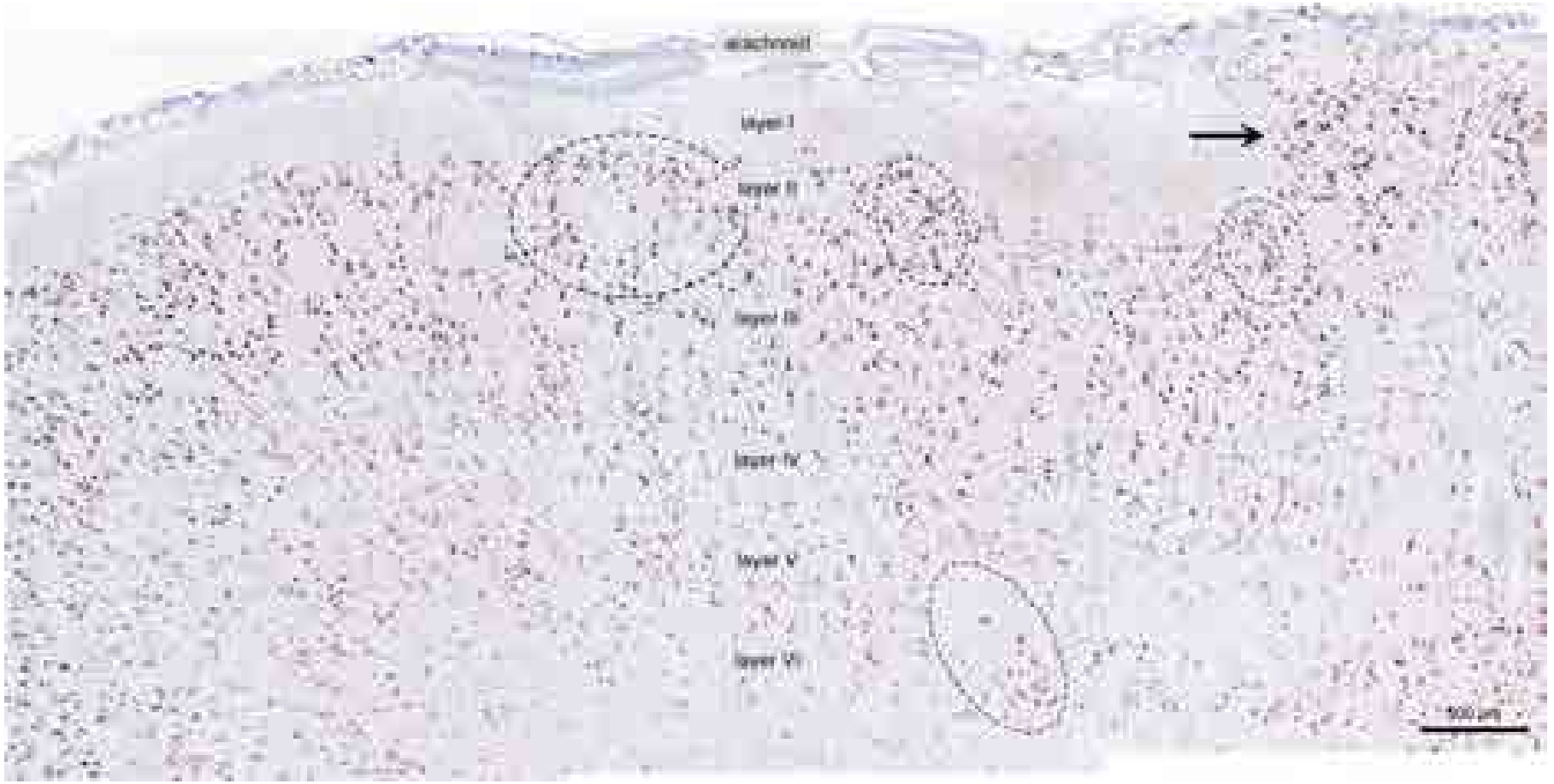
JNEN 43:395-407, 1984

cobblestone lissencephaly (malformation)

cobblestone lissencephaly (malformation)

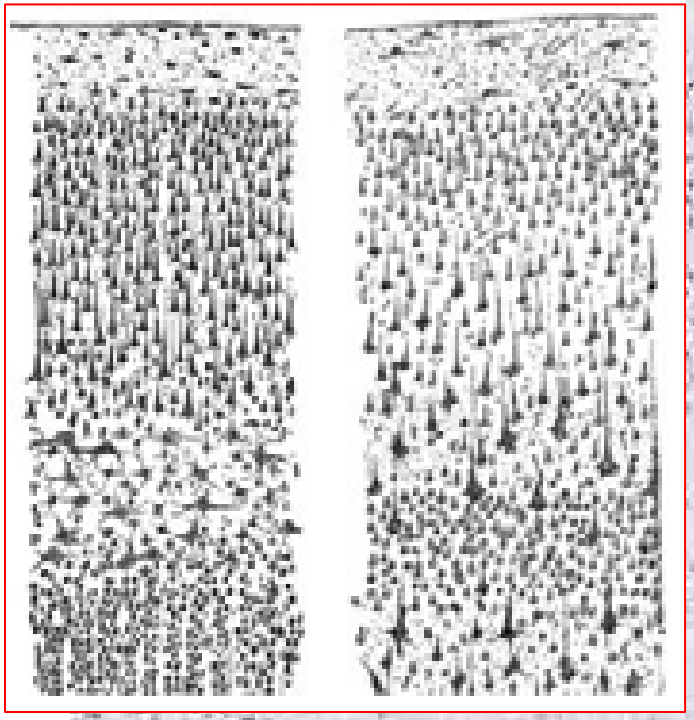
cobblestone malformation – fusion across sulci

cobblestone malformation – abnormal cortical architecture and glioneuronal heterotopion



cobblestone malformation – abnormal cortical architecture and glioneuronal heterotopion

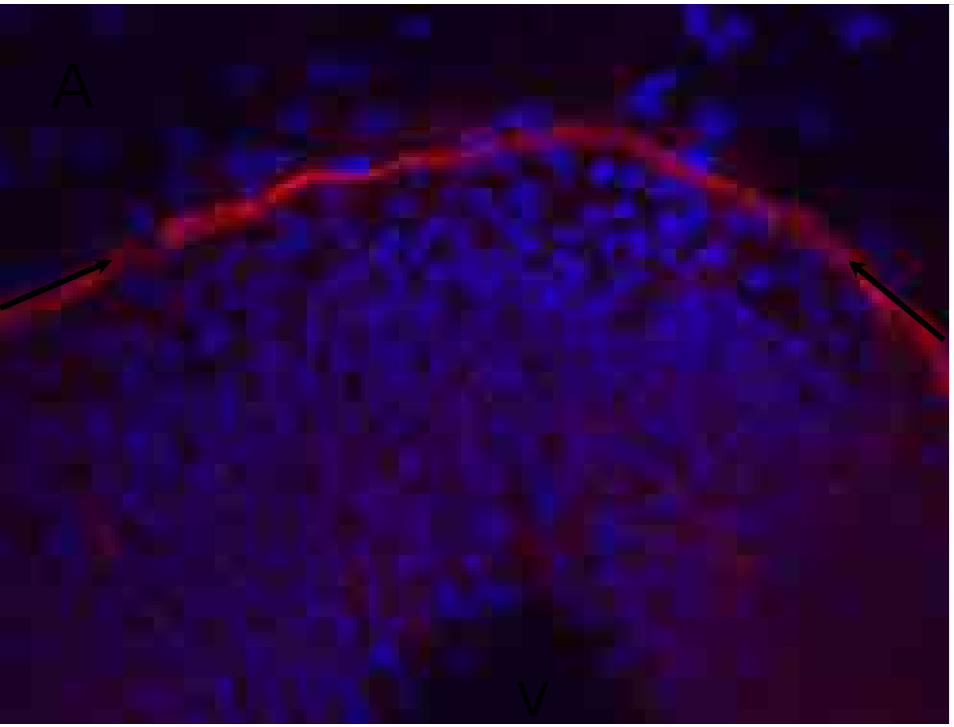
normal cortical architecture
Cajal (circa 1900)



dystroglycan immunofluorescence in DG-null brain

wt E13.5 cerebrum

DG-null E13.5 cerebrum



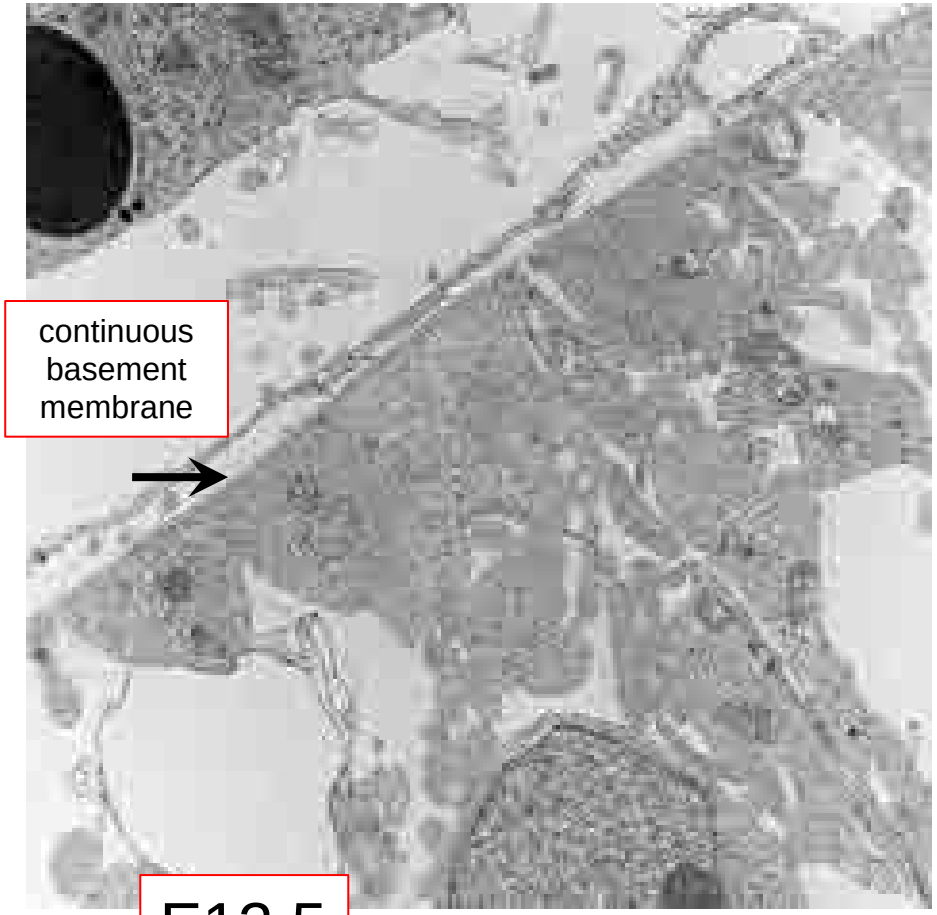
dystroglycan/DAPI

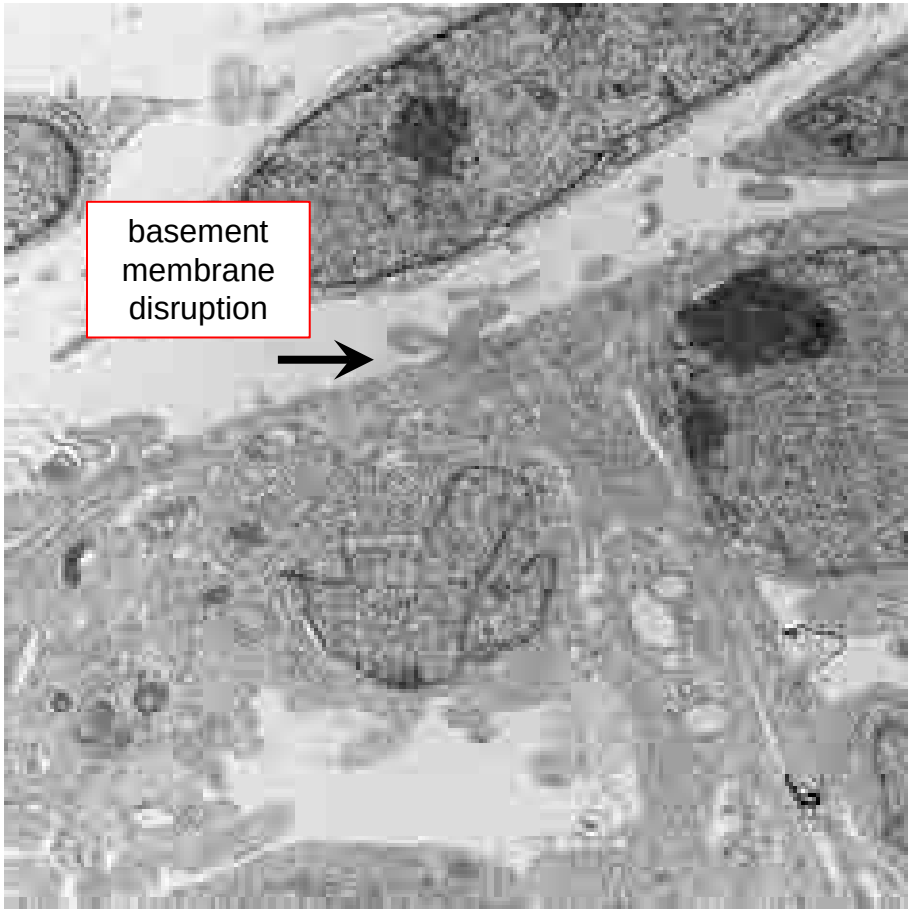
Satz et al., J Neurosci 30:14560-14572, 2010.

ultrastructural glial limitans disruption

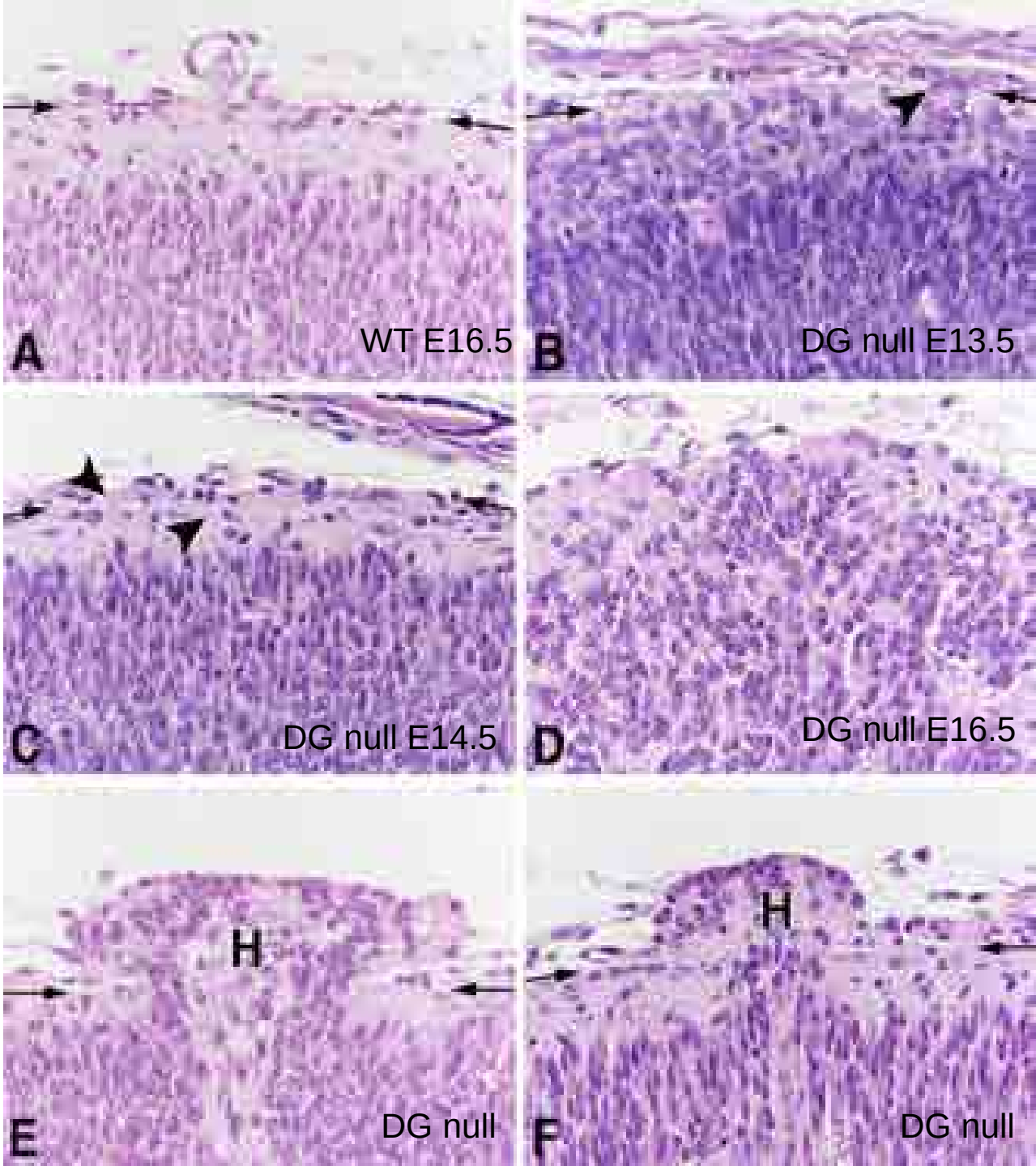
wild type

Nestin-Cre/DG-null



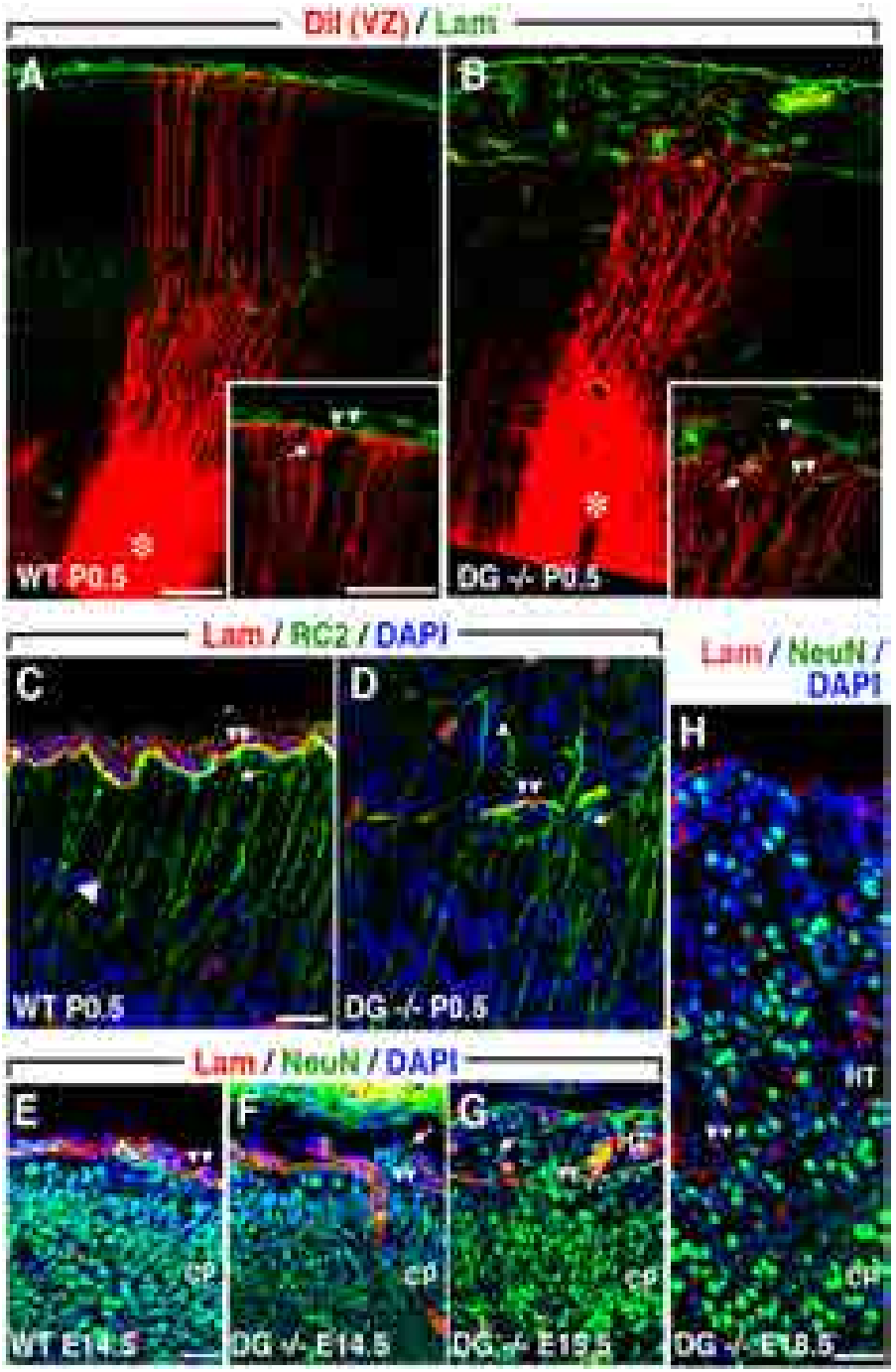


Glial-neuronal heterotopia begin to form at the same time dystroglycan is lost.



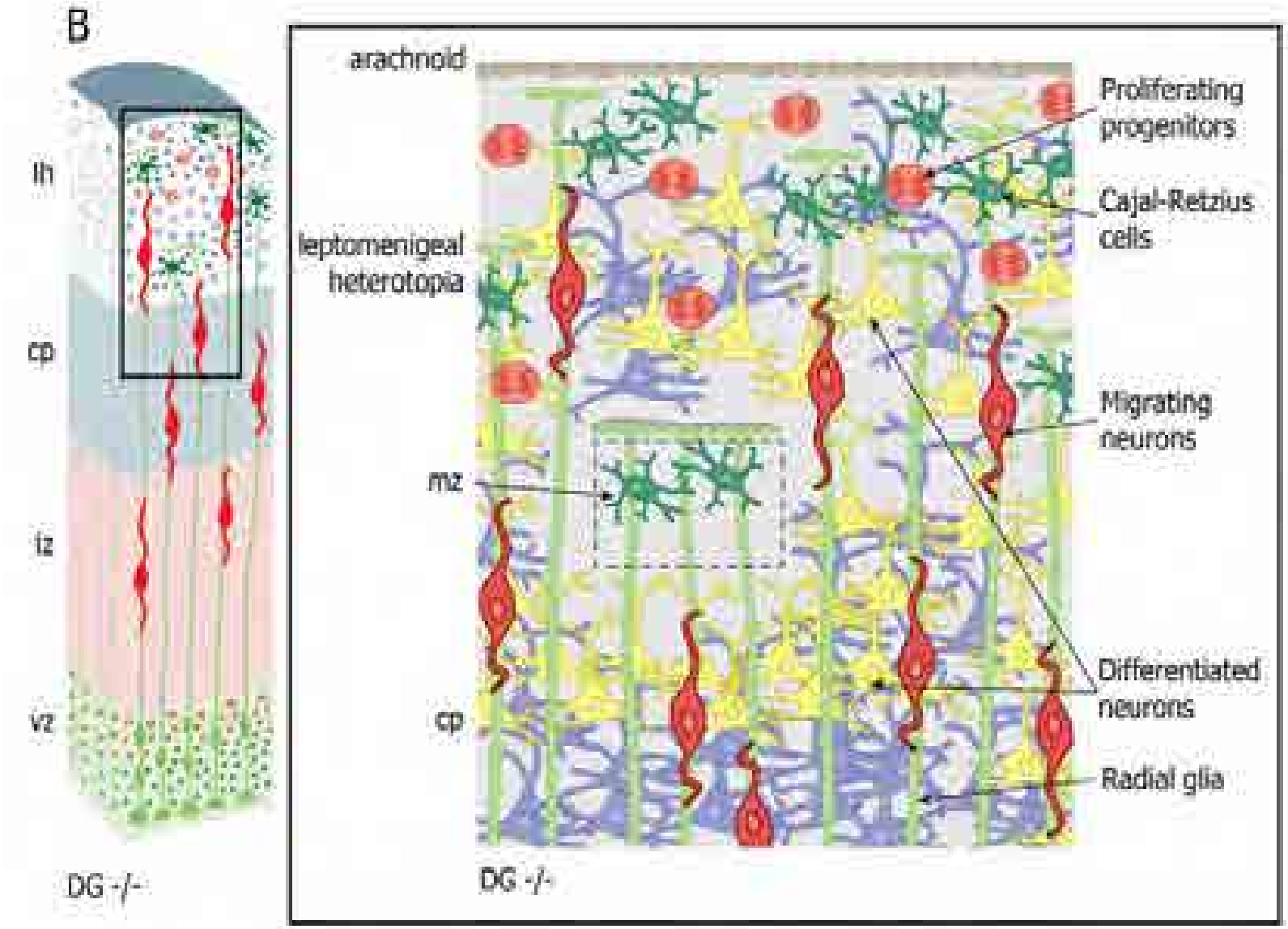
Satz et al., J Neurosci 30:14560-14572, 2010.

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



Myshrall et al., J Neuropathol Exp Neurol 71:1047-1063 2012.

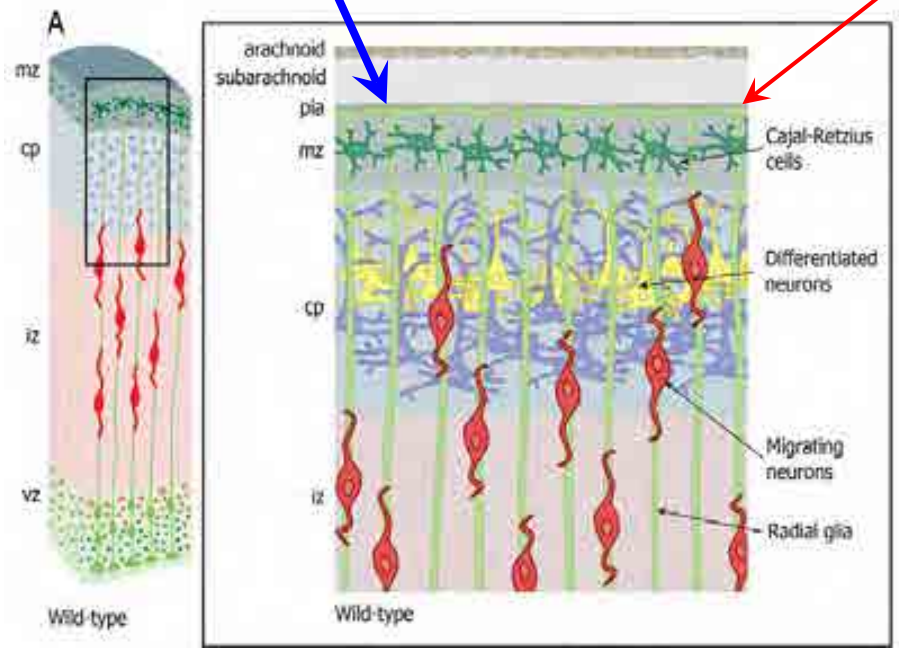
cobblestone lissencephaly (malformation)

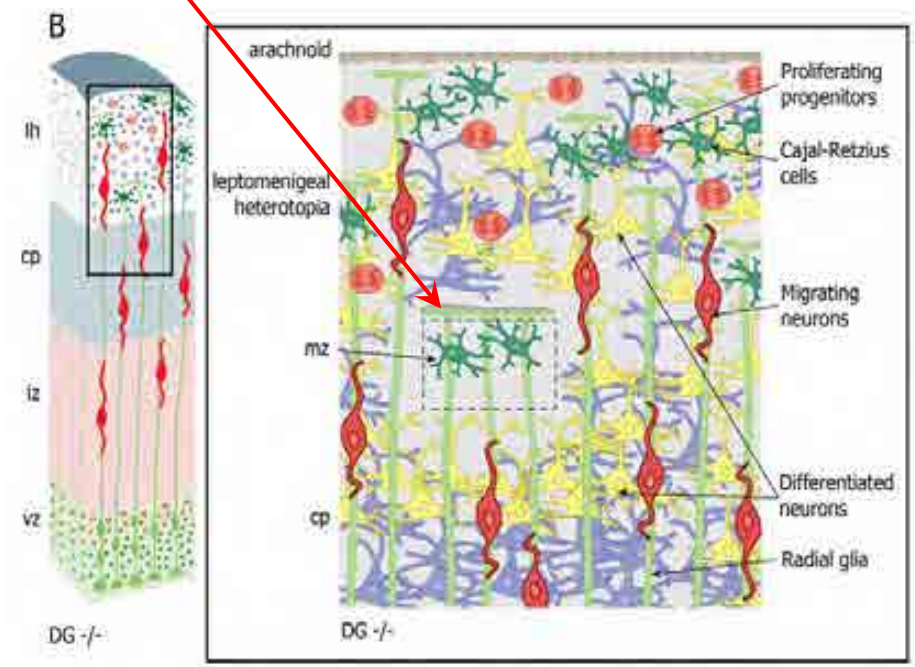


Myshrall et al., J Neuropathol Exp Neurol, 71:1047-1063 2012. *drawing by Huy Nguyen*

dystroglycan

basement membrane





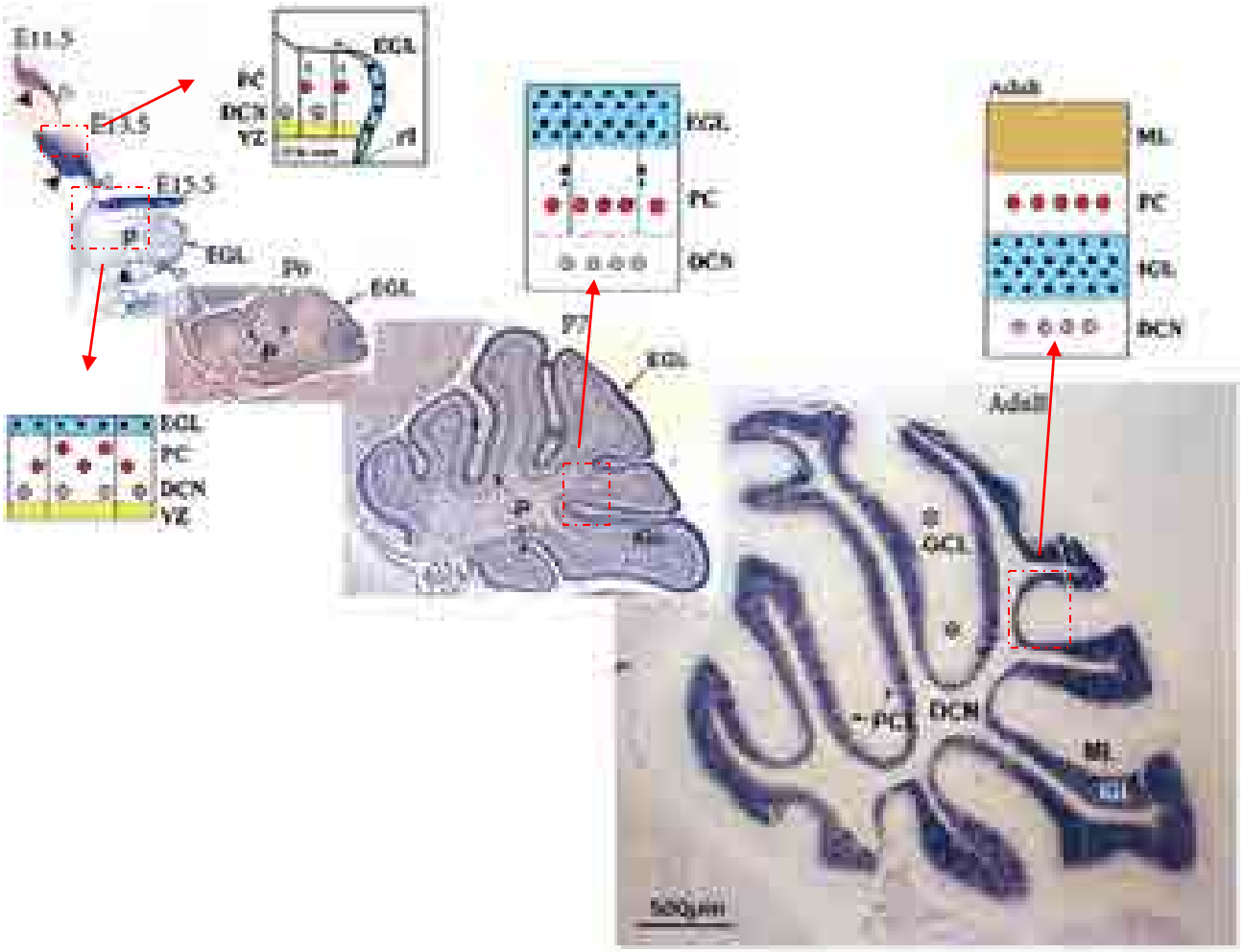
normal

cobblestone malformation

Myshrall et al., J Neuropathol Exp Neurol, 71:1047-1063 2012.

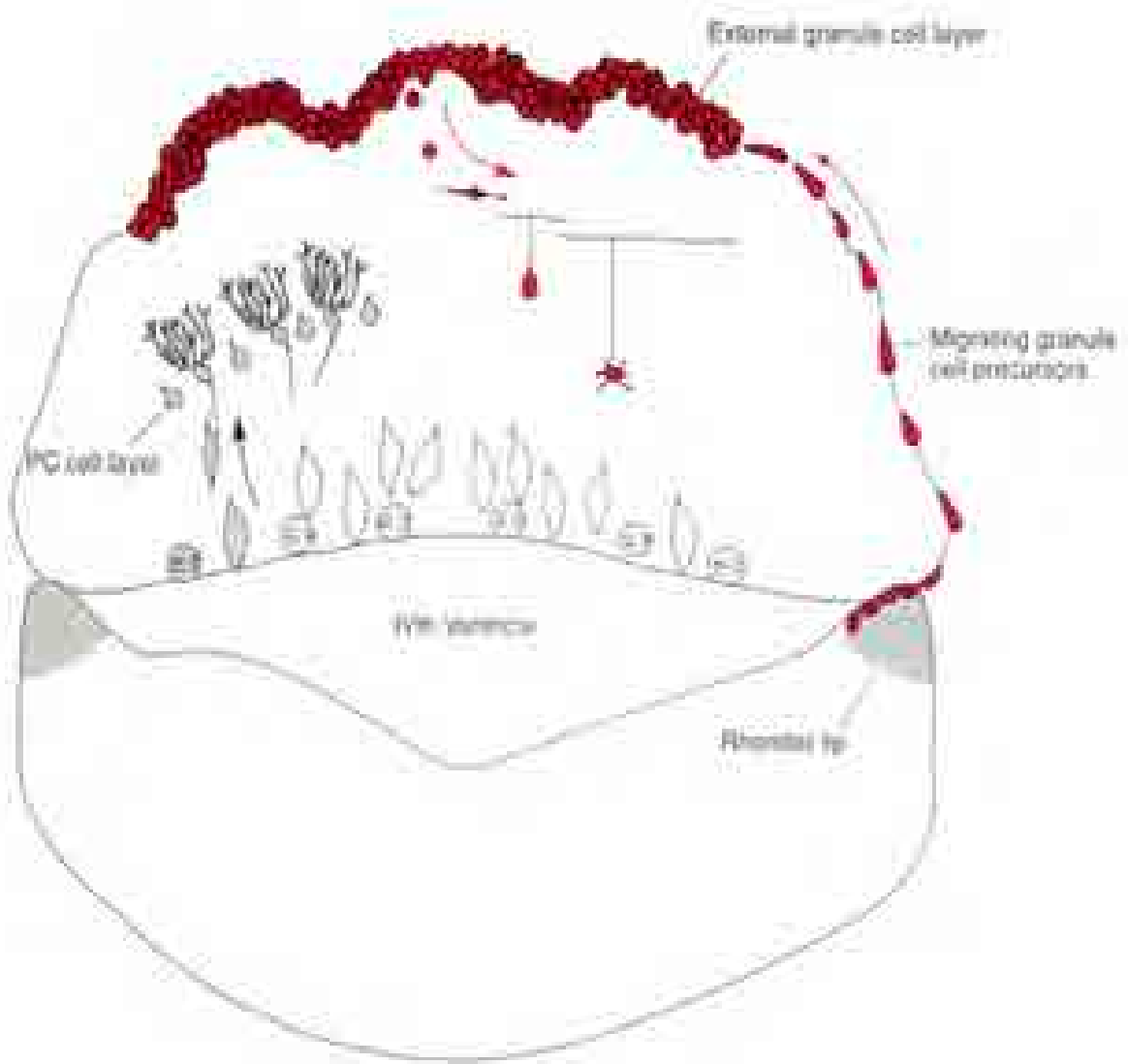
drawings by Huy Nguyen

cerebellar structure and development



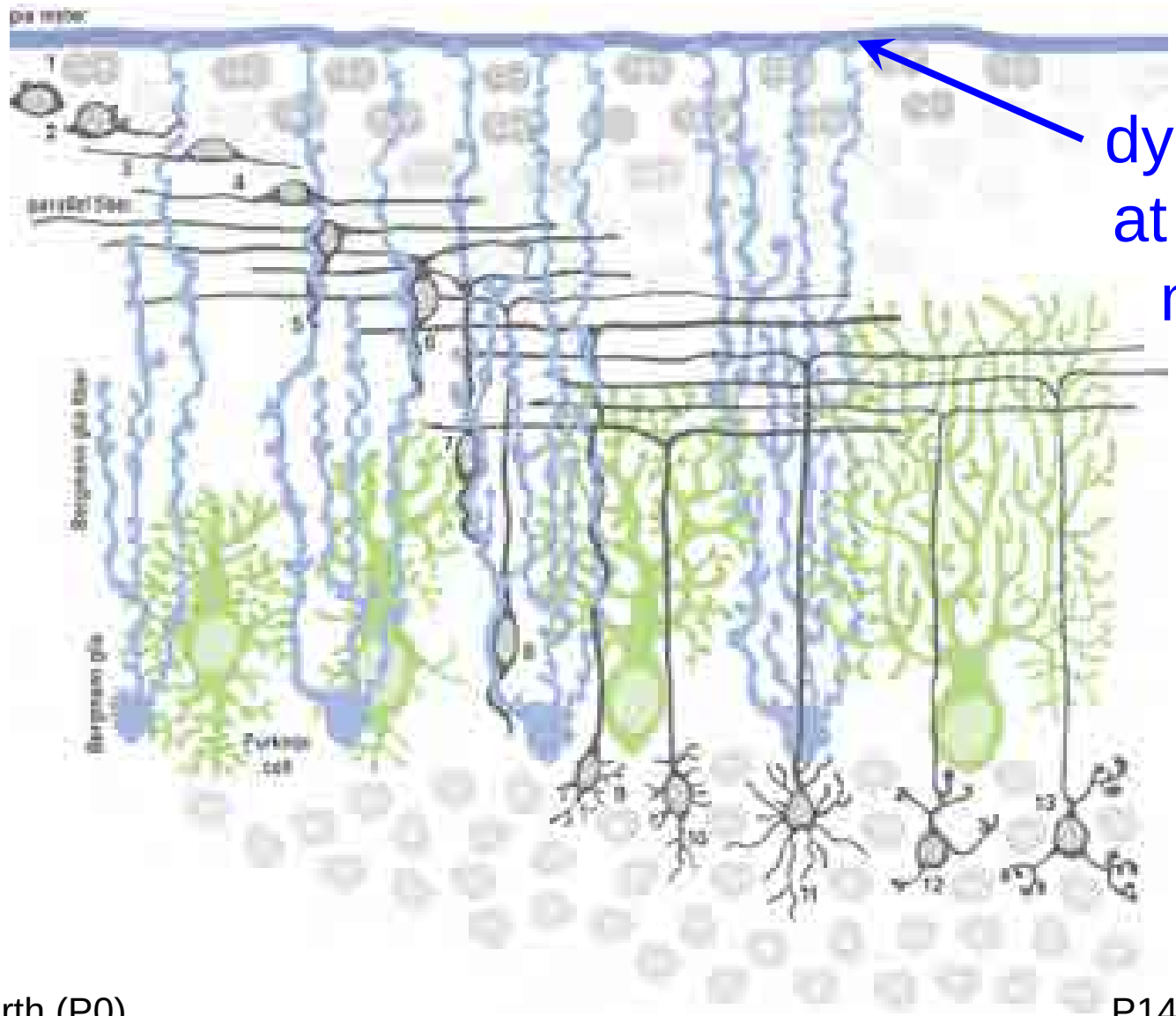
from Goldowitz and Hamre, 1998

histogenesis of cerebellar cortex



Development of the Nervous System, Sanes, Reh, and Harris, 2000

normal postnatal cerebellar development

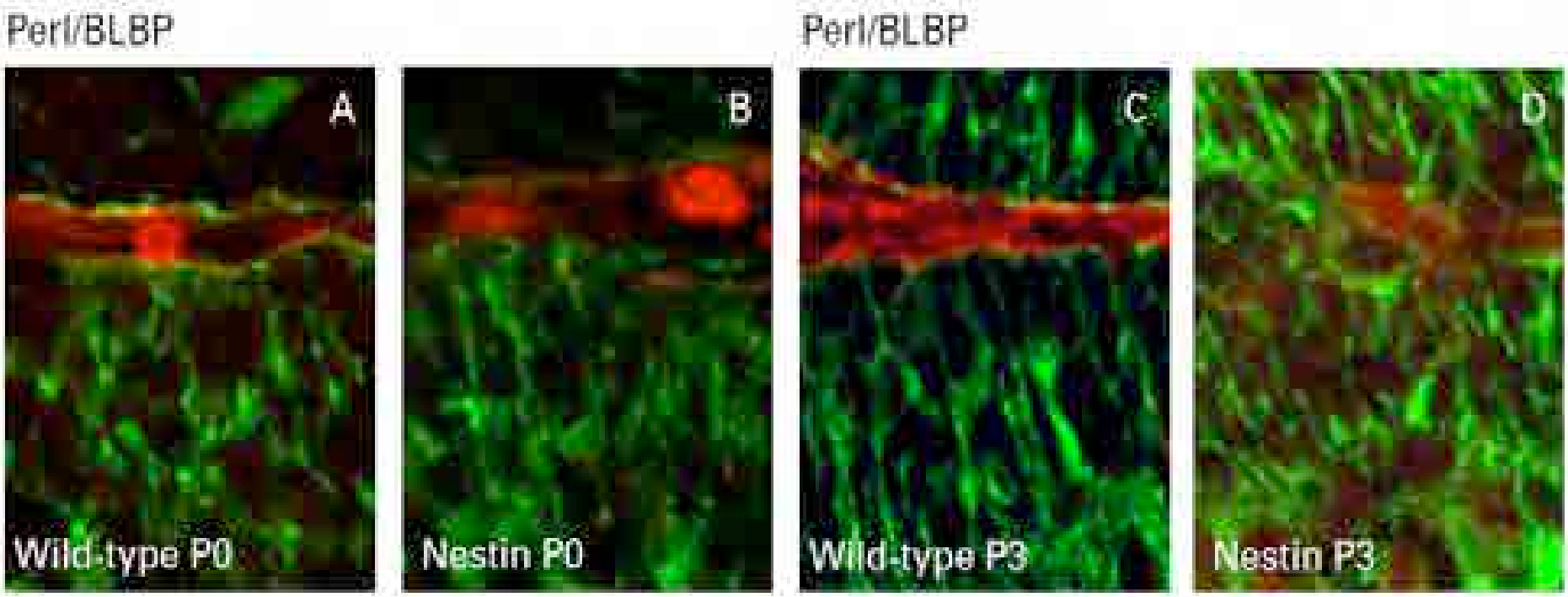


dystroglycan at basement membrane

birth (P0) → P14

drawing by Huy Nguyen

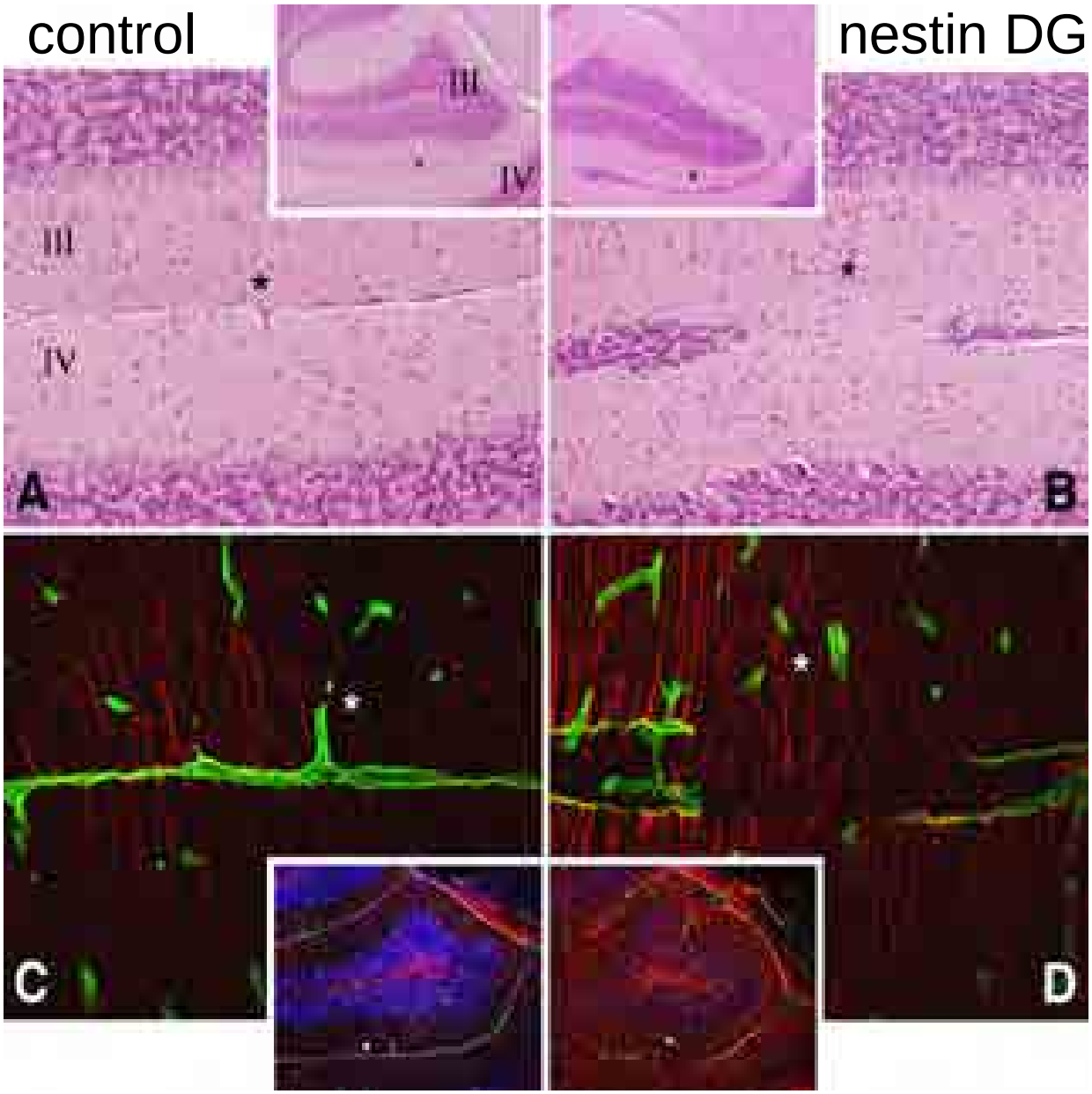
coincident glia limitans disruption and abnormalities of Bergmann glia processes in the absence of dystroglycan



perlecan
BLBP

Nguyen et al., Acta Neuropathol Comm 1:58, 2013.

P16



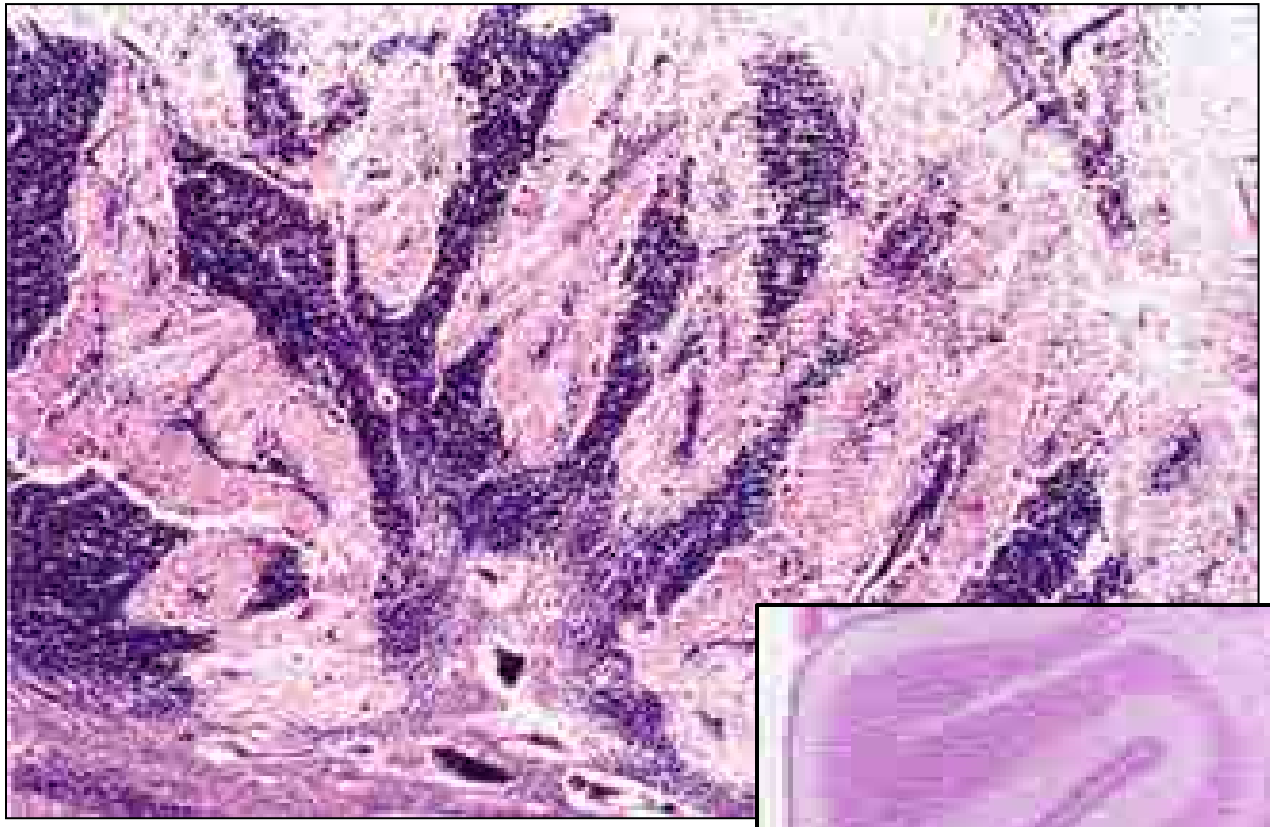
- failure of granule cell migration
- bridging across fissures

GFAP
laminin
DAPI

Nguyen et al., Acta Neuropathol Comm 1:58, 2013.

human cerebellar pathology in dystroglycanopathies

WWS cerebellum

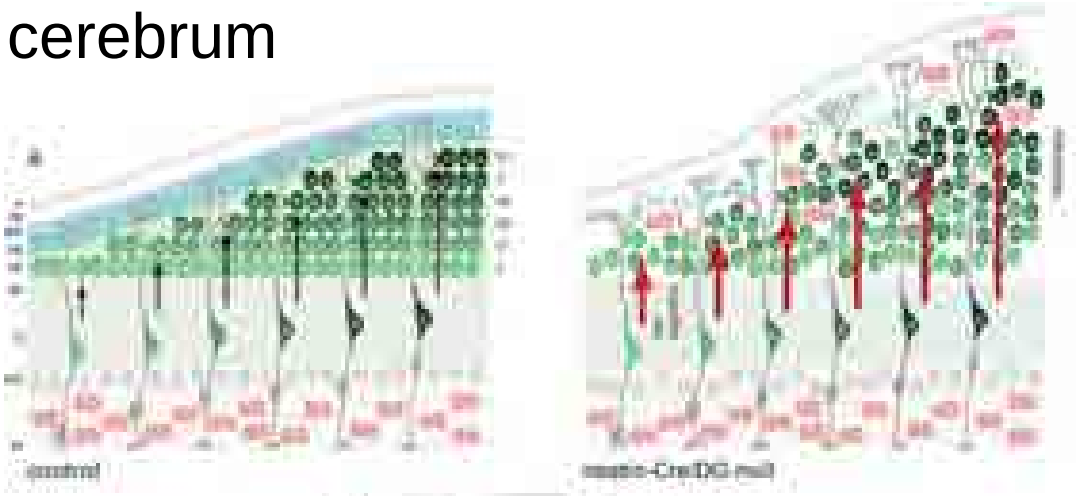


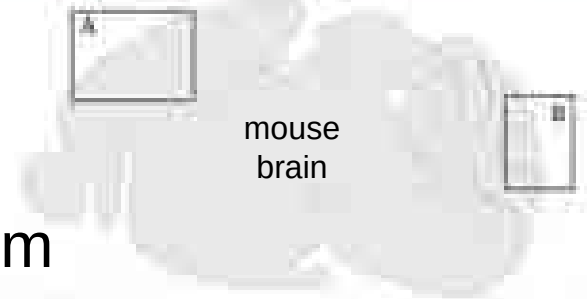
normal

Developmental Neuropathology
ISN, 2004, p.46.

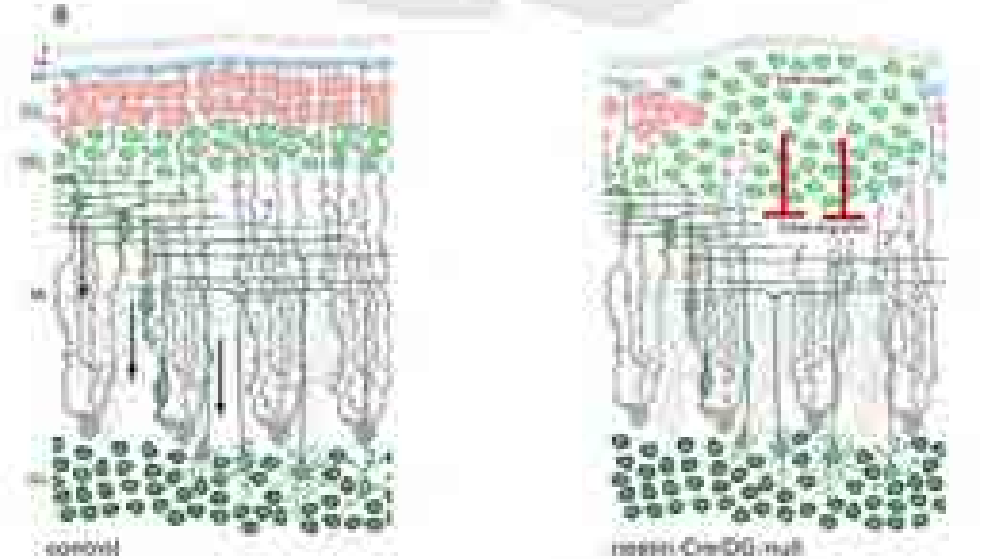
- Basement membrane disruption occurs in both cerebrum and cerebellum.
- Abnormal inside-out migration results in glial neuronal heterotopia filling the cerebral subarachnoid space.
- Abnormal outside-in migration results in cerebellar granule cell heterotopia.

cerebrum





cerebellum



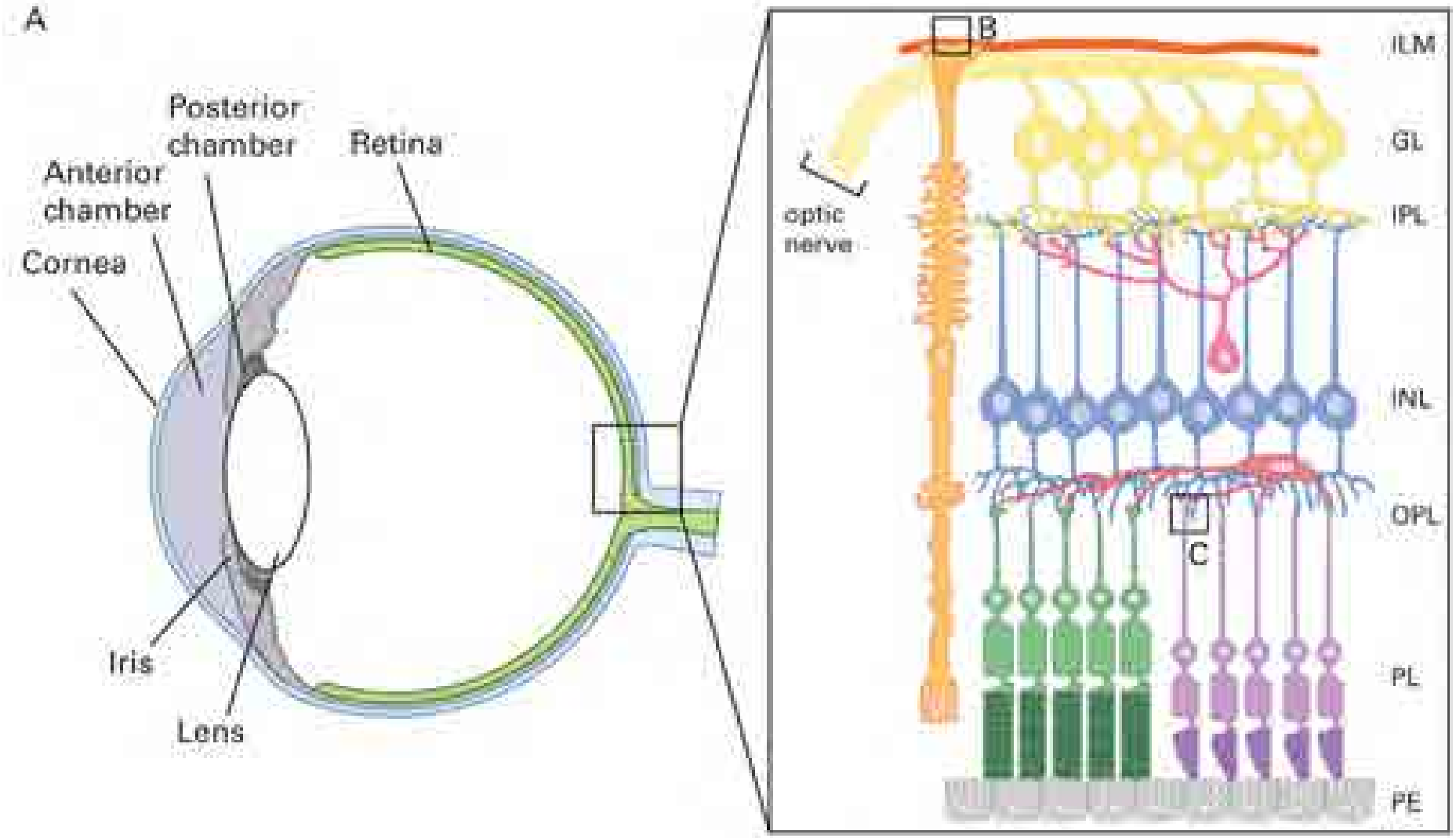
drawing by Huy Nguyen

eye abnormalities in the dystroglycanopathies

- congenital cataracts
- abnormally small eyes (microphthalmia)
- abnormally large eyes (buphthalmos)
- coloboma
- glaucoma
- retinal dysplasia
- optic nerve hypoplasia

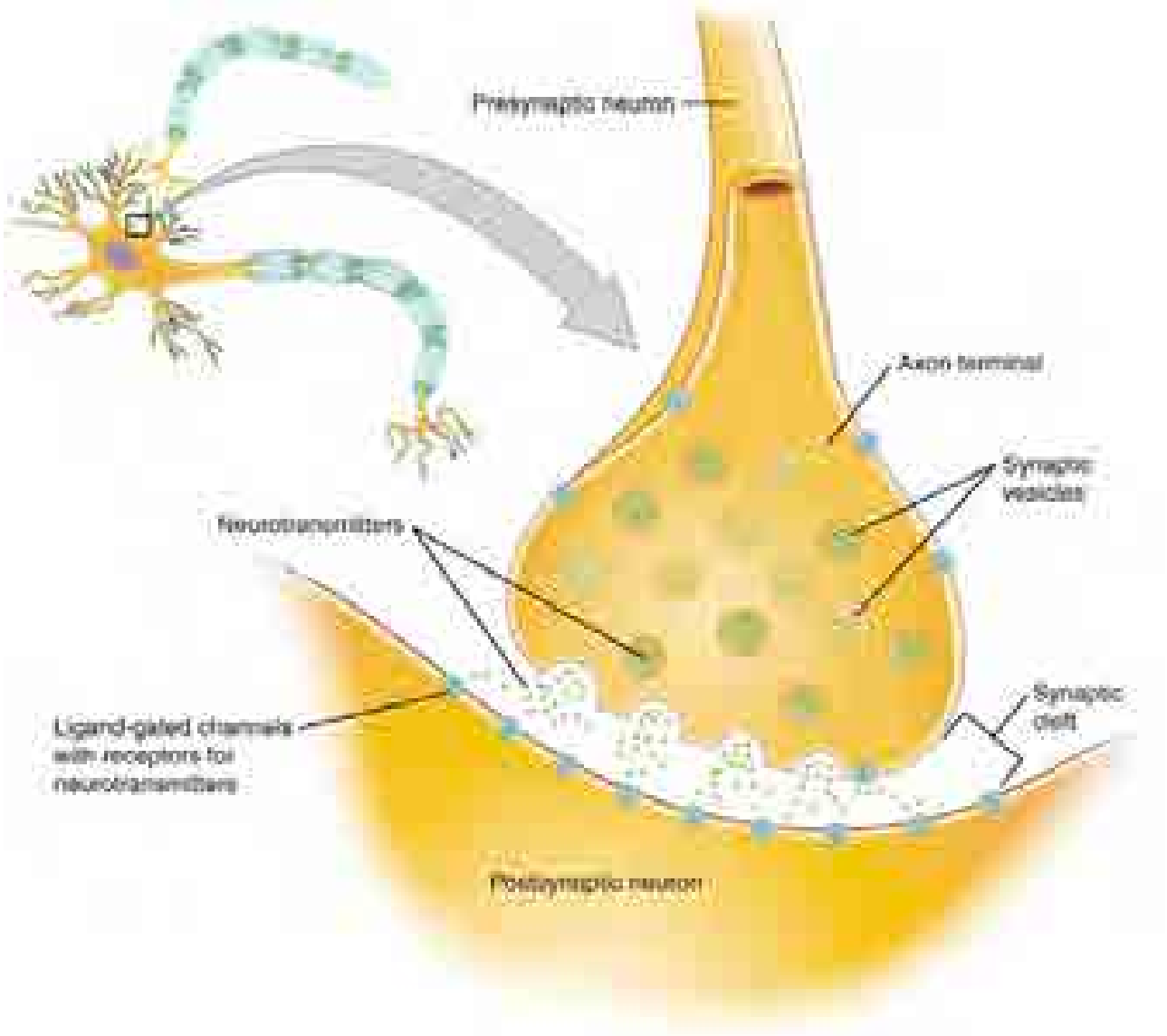
eye

retina

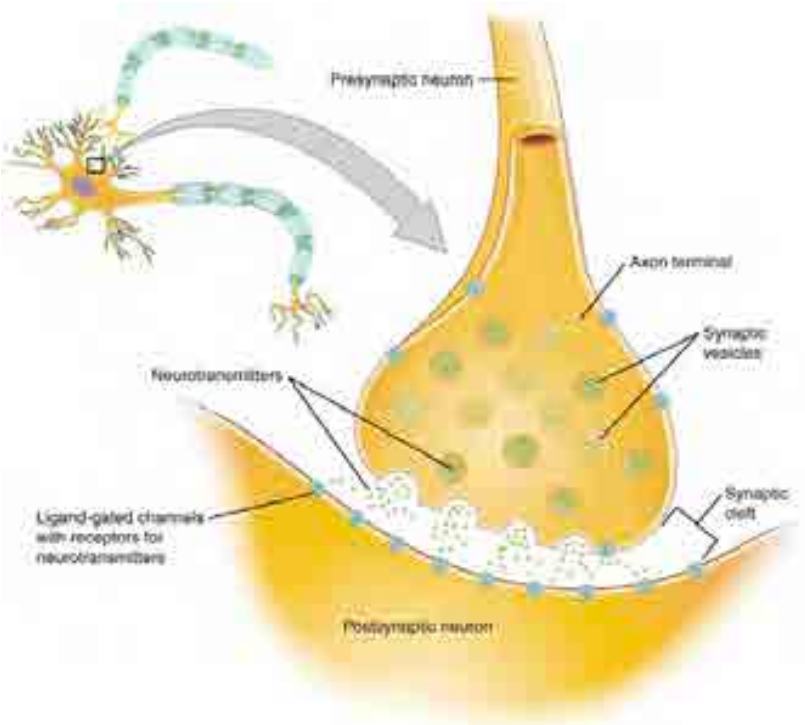


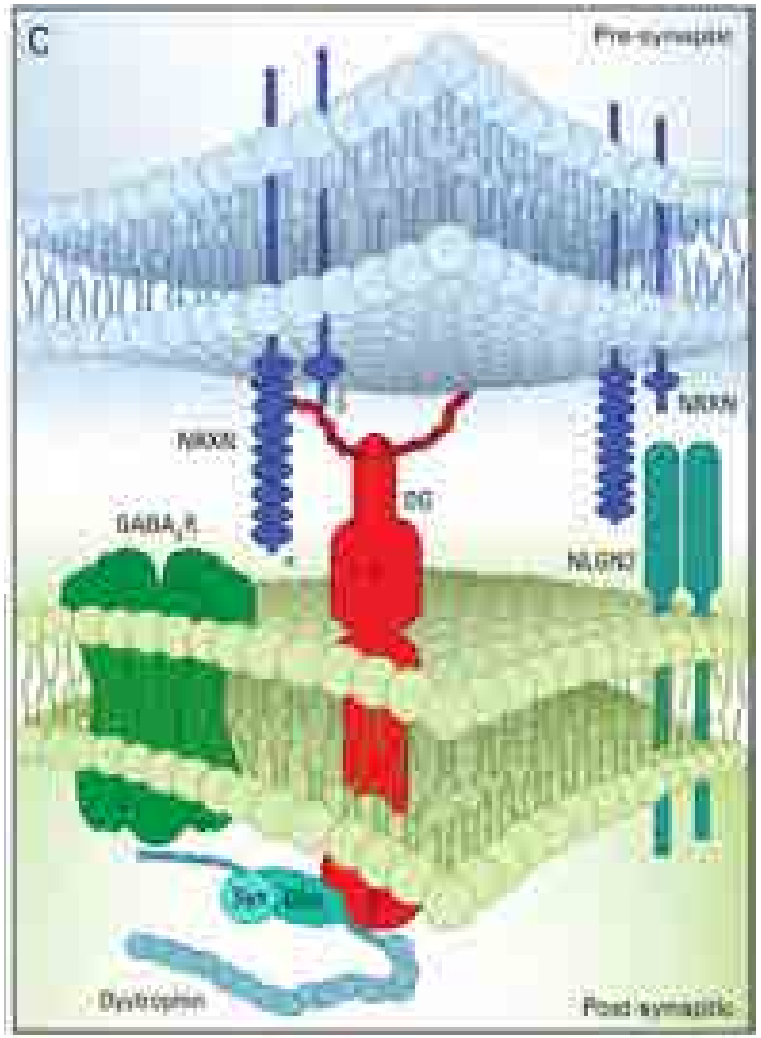
drawing by Huy Nguyen

synapse structure



neuronal dystroglycan



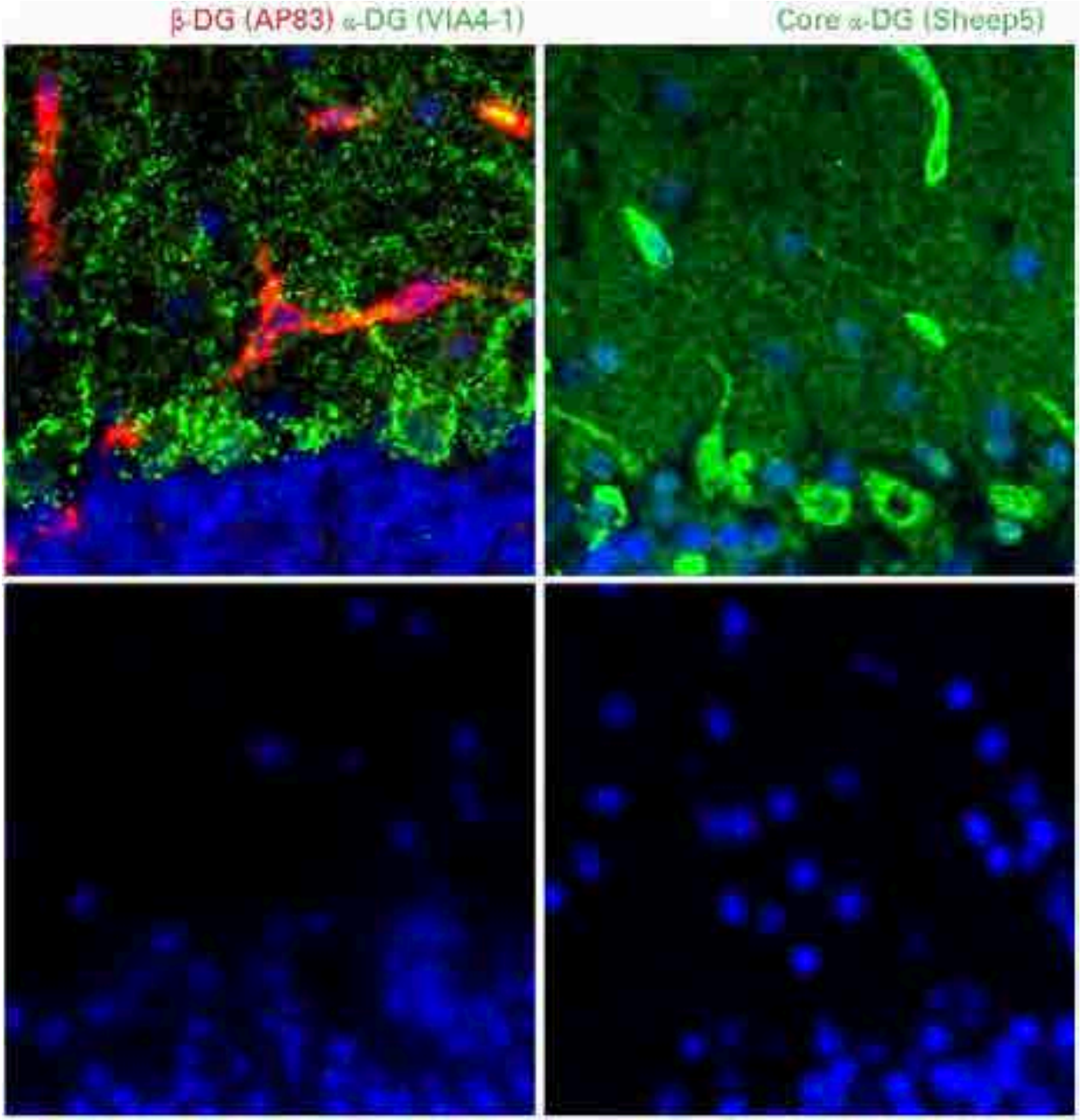


drawing by Huy Nguyen

cerebellar cortex

control wt mouse

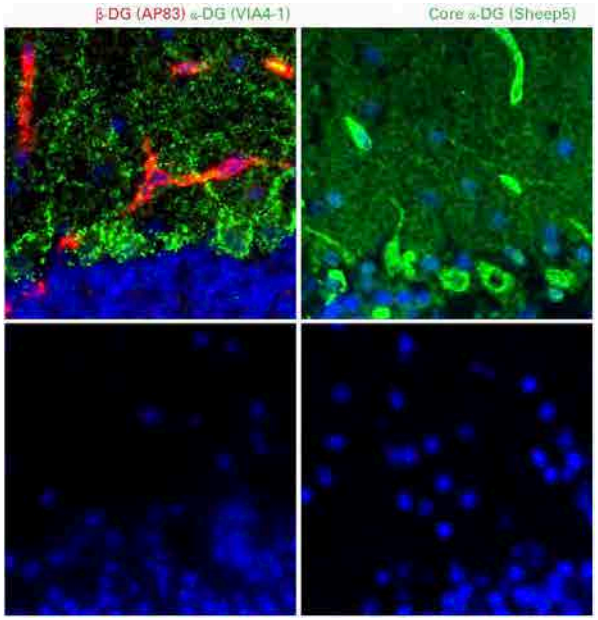
Large^{myd} mouse

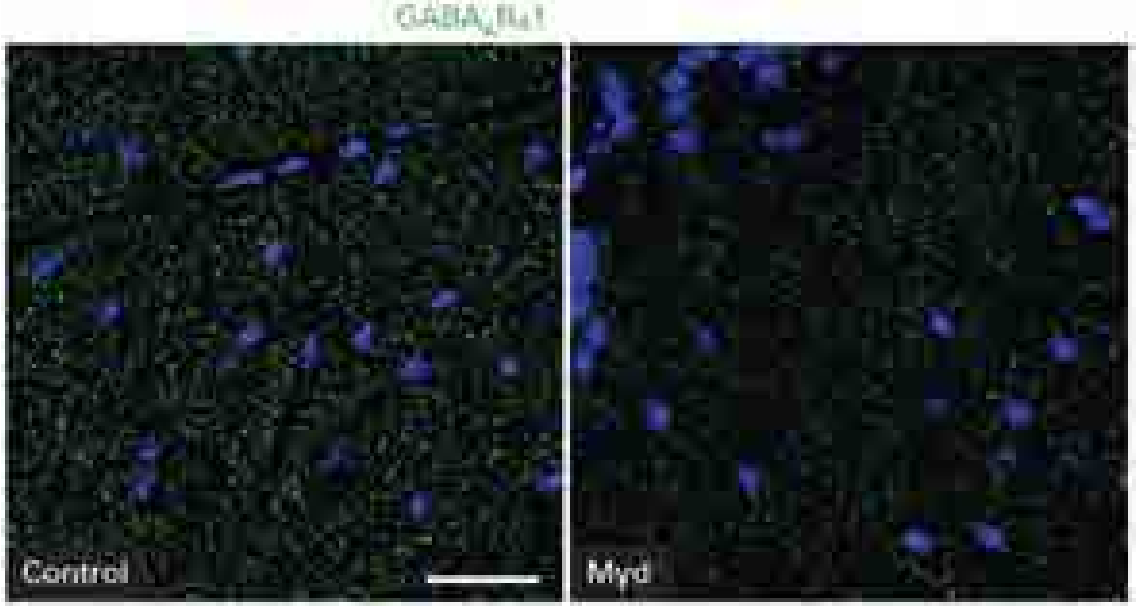


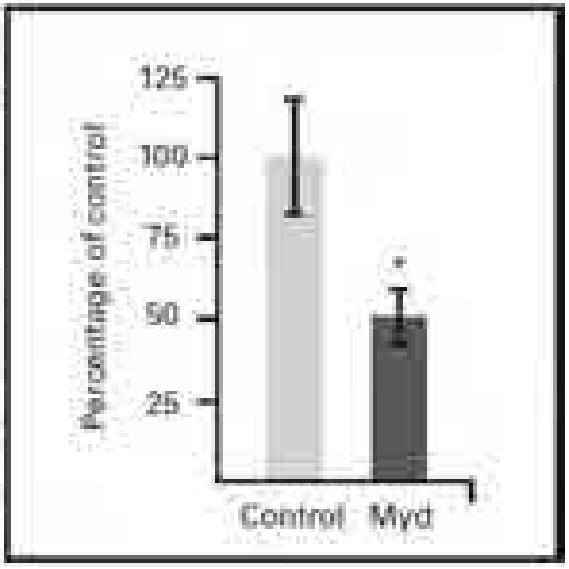
partial loss of $GABA_AR\alpha1$ from cerebellar cortex

control
wt mouse

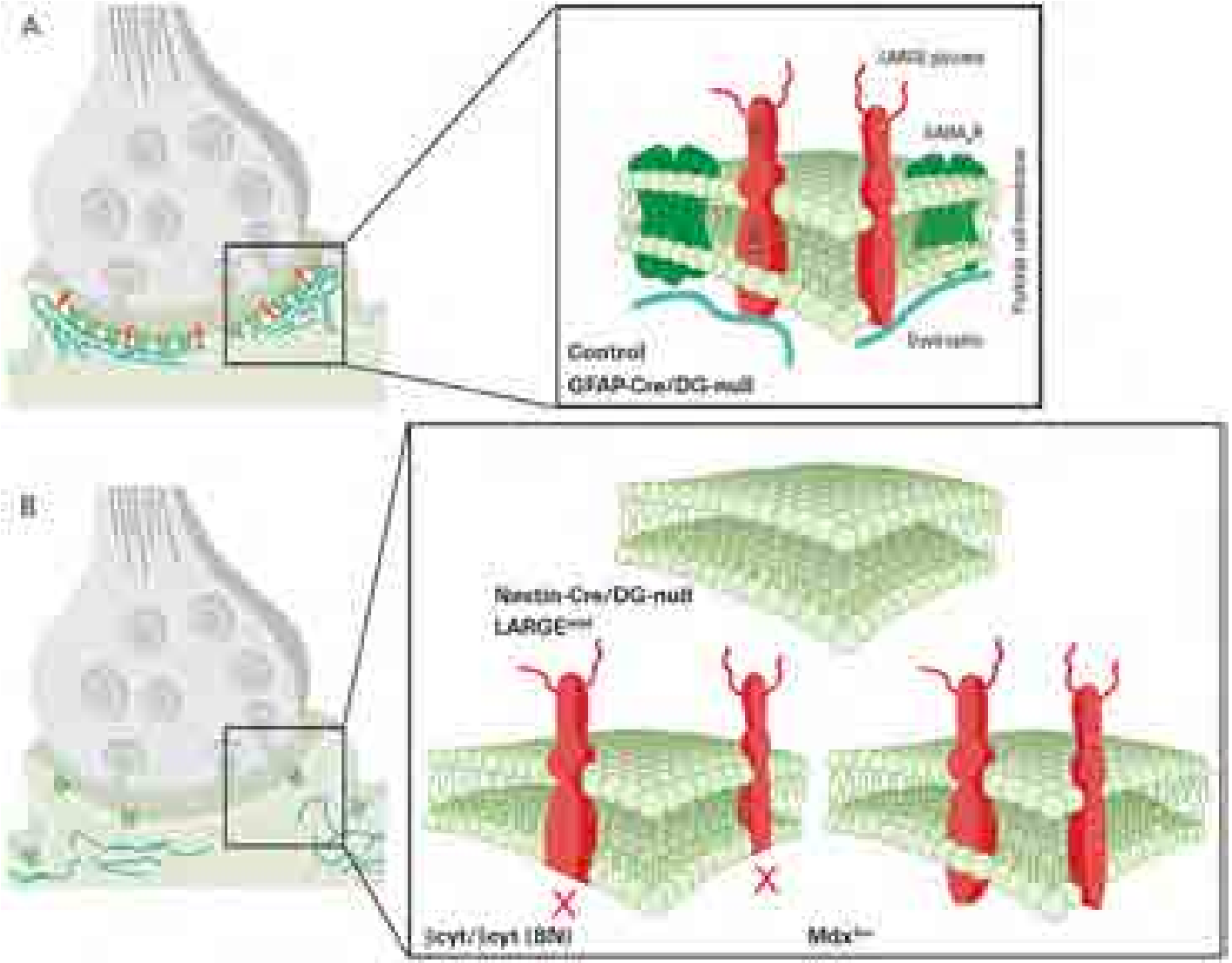
Large^{myd}
mouse







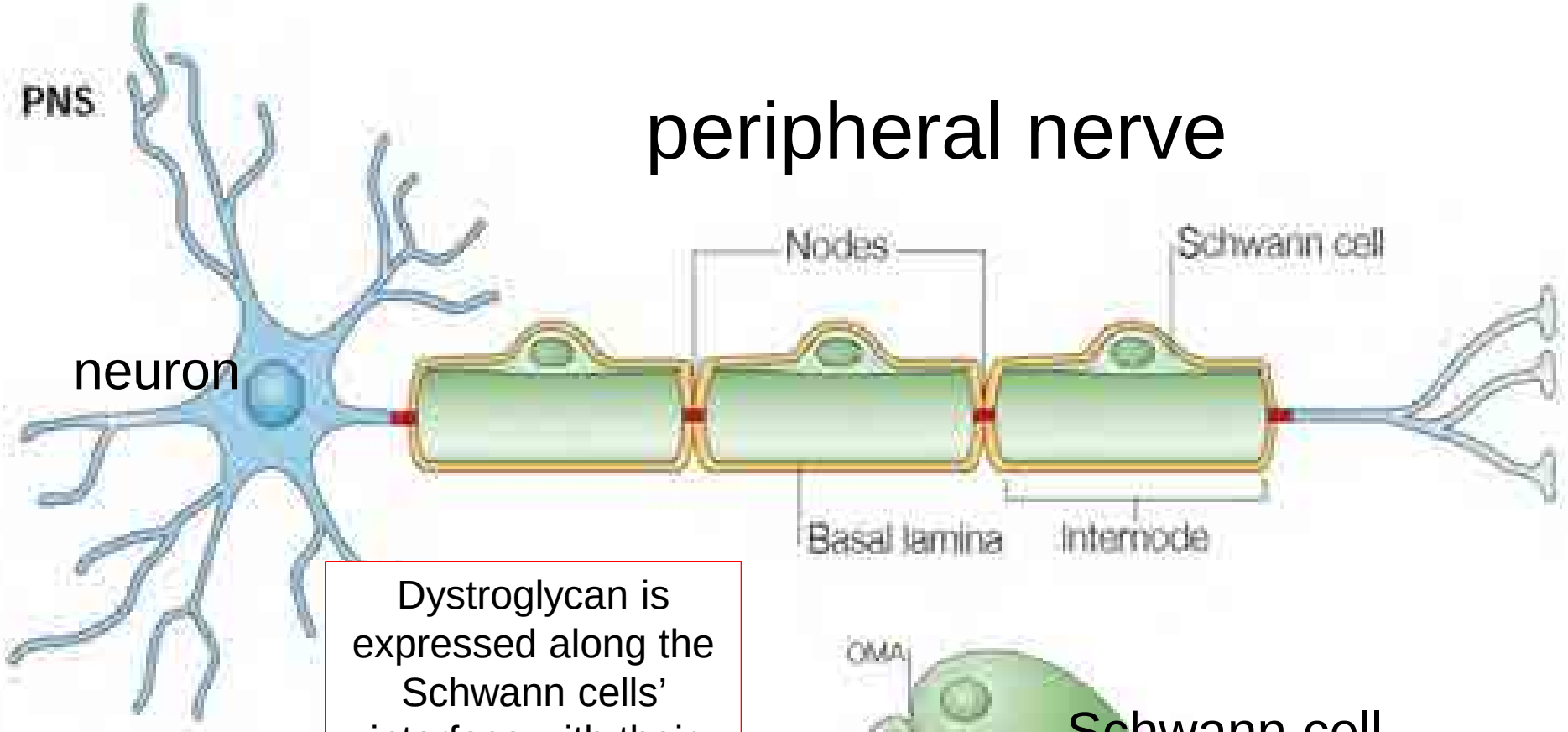
localization of Purkinje cell $GABA_AR\alpha1$ is dependent on DGC



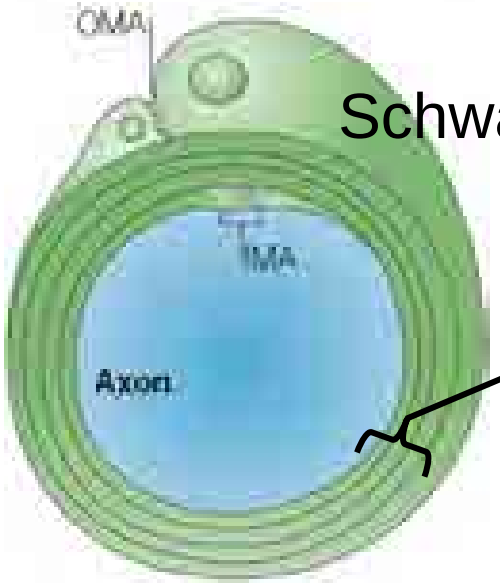
abnormal electrophysiology in dystroglycanopathies

- brain – blunted long term potentiation (LTP), the electrophysiology associated with memory formation
- seizures
- eye – abnormal electroretinograms (ERG)
- muscle – abnormal neuromuscular junctions; congenital myasthenic syndrome

peripheral nerve



Dystroglycan is expressed along the Schwann cells' interface with their basement membrane (basal lamina) and at nodes of Ranvier.



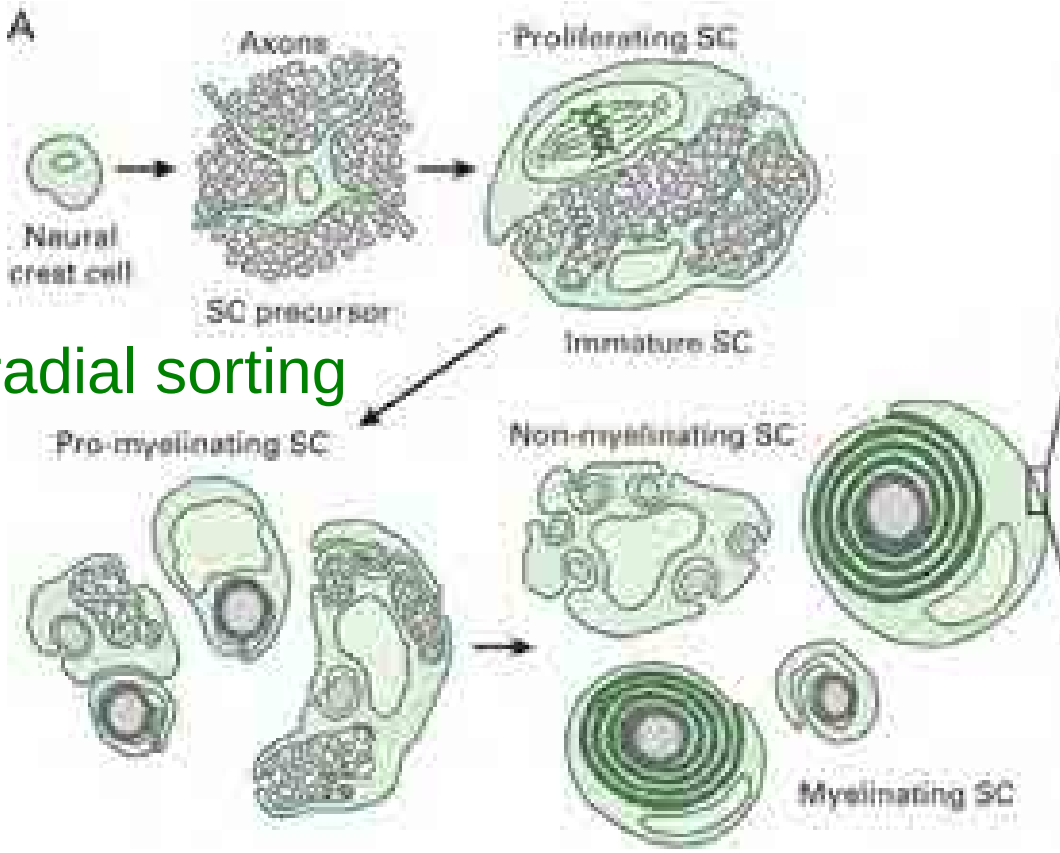
Schwann cell

myelin sheath

modified from Nature Reviews Neuroscience 4:969, 2003

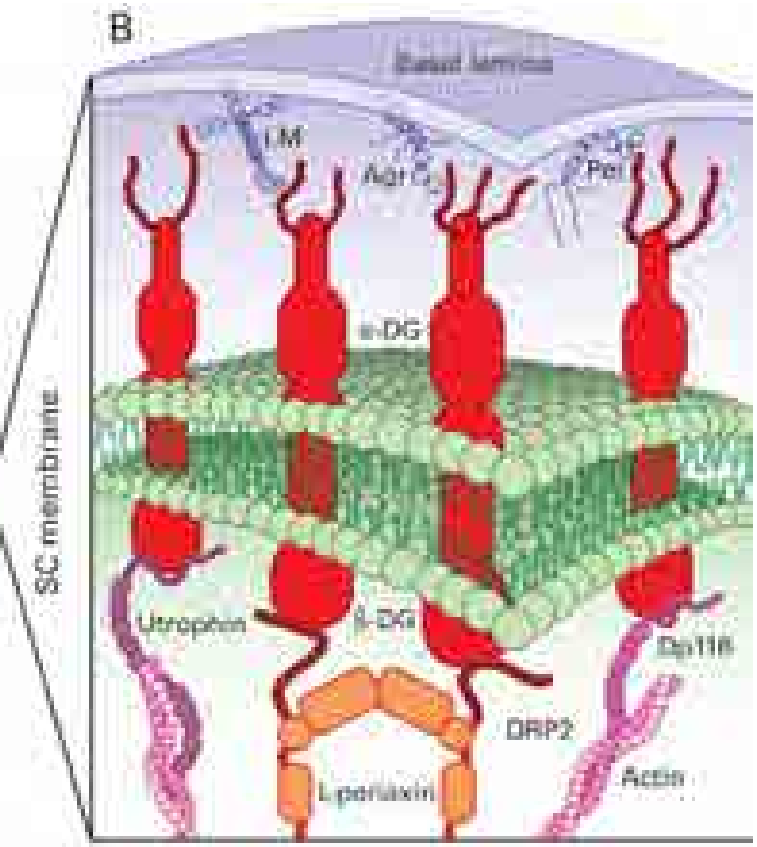
peripheral nerve development

Schwann cell dystroglycan



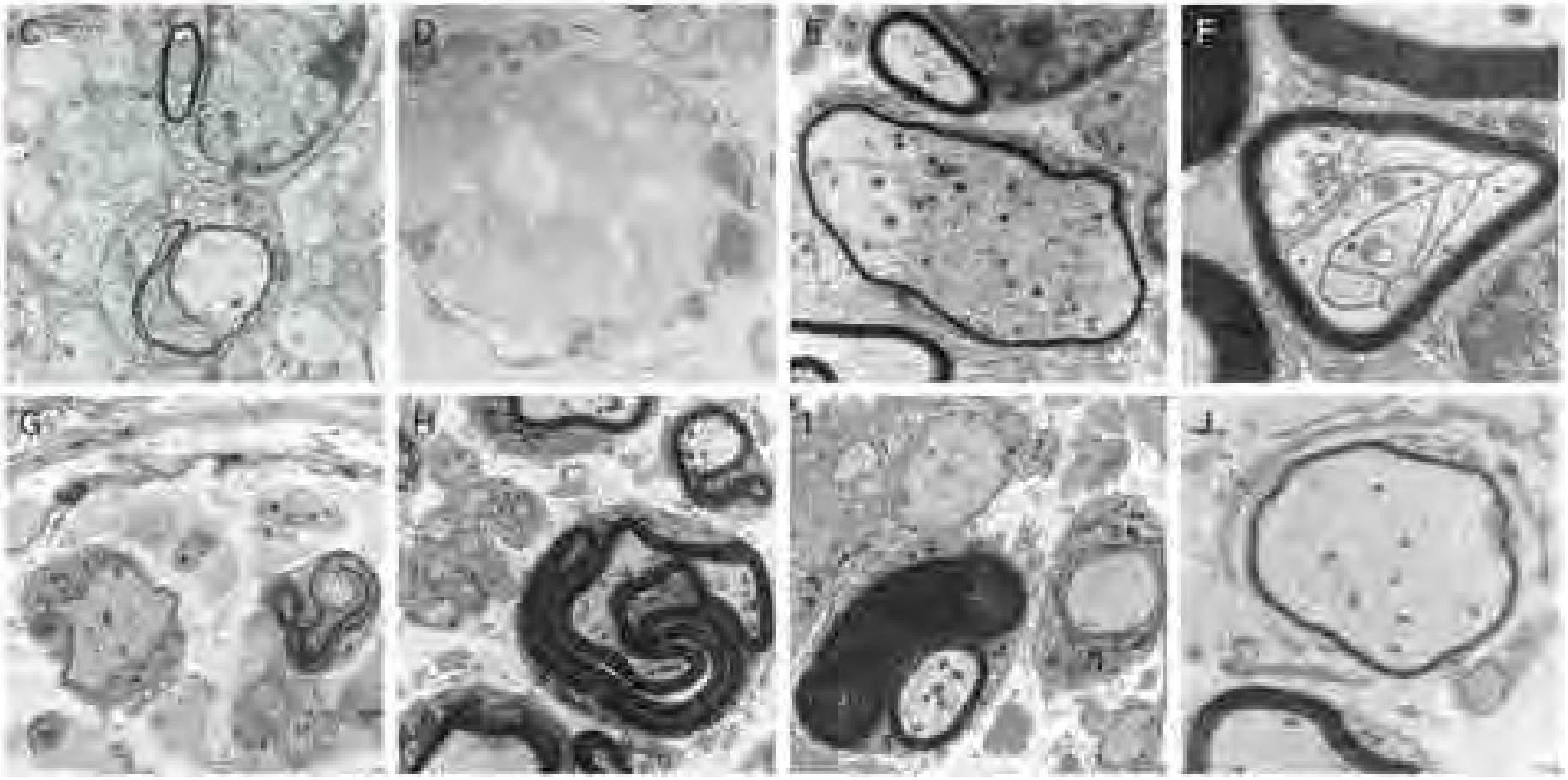
radial sorting

myelination

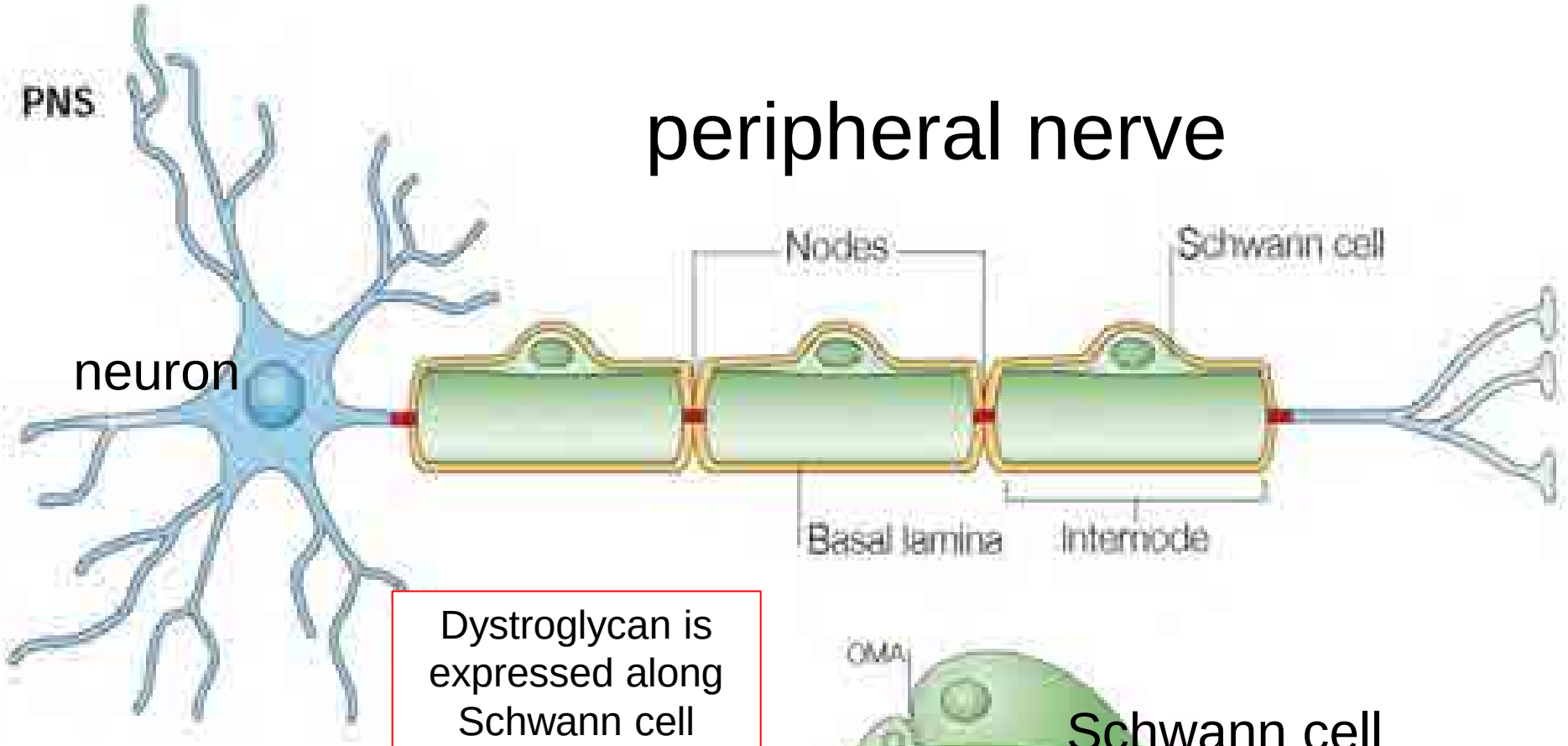


drawing by Huy Nguyen

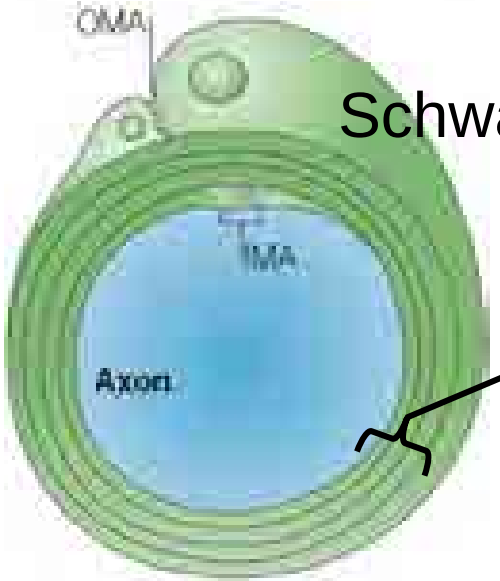
peripheral nerve pathology in the absence of dystroglycan



peripheral nerve



Dystroglycan is expressed along Schwann cell membranes and at nodes of Ranvier.

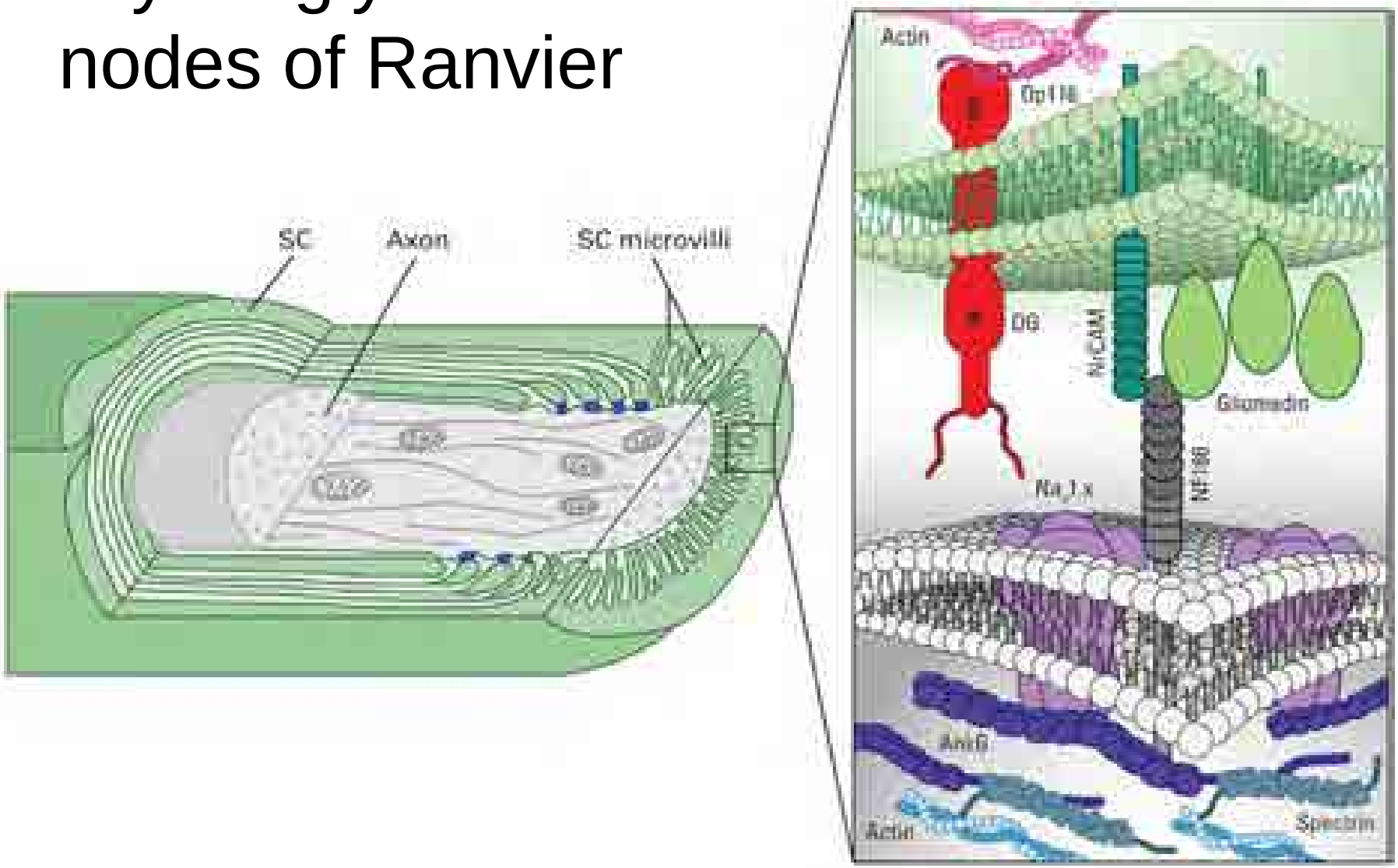


Schwann cell

myelin sheath

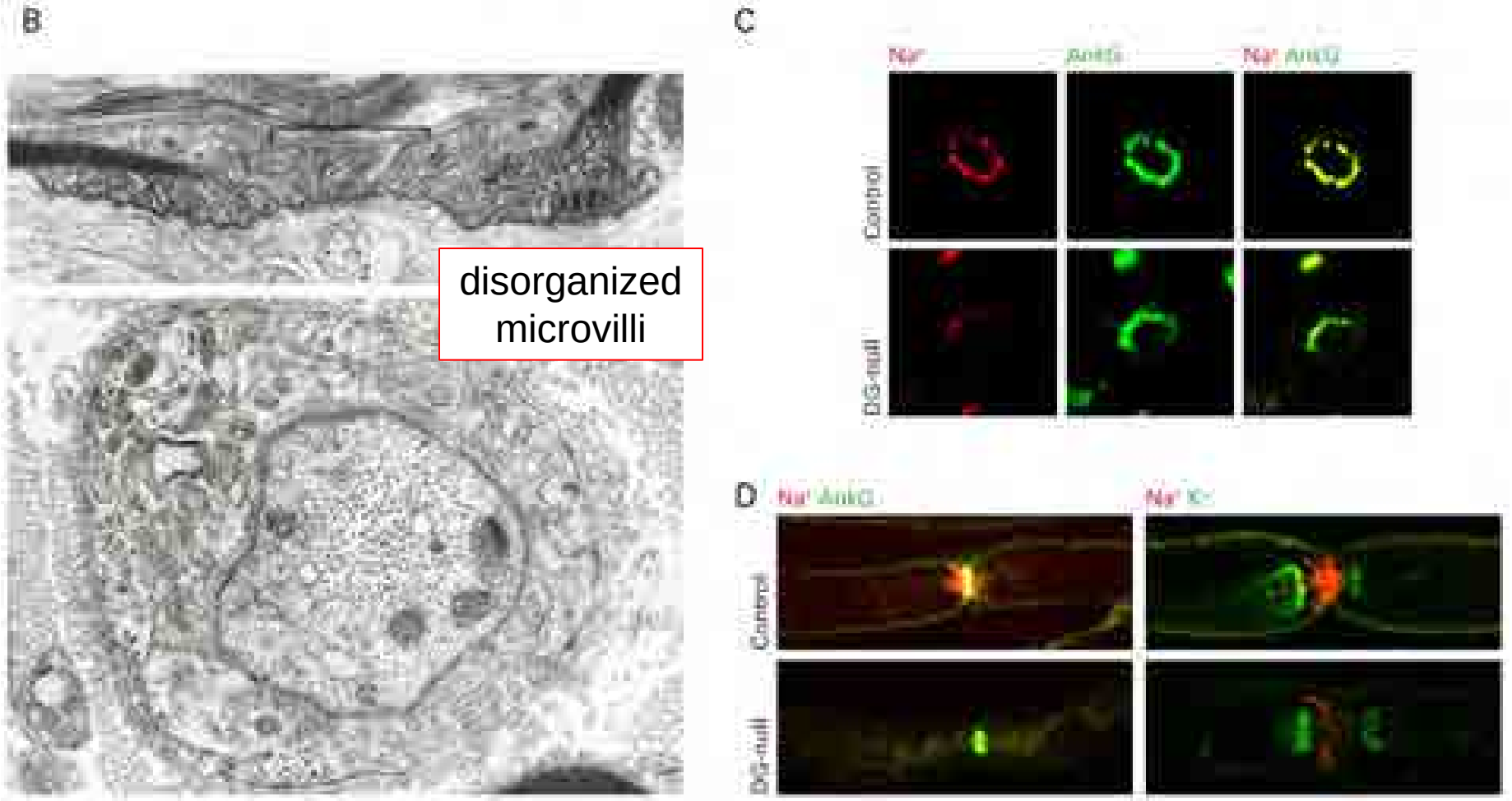
modified from Nature Reviews Neuroscience 4:969, 2003

dystroglycan at nodes of Ranvier



drawing by Huy Nguyen

pathology at nodes of Ranvier in the absence of dystroglycan



disorganized microvilli

immunostains by Rita Barresi

abnormally slow conduction velocity

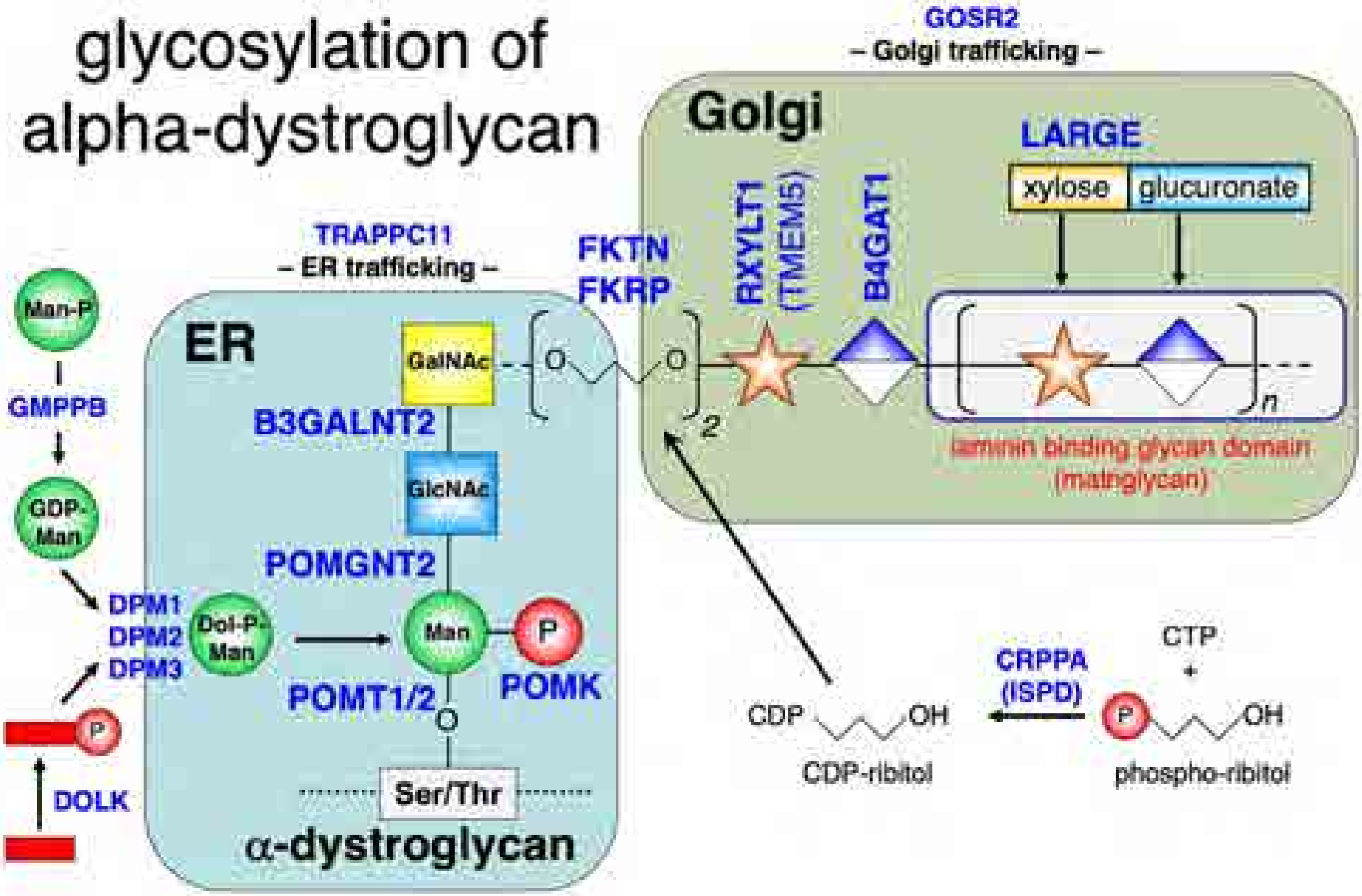
Summary

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

Thank you!

Any questions?

glycosylation of alpha-dystroglycan



slide modified from original by Toby Wiles