Leukodystrophies: how to find the way in the maze

M. Bugiani m.bugiani@amsterdamumc.nl

Amsterdam leukodystrophy center

Amsterdam UMC VUmc VU University Medical Center Amsterdam

Amsterdam Neuroscience

Nothing to declare

What is a leukodystrophy?

- 1980's
- genetic, progressive disorders primarily affecting myelin (myelin loss or insufficient myelination), either directly or through oligodendrocytes

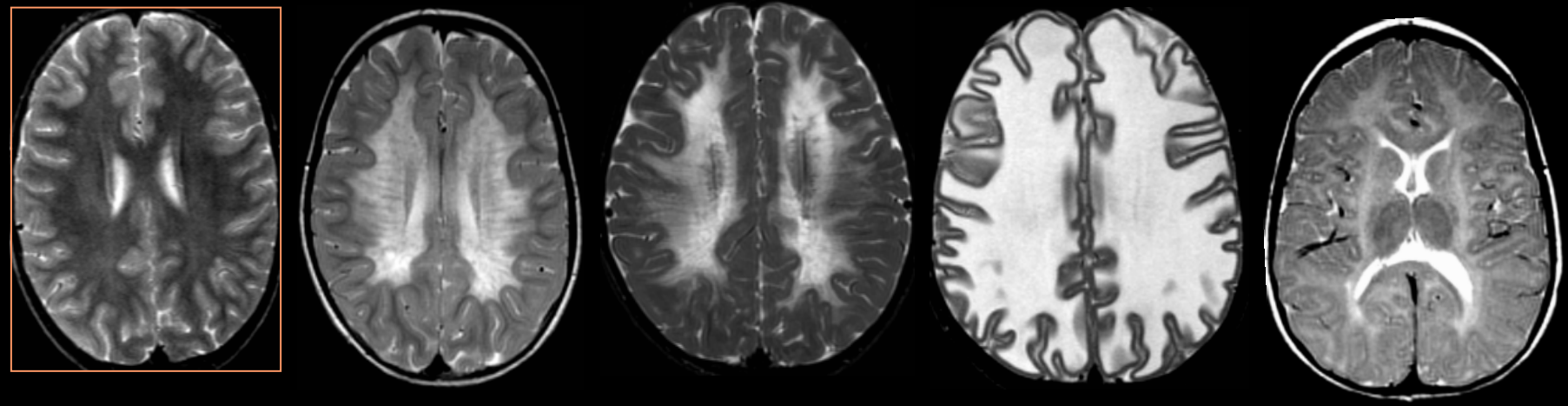
Morell & Wiesmann, Neuropediatrics 1984; 15 (suppl): 62
Seitelberger, Neuropediatrics 1984; 15 (suppl): 53

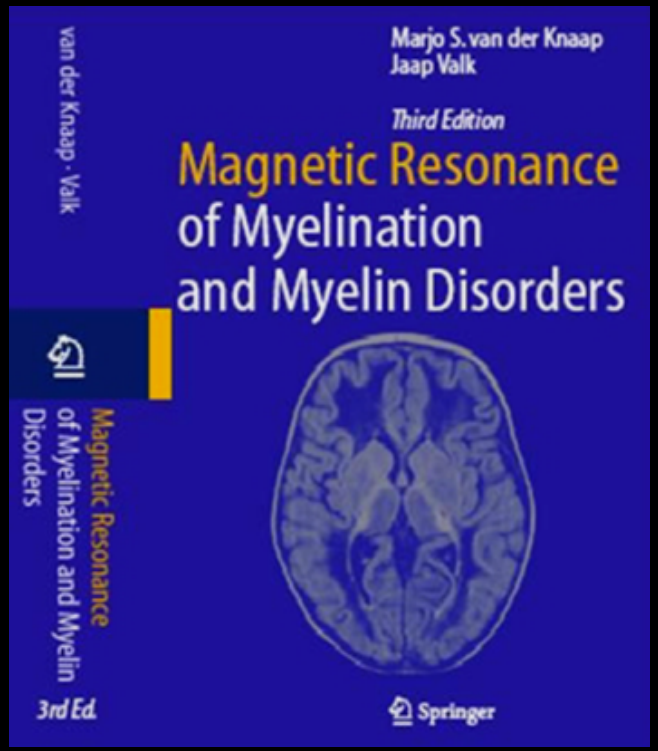
- No known gene defects
- MRI had not entered clinical practice
- Data available from pathology, biochemical analyses of brain tissue and knowledge of several metabolic and enzymatic defects

- Curative treatment focused on stopping myelin loss and on remyelination

1980's: introduction of MRI

- Very high sensitivity for white matter abnormalities
- Replaced neuropathology



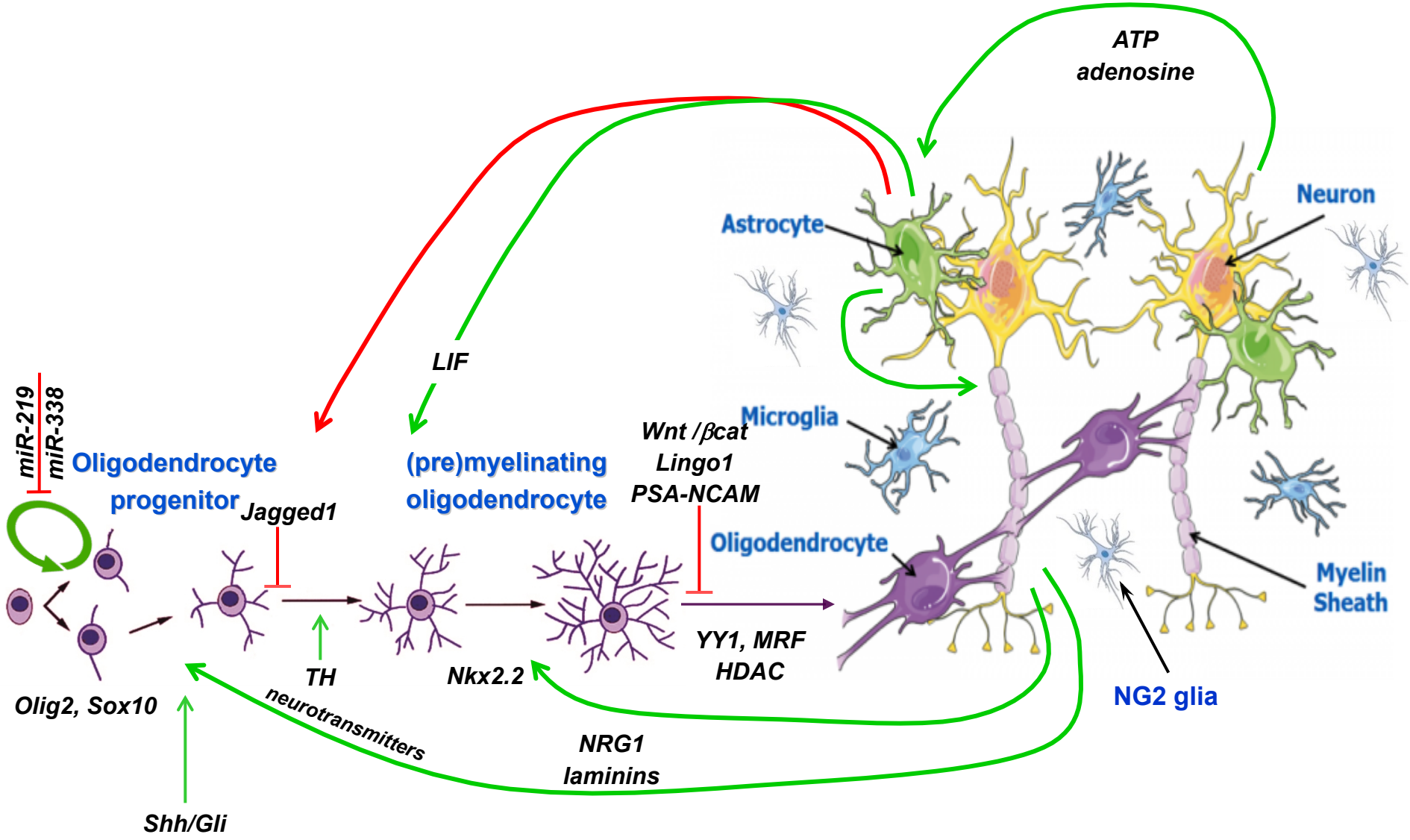


MRI pattern recognition

Next generation sequencing

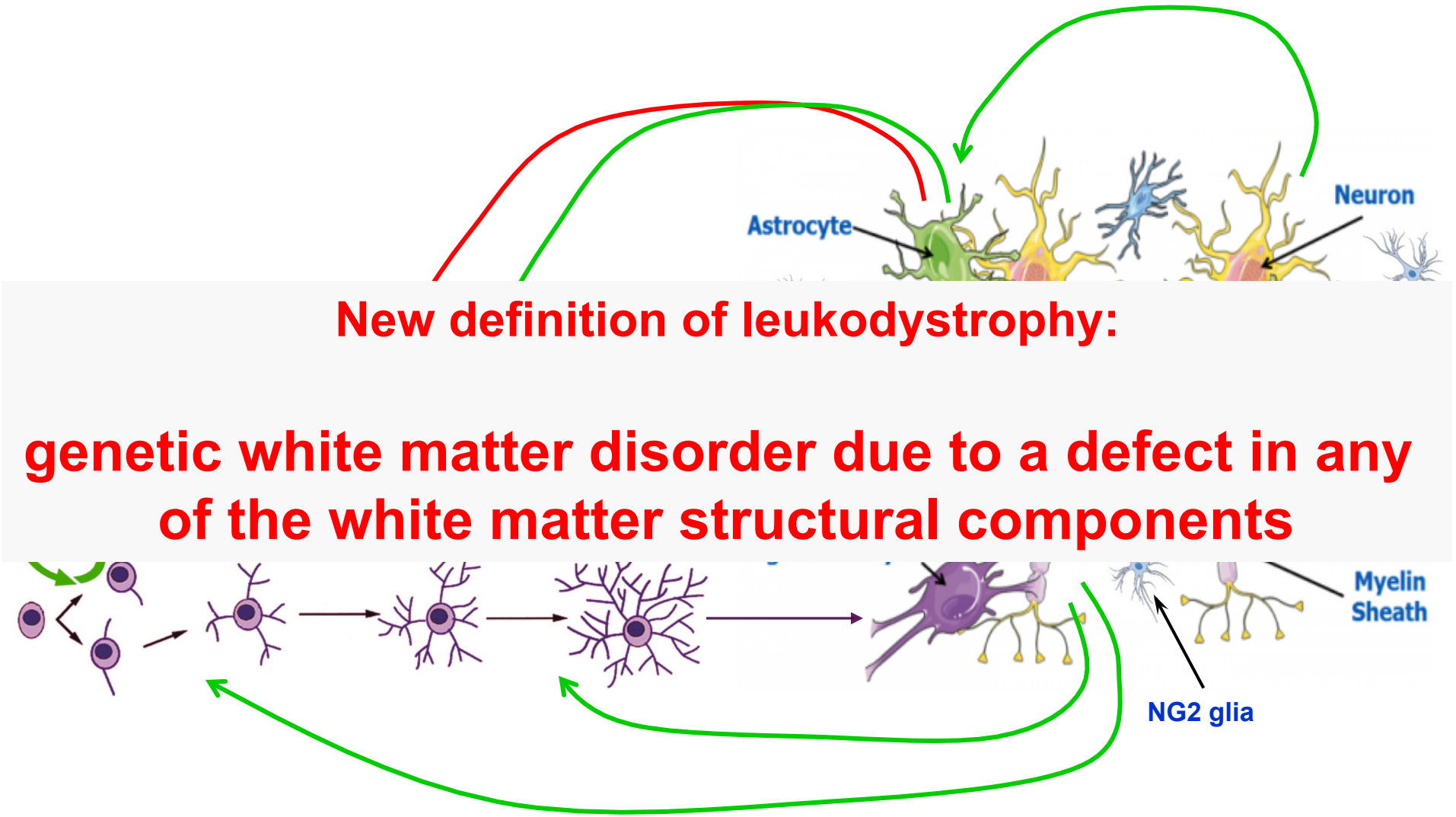
Most leukodystrophies are due to defects in gene encoding proteins specific for cell types other than the oligodendrocytes

Oligodendrocyte development, myelination, myelin maintenance and regeneration: teamwork required



Are all genetic white matter disorders leukodystrophies?

Oligodendrocyte development, myelination, myelin maintenance and regeneration: teamwork required



New definition of leukodystrophy:

genetic white matter disorder due to a defect in any of the white matter structural components

A new classification of leukodystrophies

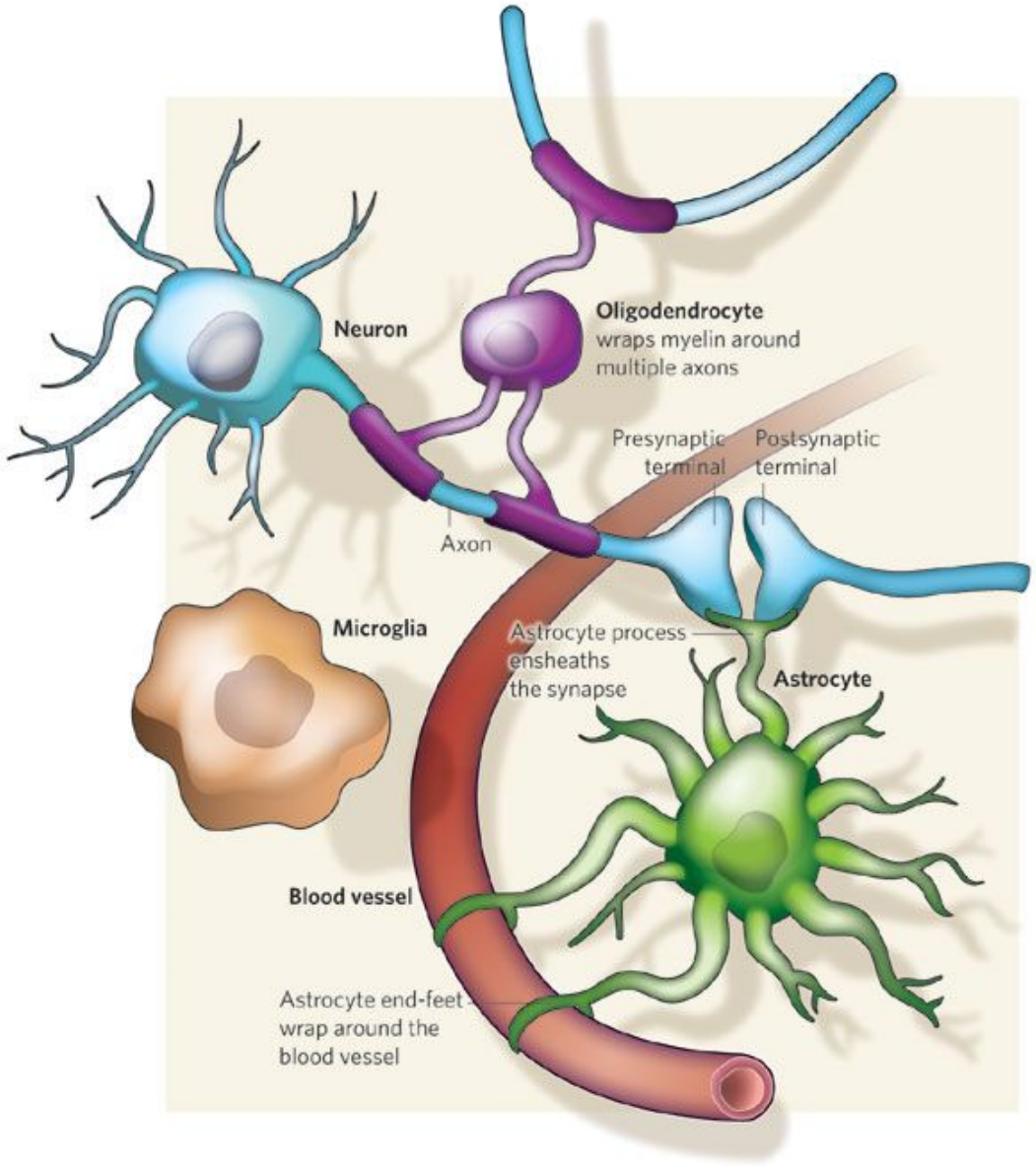
Myelin disorders

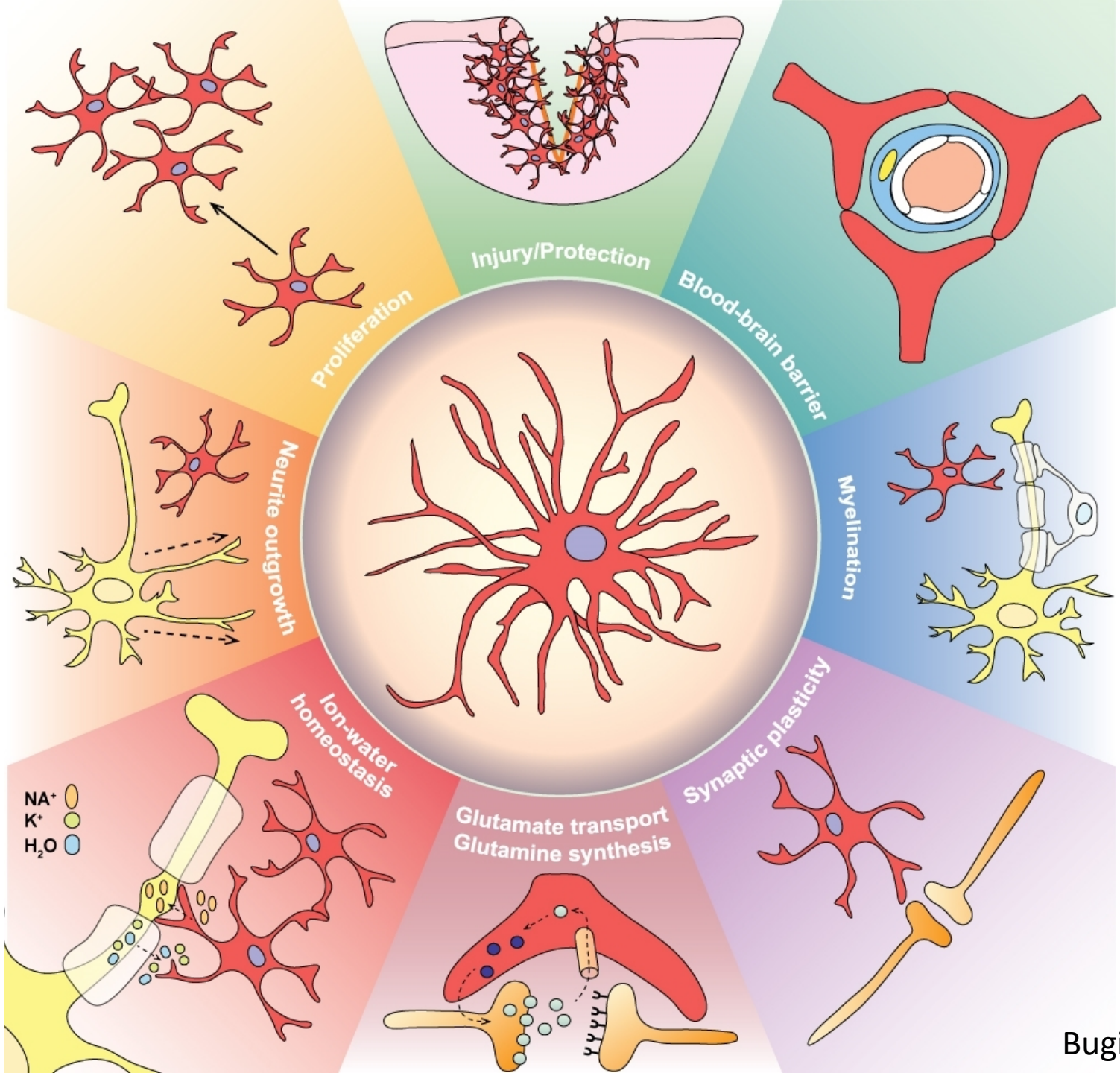
Astrocytopathies

Leuko-axonopathies

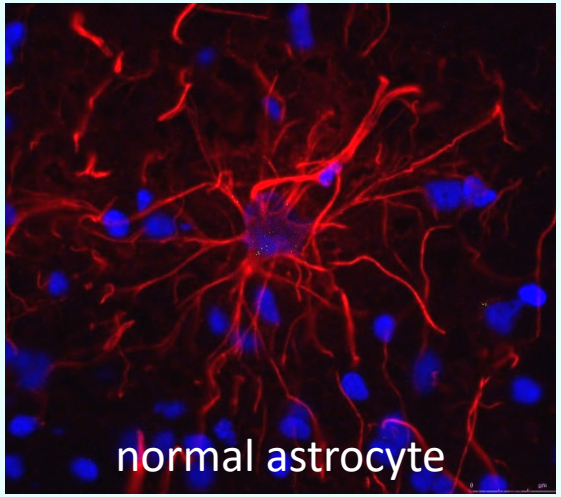
Leuko-microgliopathies

Leukovasculopathies



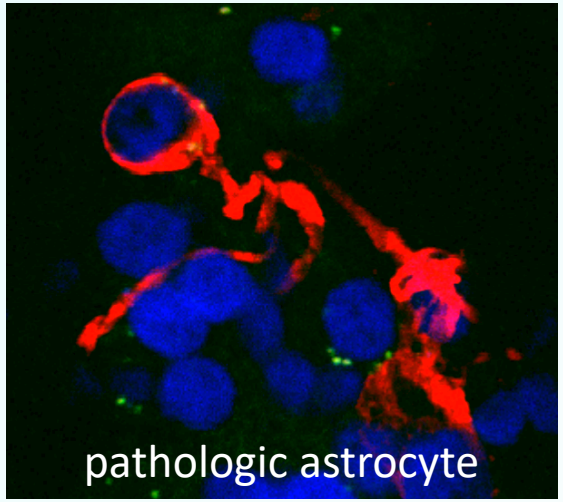


Bugiani & Breur, 2018



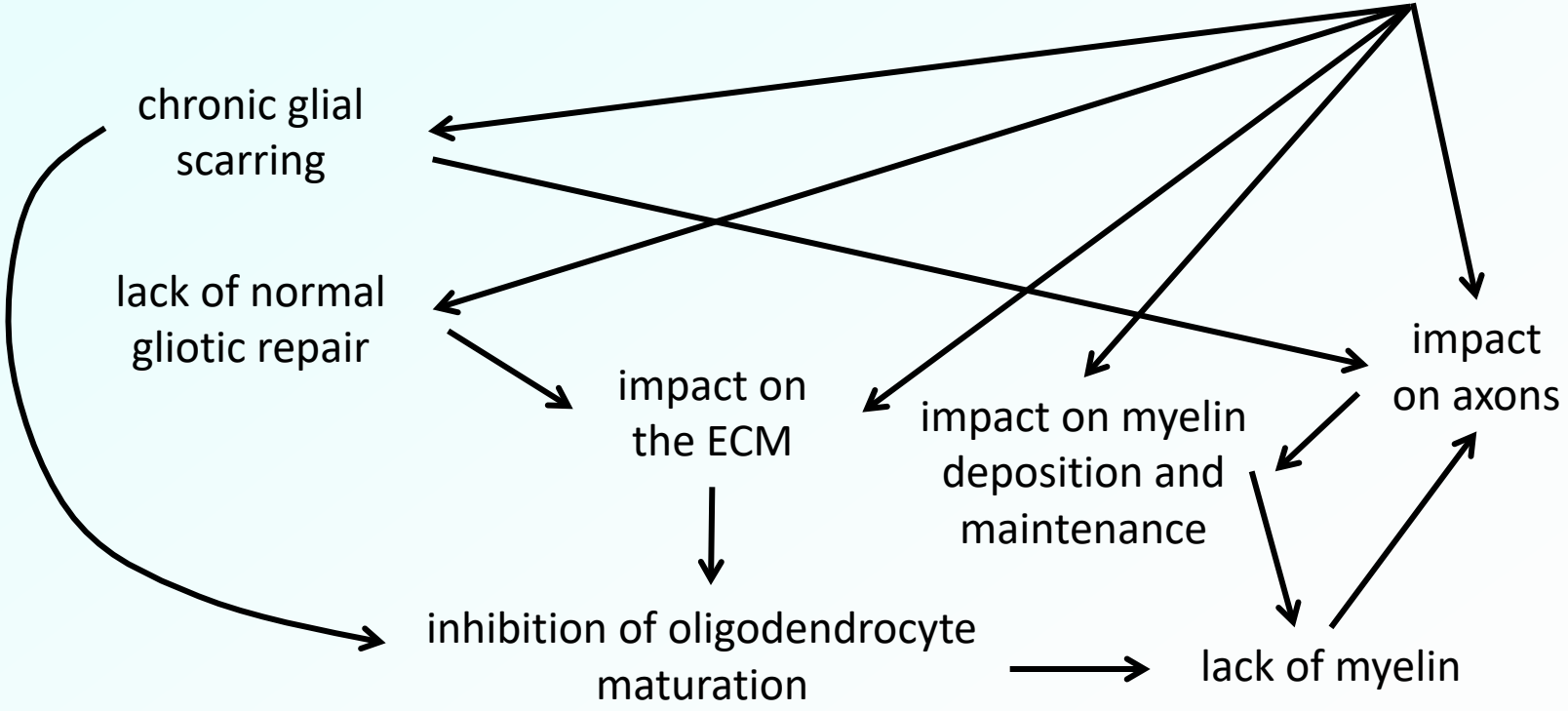
DISEASE

↑ and ↓ of specific proteins



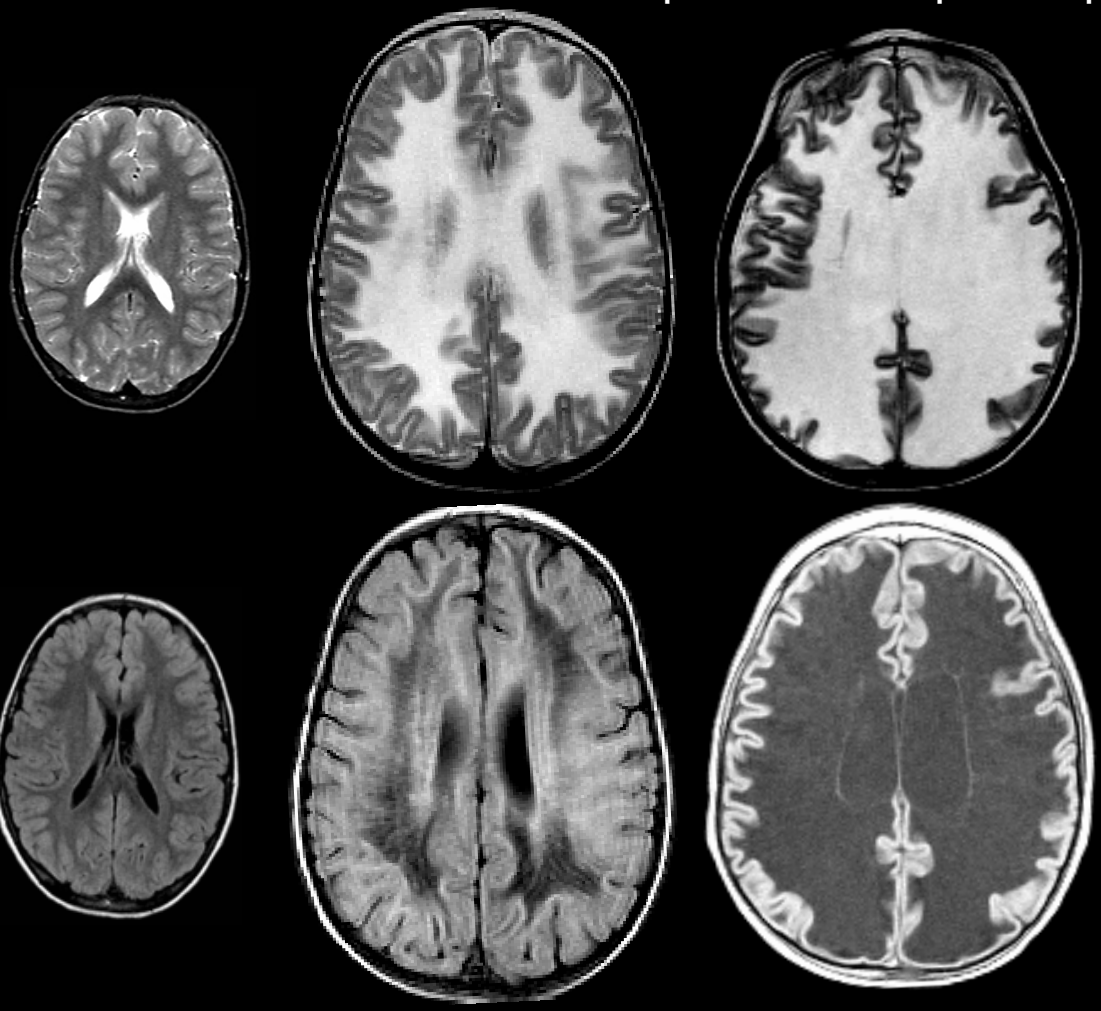
LOSS OF PHYSIOLOGIC FUNCTIONS

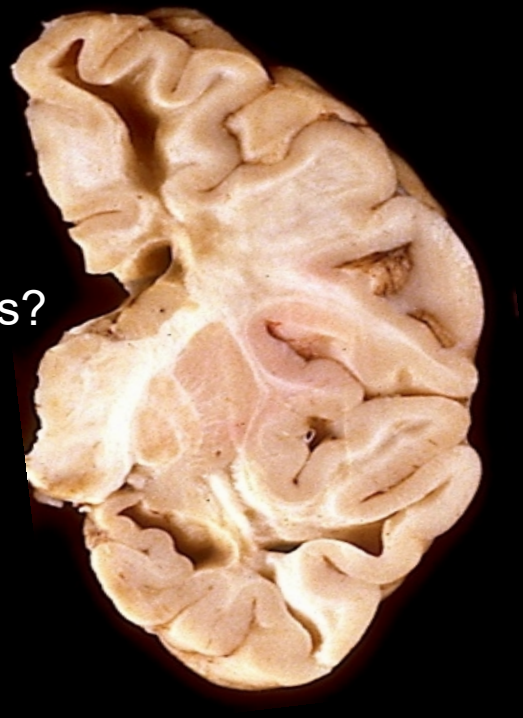
GAIN OF PATHOLOGIC FUNCTIONS

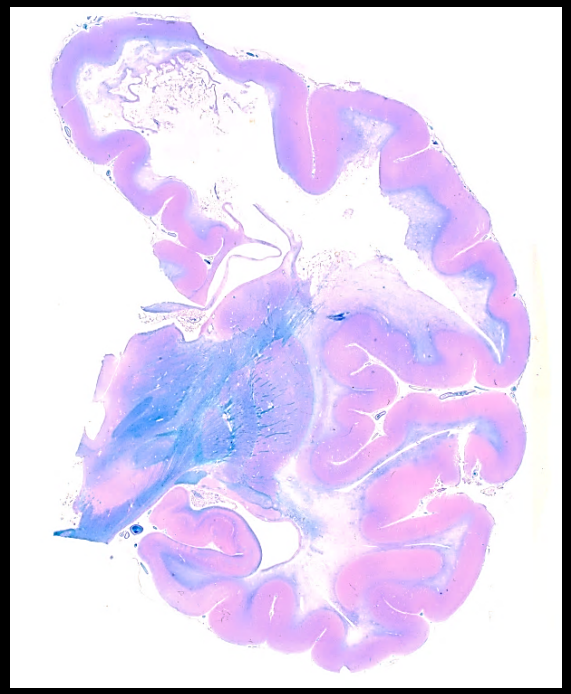


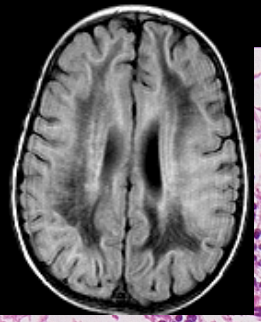
Vanishing White Matter

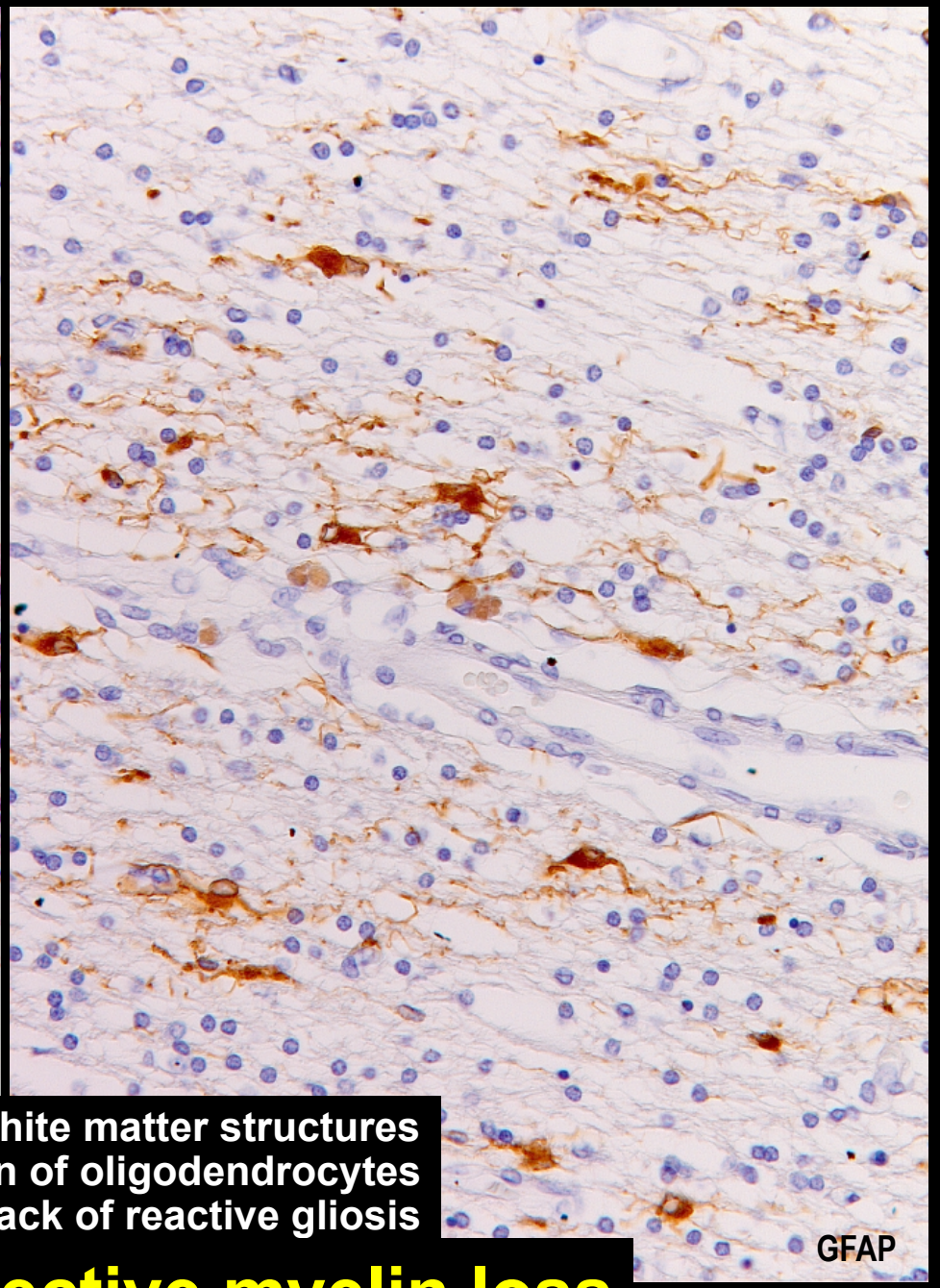
- Mutations in *EIF2B1-5*, encoding the 5 eIF2B subunits
- eIF2B: initiation of translation of all mRNAs
  regulation of general mRNA translation rate
- Disease mechanisms? Altered expression of specific proteins?







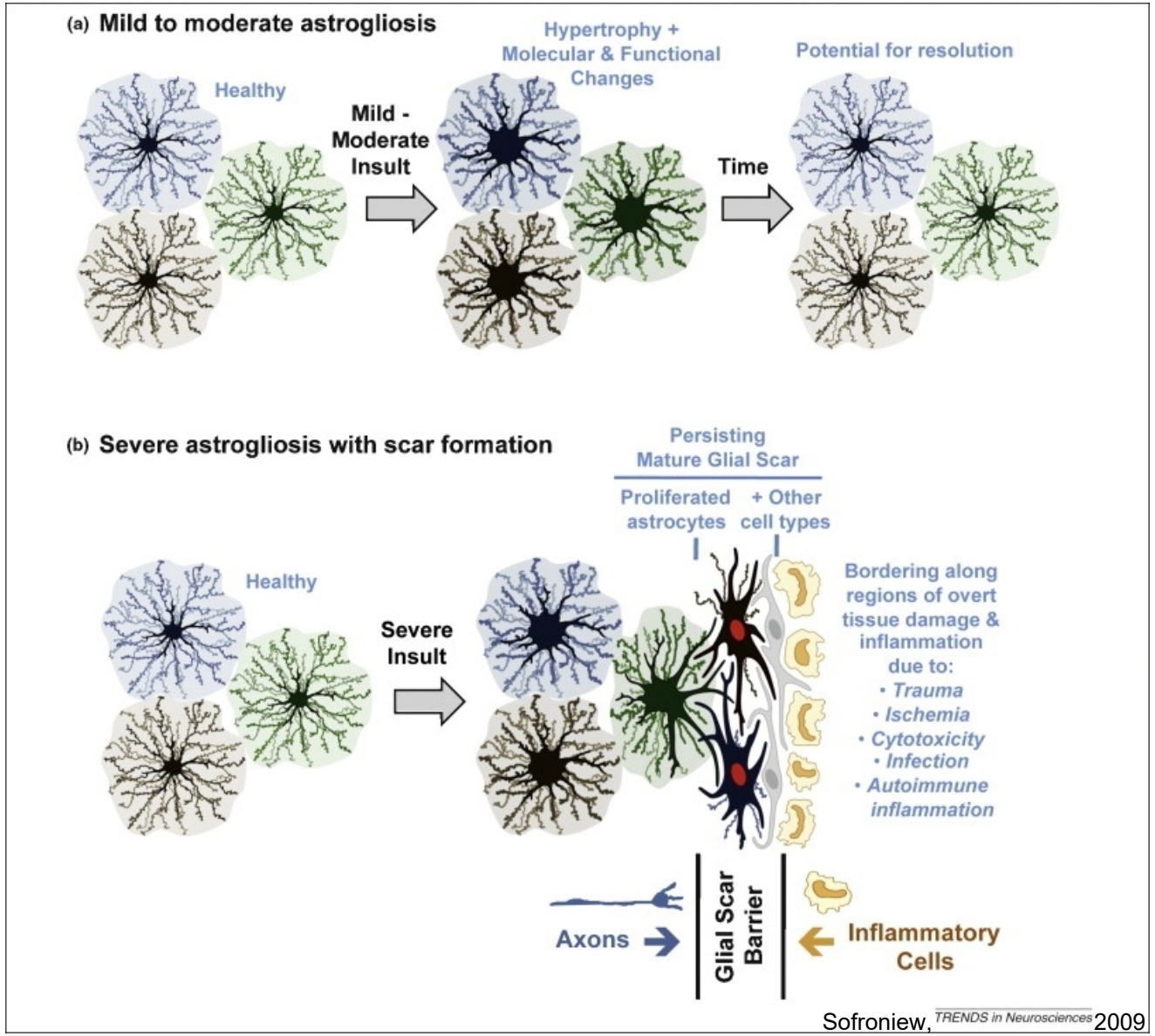




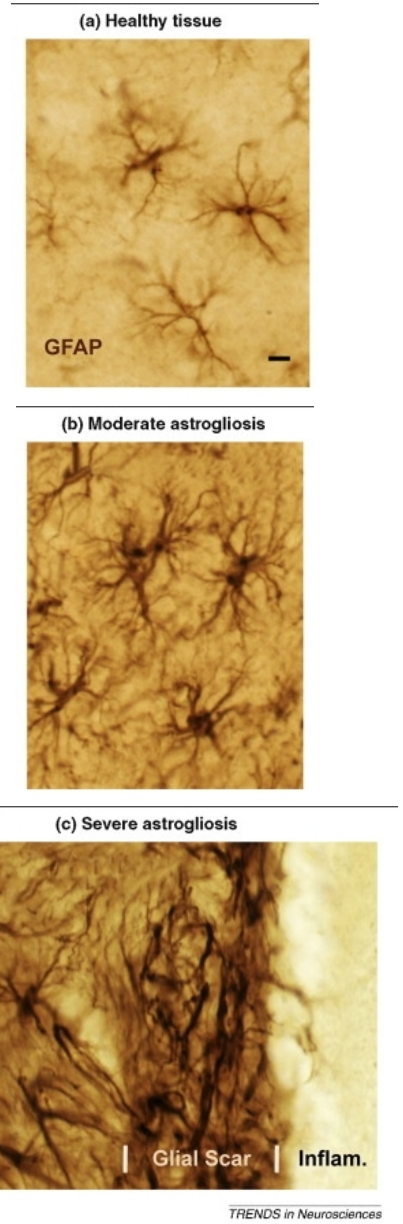
loss of all white matter structures
proliferation of oligodendrocytes
lack of reactive gliosis

no selective myelin loss

Reactive gliosis

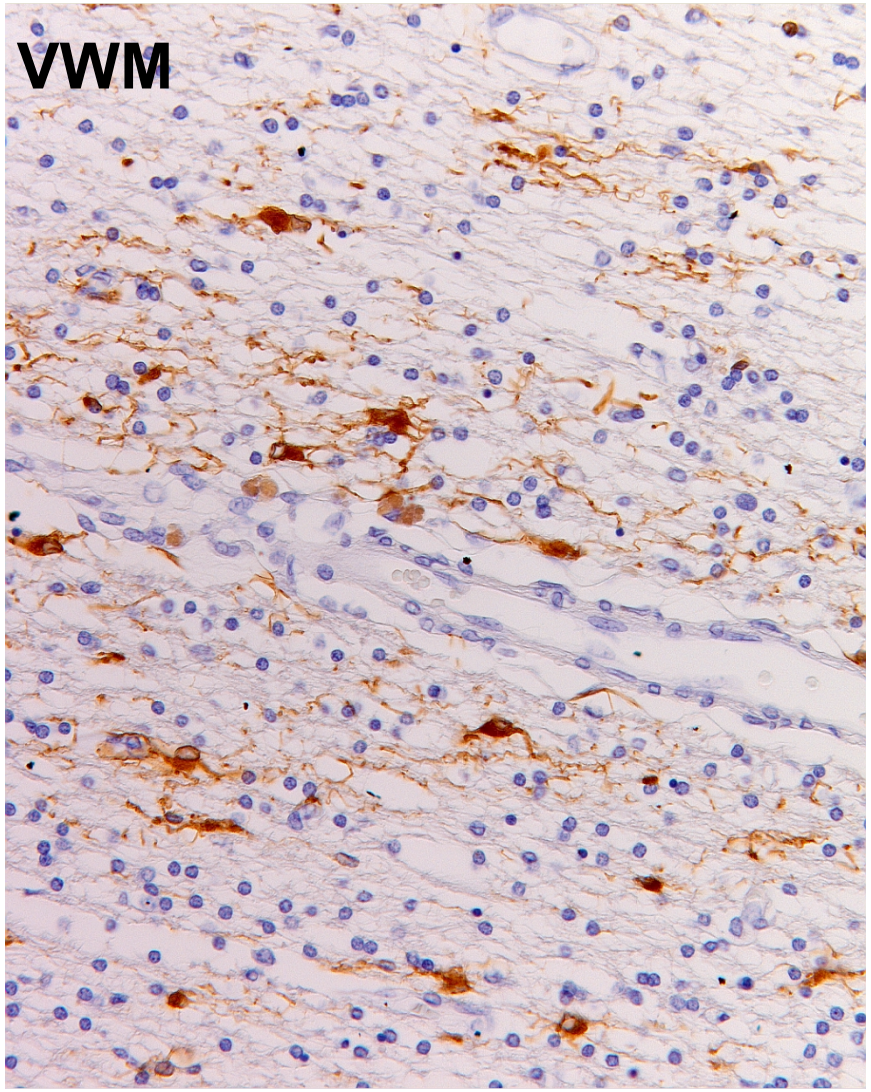


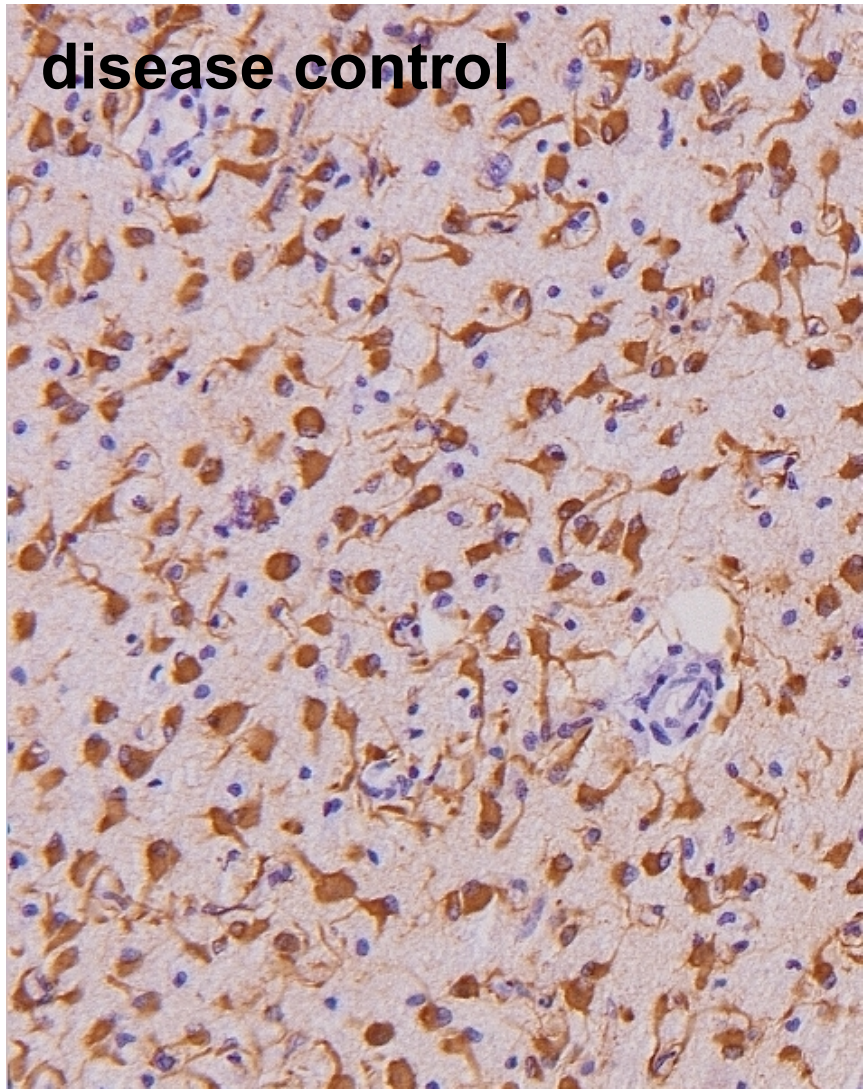
Sofroniew, TRENDS in Neurosciences 2009



TRENDS in Neurosciences

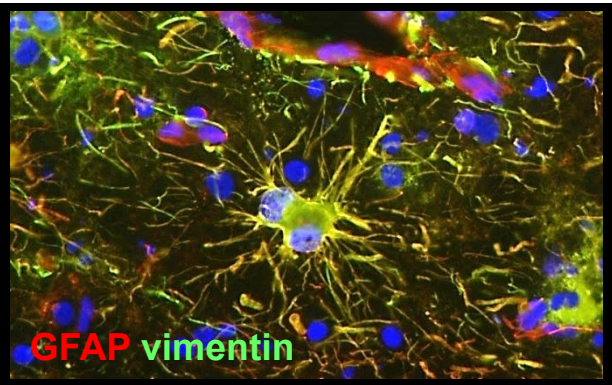
VWM white matter astrocytes proliferate, remain immature and lack mature function (e.g. astrogliotic scar tissue formation)

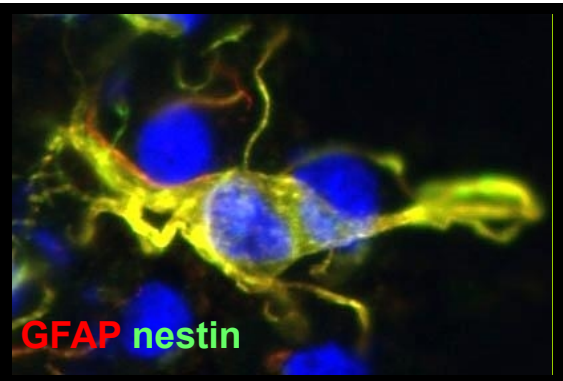


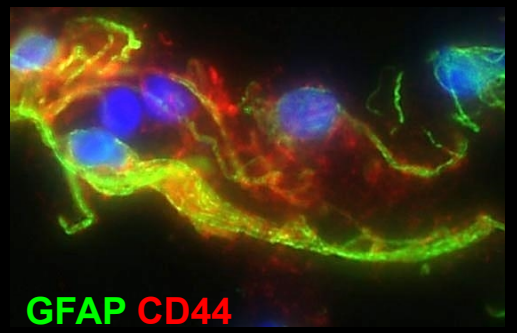


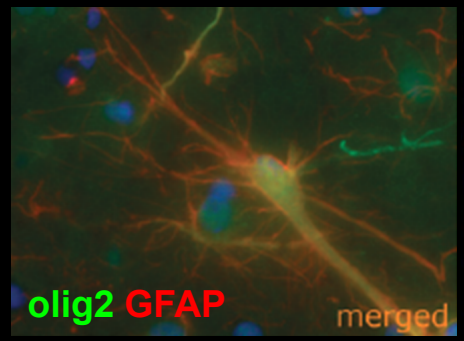
Bugiani *et al*., J Neuropathol Exp Neurol 2010; 69: 987-996
Bugiani *et al*., J Neuropathol Exp Neurol 2011; 70: 69-82

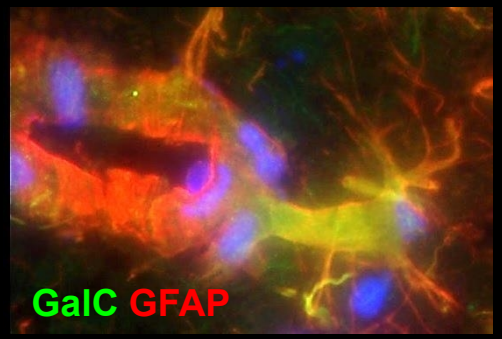
VWM white matter astrocytes remain immature

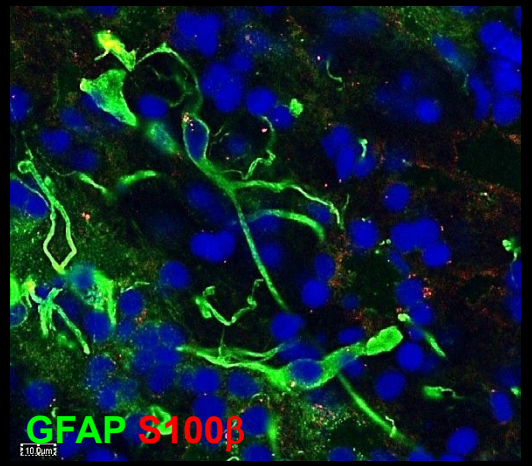


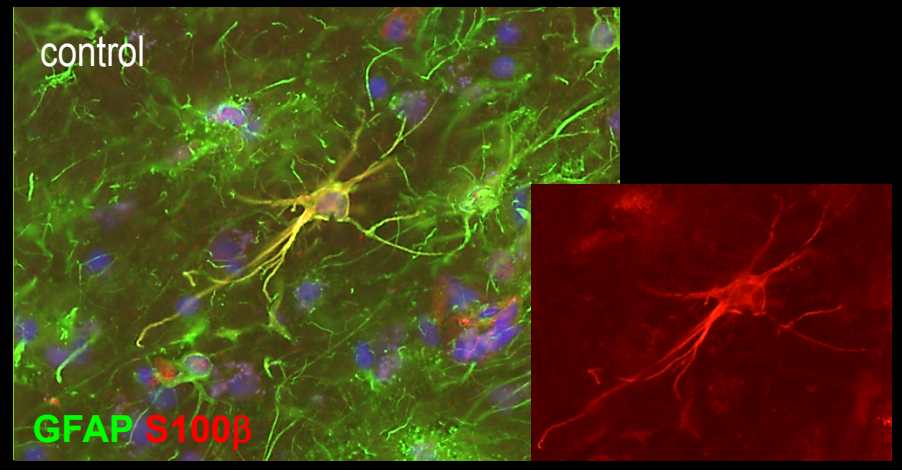






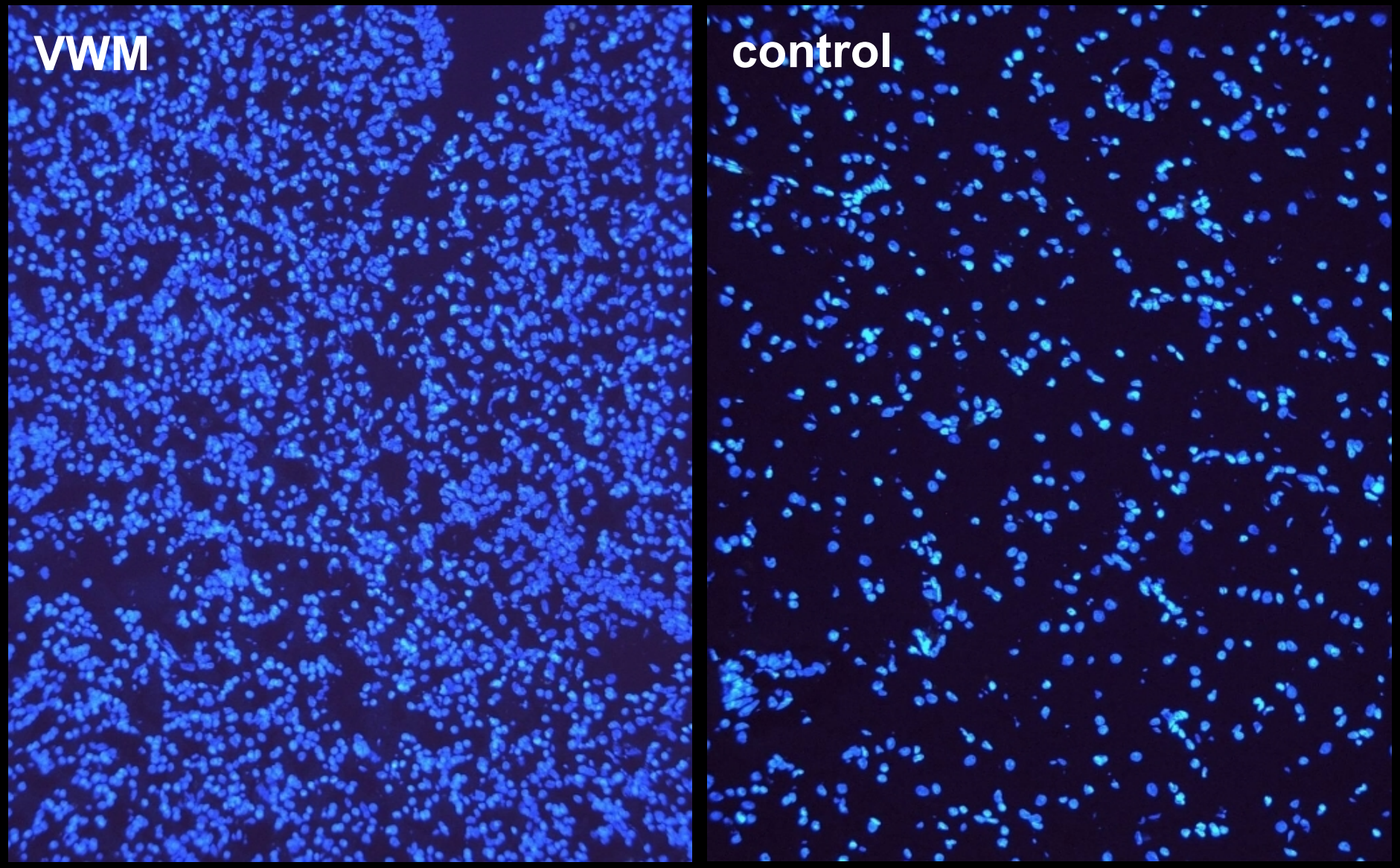




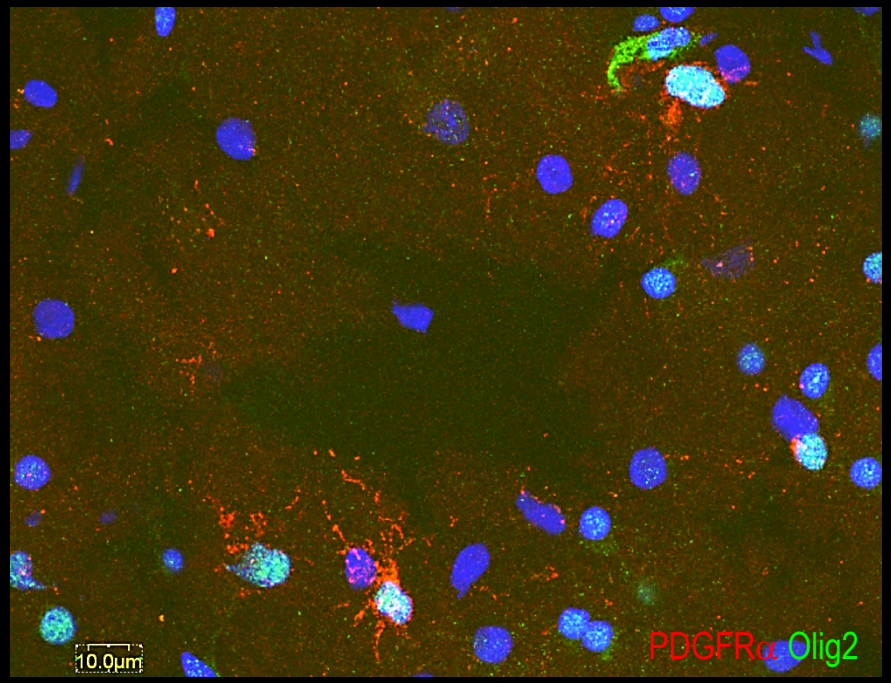


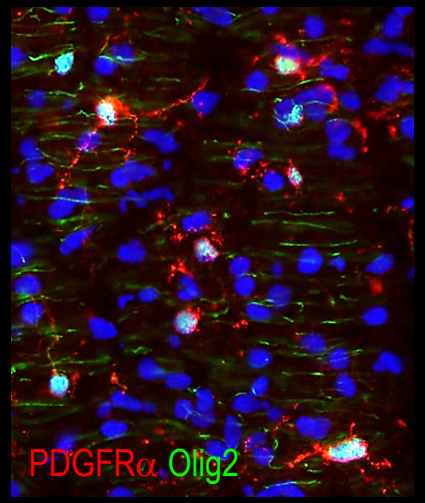
Bugiani *et al*., J Neuropathol Exp Neurol 2010; 69: 987-996
Bugiani *et al*., J Neuropathol Exp Neurol 2011; 70: 69-82

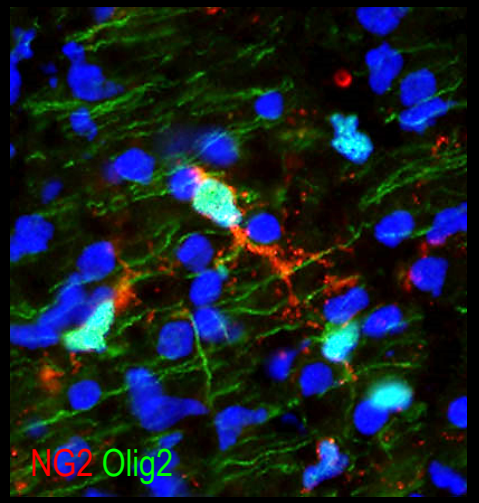
VWM white matter:
lack of myelin but too many oligodendrocytes

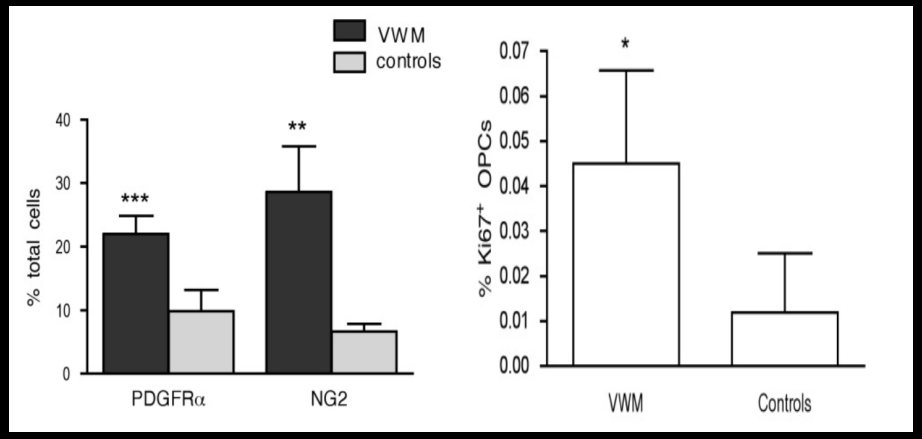


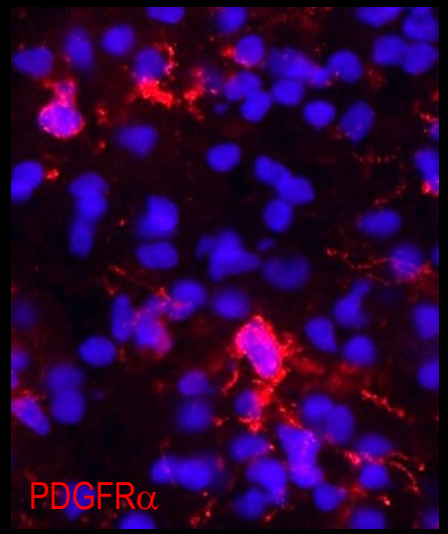
Oligodendrocytes proliferate and are increased in number, but they remain immature and lack of mature myelination function

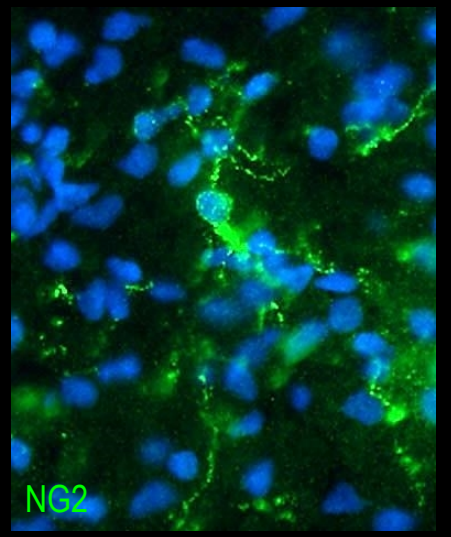






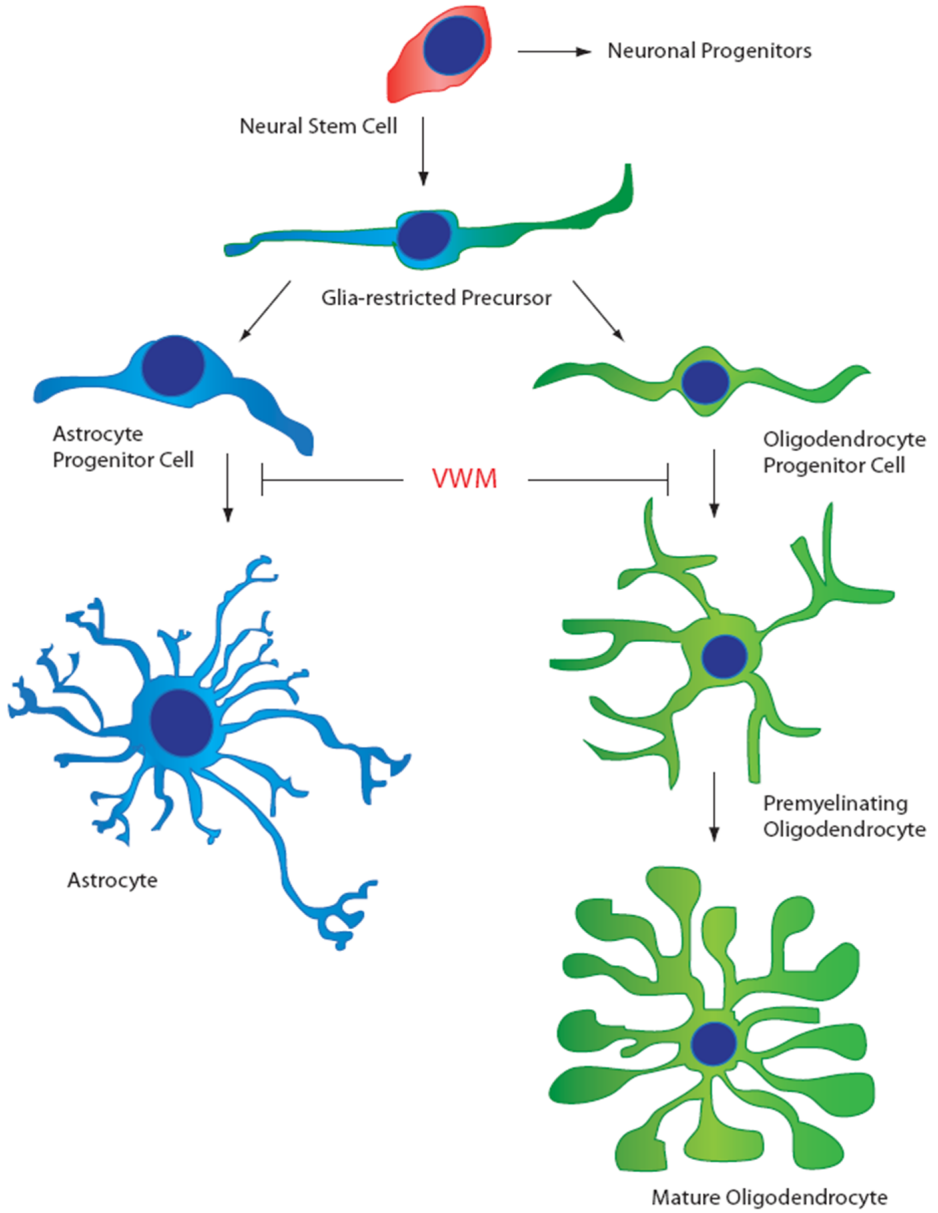






Bugiani *et al.*, J Neuropathol Exp Neurol 2011; 70: 69-82

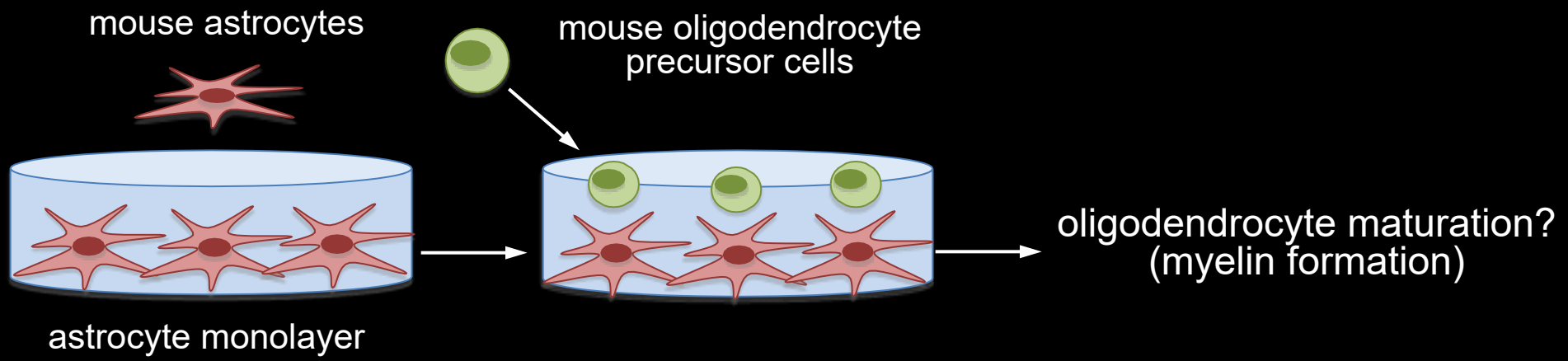
Deficient maturation of macroglial cells in VWM white matter driven by astrocytic dysfunction



Courtesy of GC Scheper

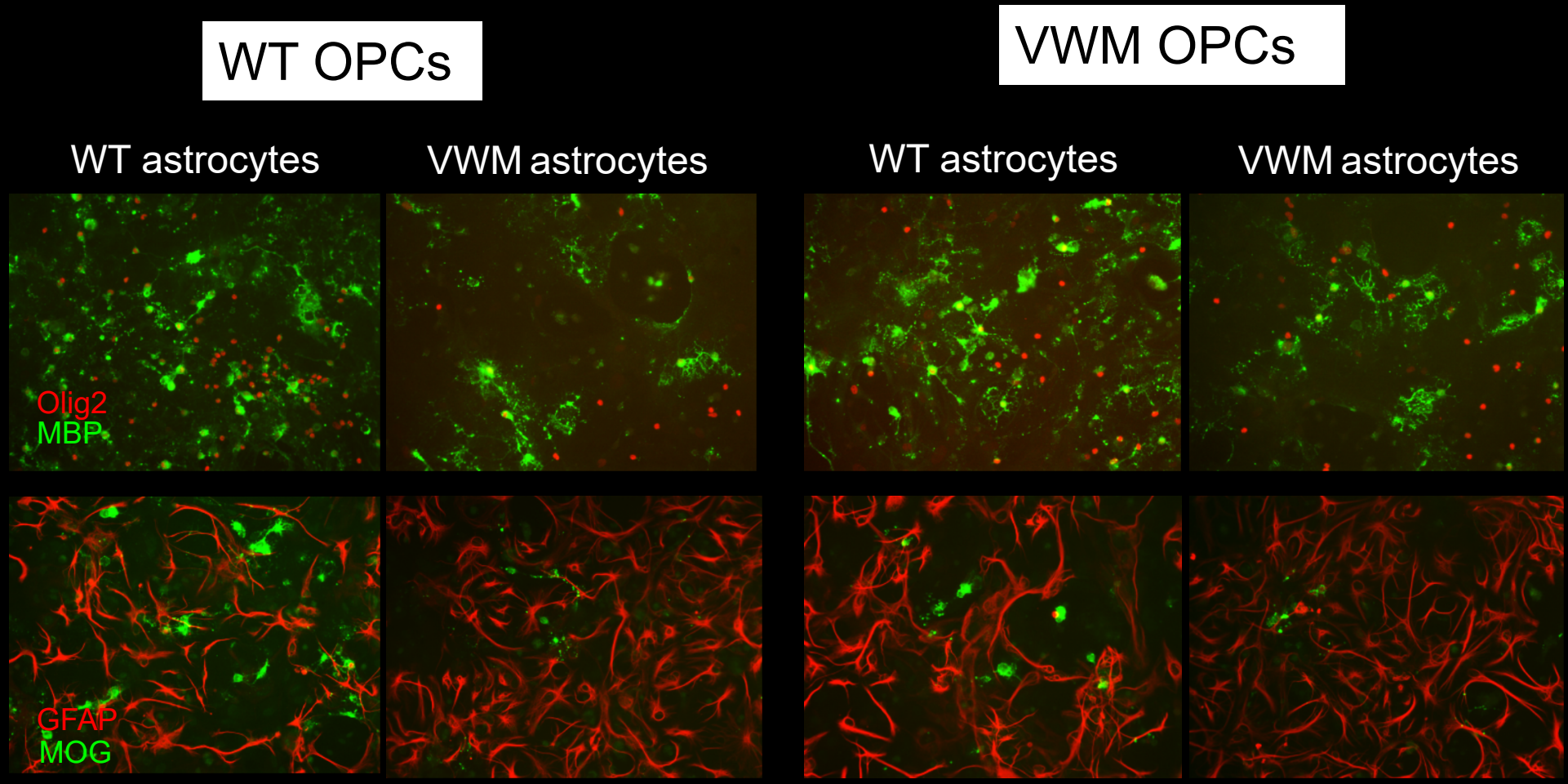
Does the VWM defect impact oligodendrocytes and astrocytes at the same time or is one causing the dysfunction of the other?

Studies in cocultures, using VWM mouse cells



Dooves S & Bugiani M, *et al.*
J Clin Invest 2016; 126: 1512-1524

VWM astrocytes have a negative impact on both WT and VWM oligodendrocytes, but VWM oligodendrocytes display normal myelin production with WT astrocytes

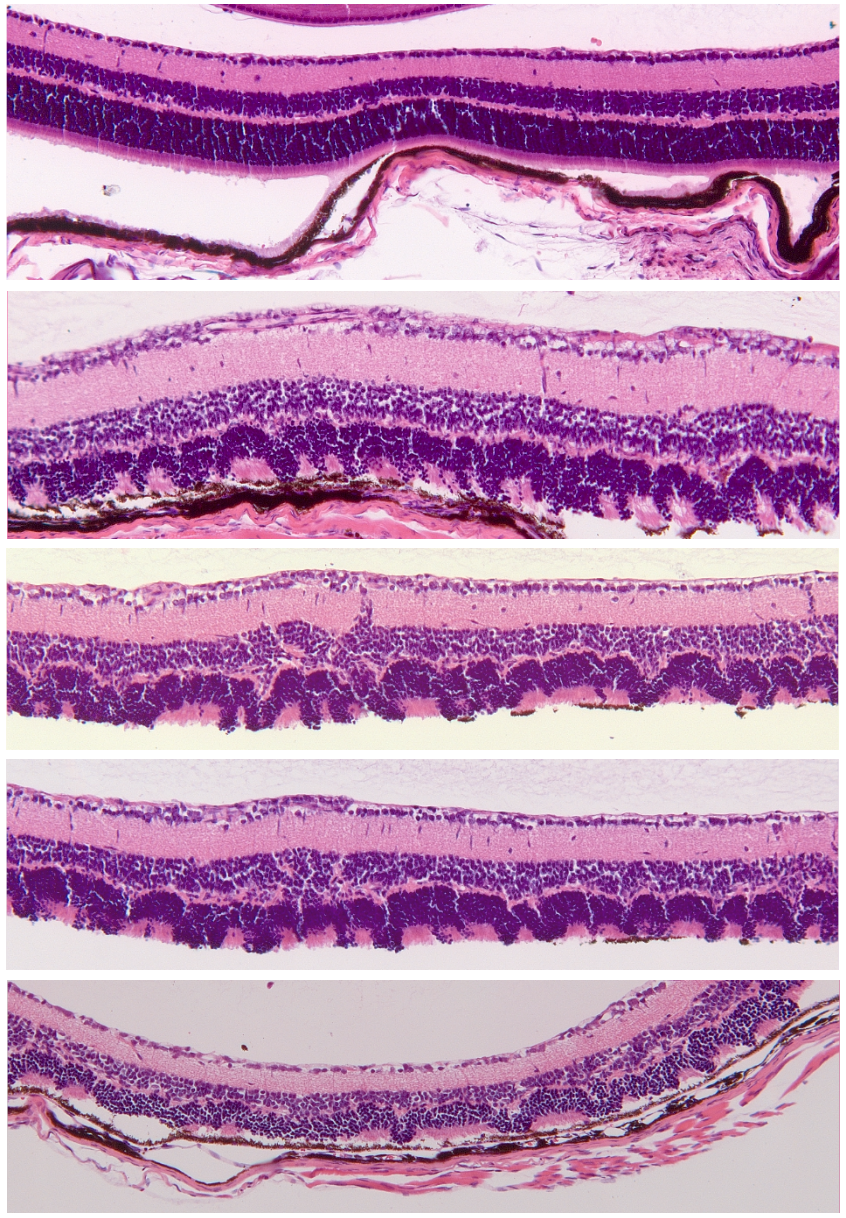


- So, VWM OPCs do not have an intrinsic problem

VWM mice: the eye pathology

Wild-type

2b4/2b5



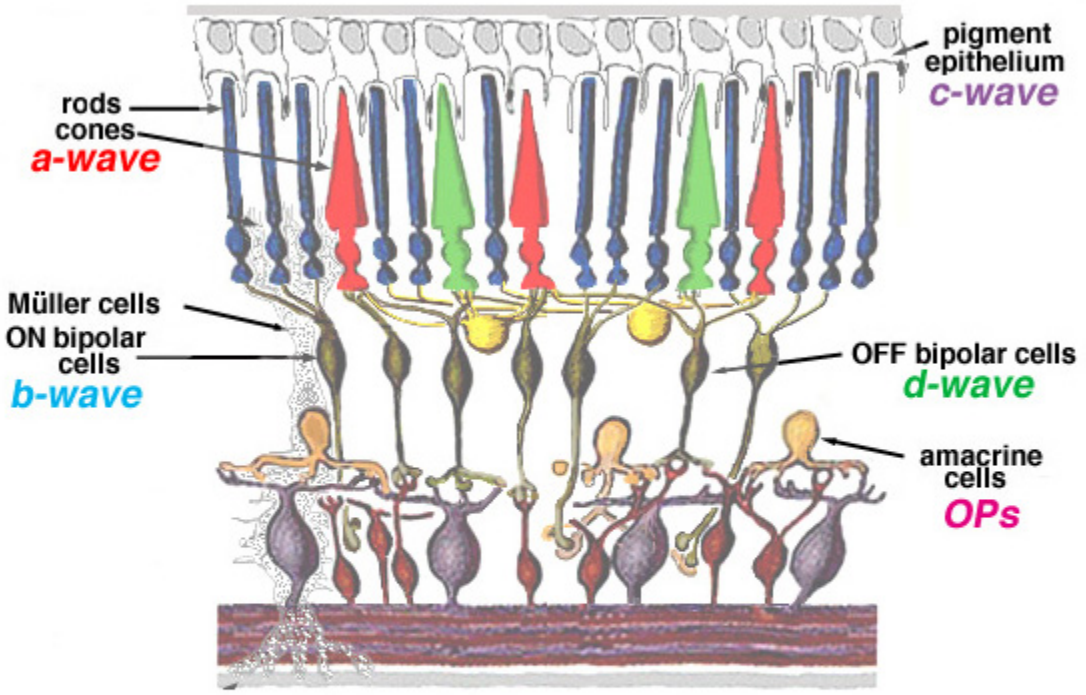


Fig.3 Cartoon of the retina to show where the major components of the ERG originate.

A new classification of leukodystrophies

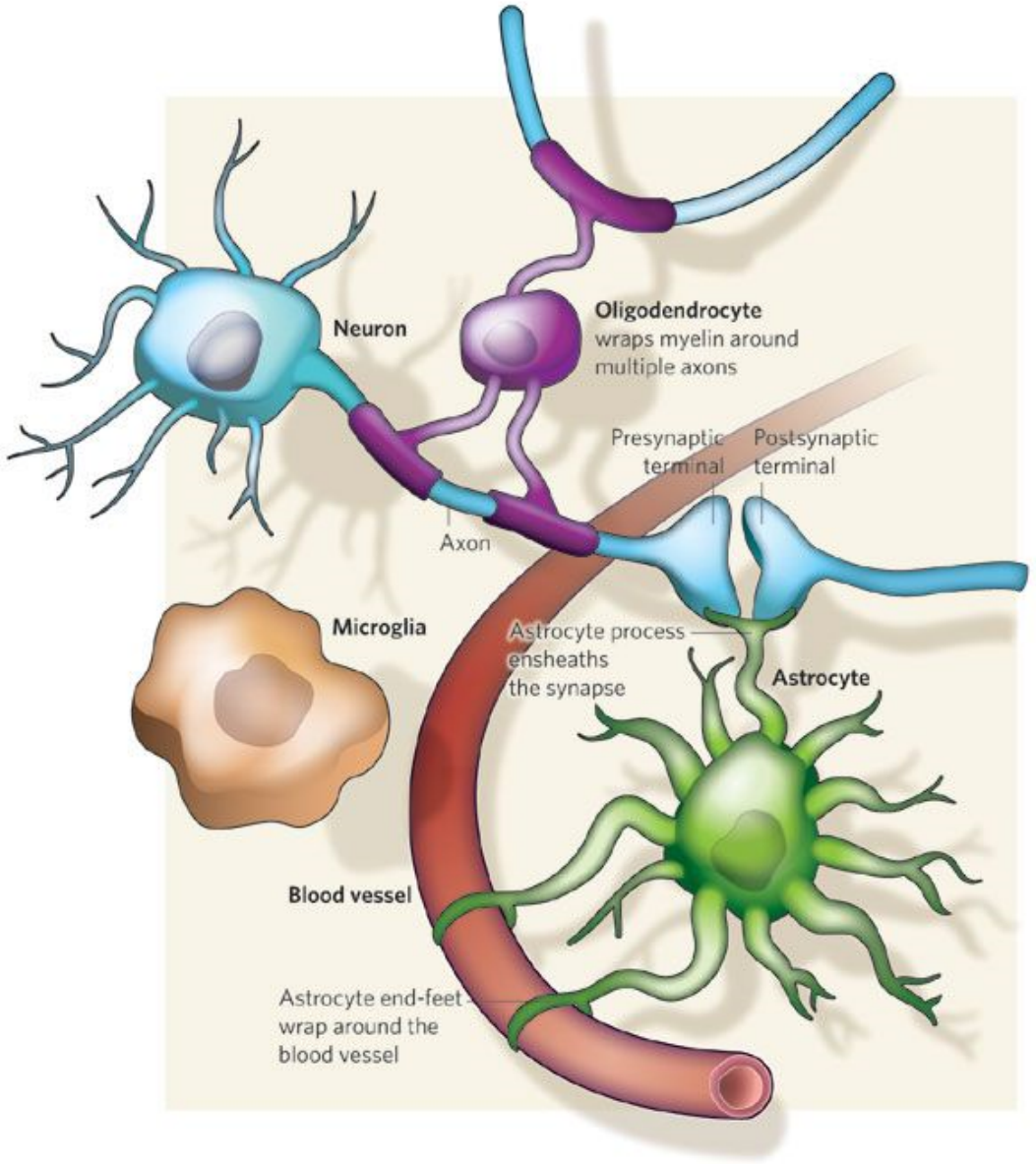
Myelin disorders

Astrocytopathies

Leuko-axonopathies

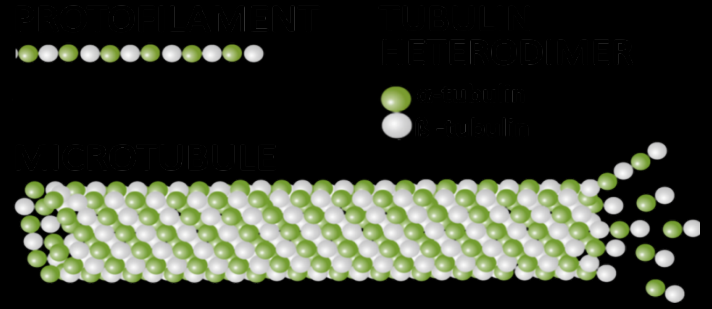
Leuko-microgliopathies

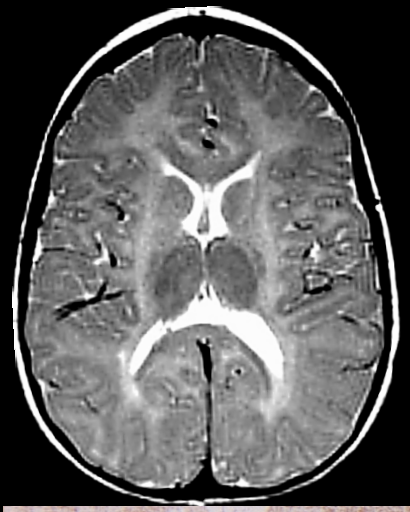
Leukovasculopathies

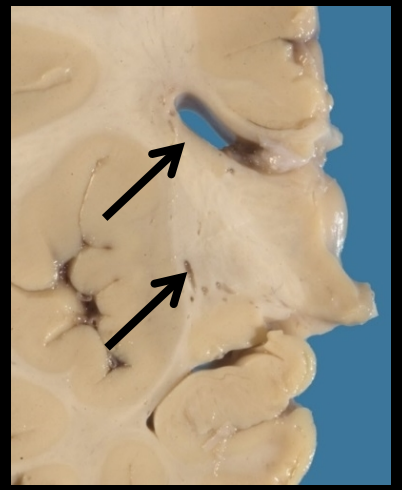


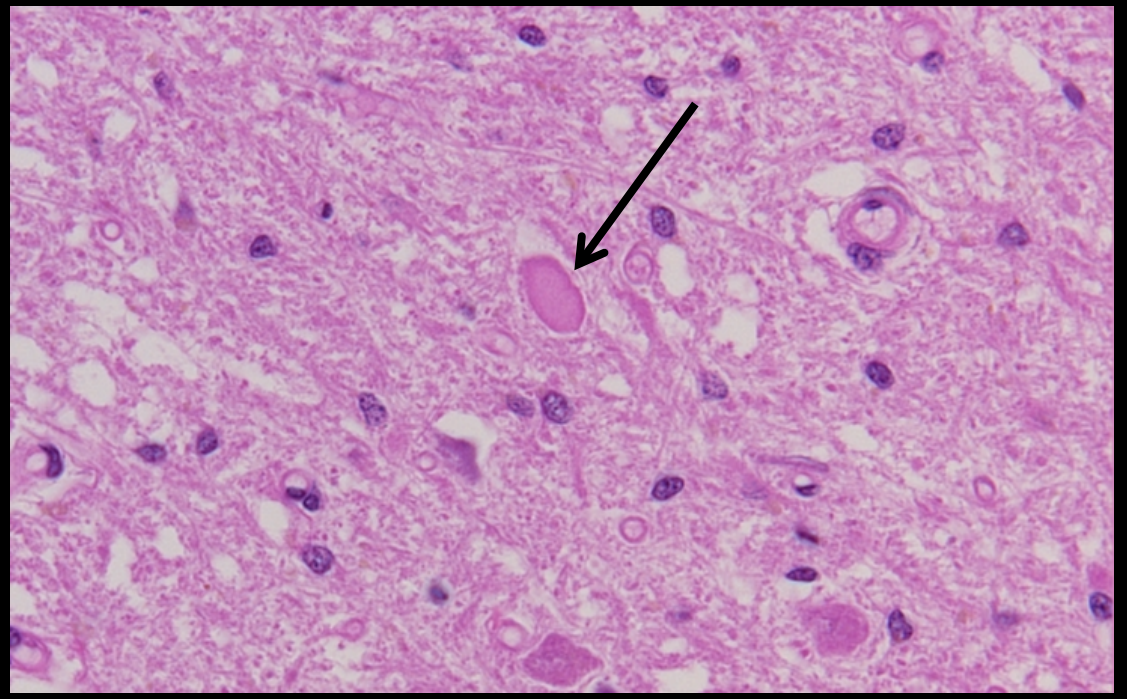
Hypomyelination with Atrophy of Basal ganglia and Cerebellum

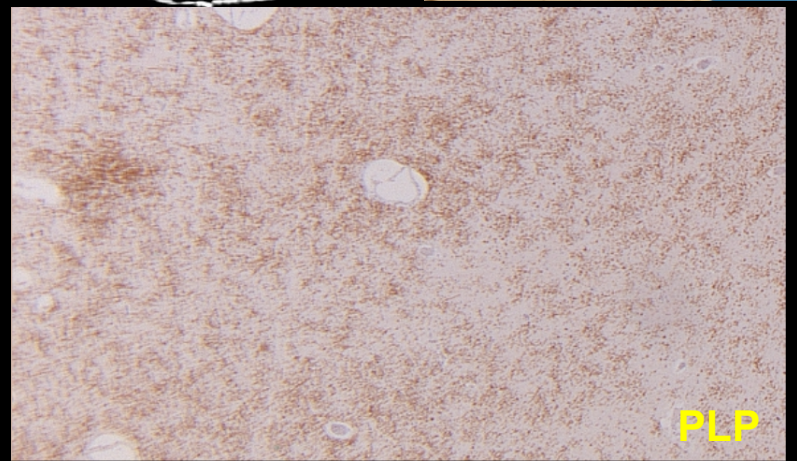
- Mutations in *TUBB4A*
- Defect in β-tubulin, affecting microtubules
- Probably affecting axonal transport





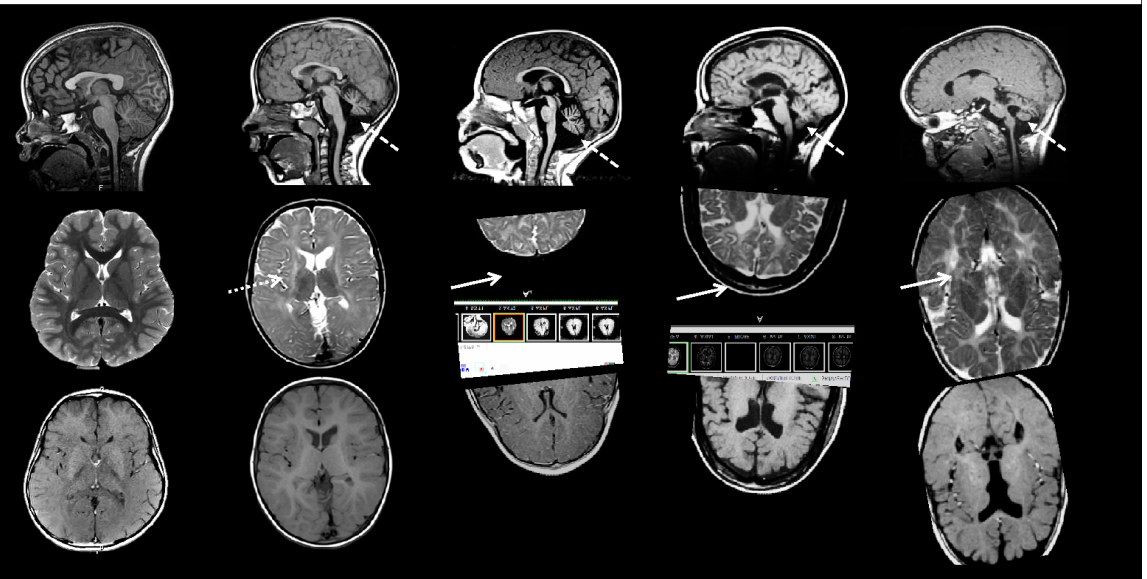


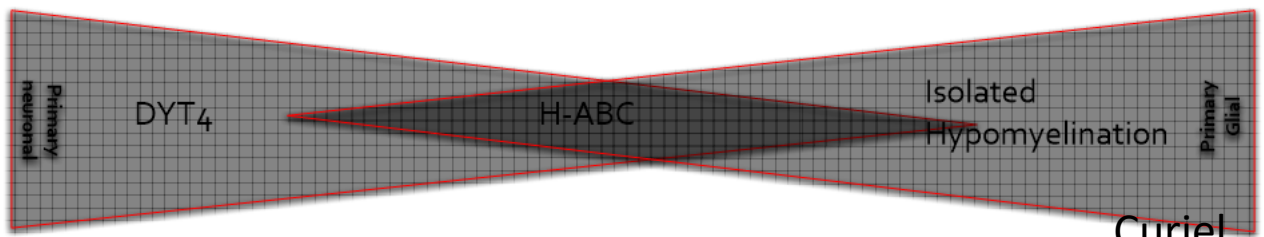




axonal spheroids
lack of myelin
lack of oligodendrocytes
mild gliosis

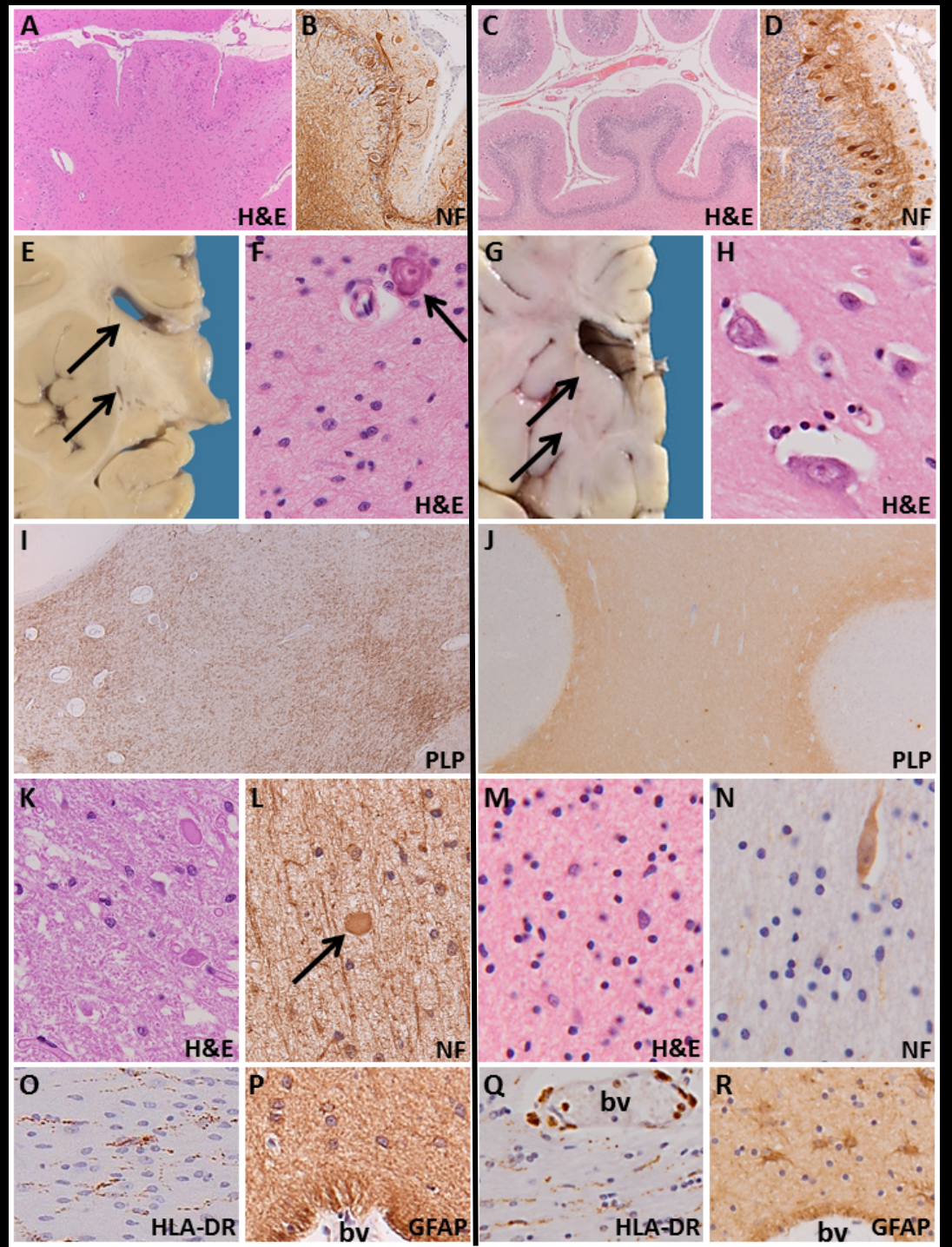
axonal dysfunction
secondary lack of myelin deposition

Disease description	Whispering Dysphonia (DYT4)	H-ABC	Isolated Hypomyelination	Isolated Hypomyelination	Early infantile encephalopathy
Amino acid change	p.Arg2Gly	p.Asp249Asn	p.Val255Ile	p.Arg282Pro	p.Asn414Lys
Nucleic acid change	c.4C>G	c.745G>A	c.763G>A	c.845G>C	c.1242C>G
Sagittal T_1 Axial T_2 Axial T_1					
	5 yo healthy male	4 yo female	5 yo female	45 yo female	3 yo male
Imaging features	No structural Abnormalities	Hypomyelination and atrophy of the basal ganglia, cerebellum, and corpus callosum	Hypomyelination and atrophy of cerebellum	Hypomyelination and atrophy of the cerebellum	Severe hypomyelination, normal basal ganglia, severe atrophy of cerebellum
Clinical features	Dysphonia, gait affected, and dystonia	Ataxia, dystonia and intellectual disability	Spastic quadriparesis, ataxia	Spastic paraparesis, intellectual disability	Severe intellectual disability, motor deterioration, epilepsy, early death



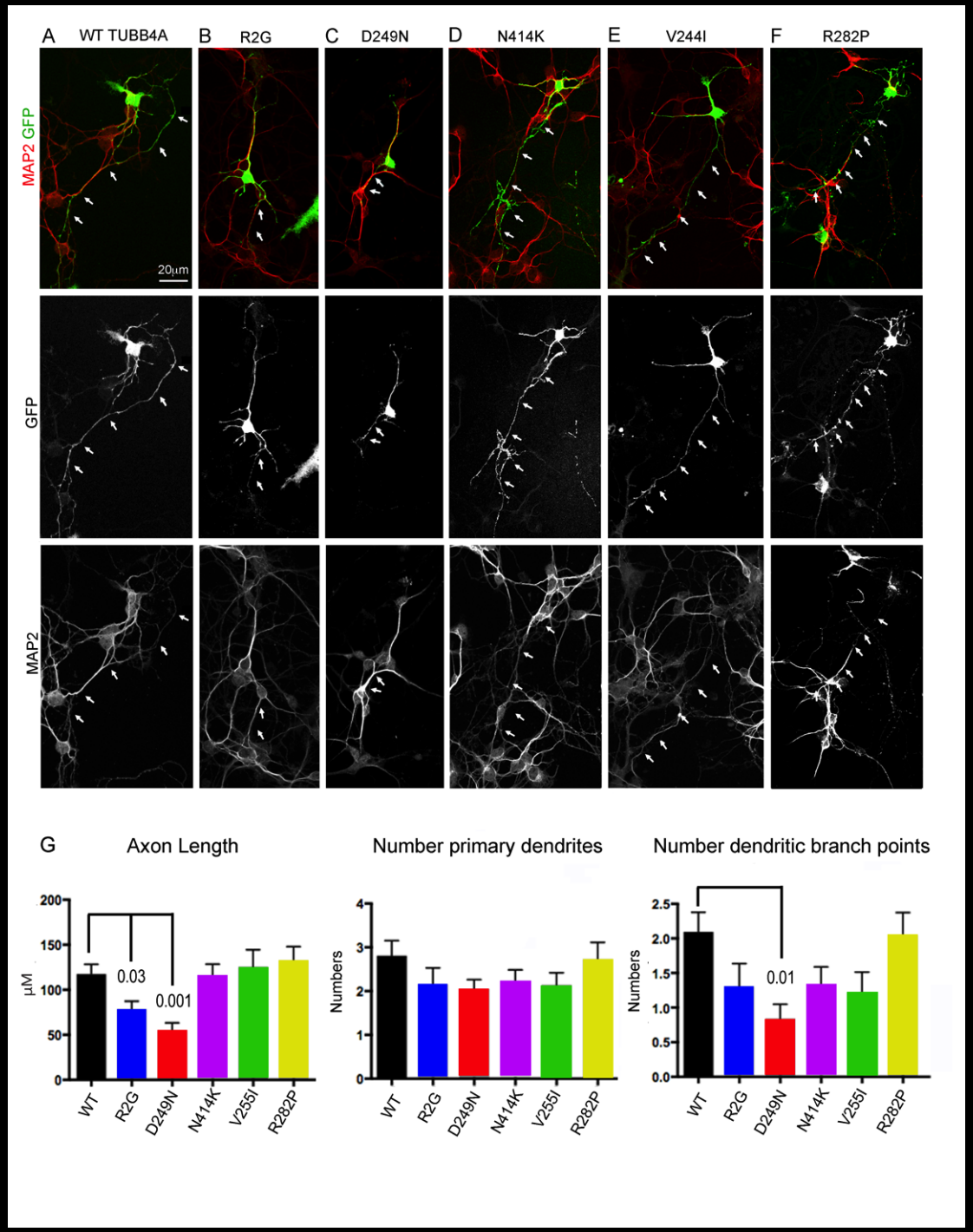
Curiel, … Bugiani, 2017

H-ABC: two distinct neuropathological phenotypes



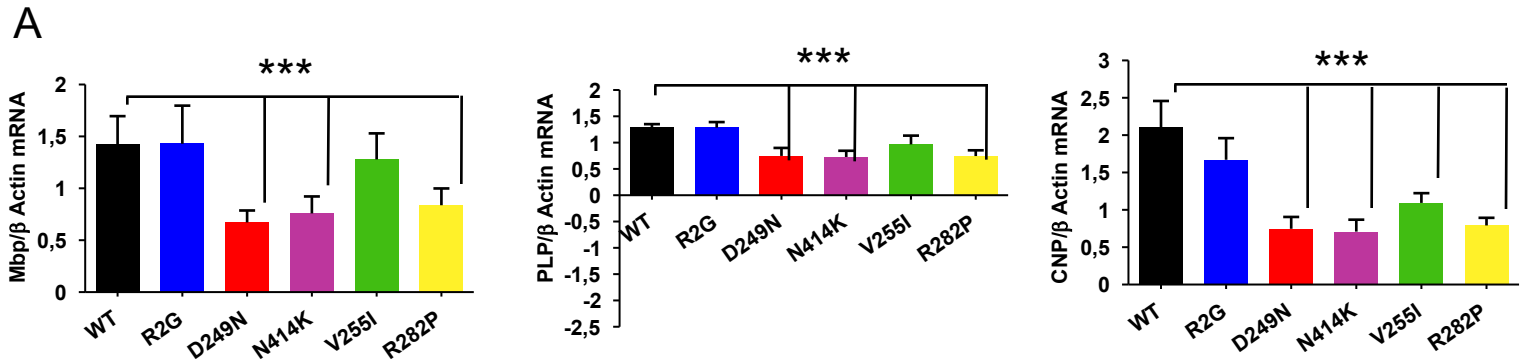
Curiel, … Bugiani, 2017

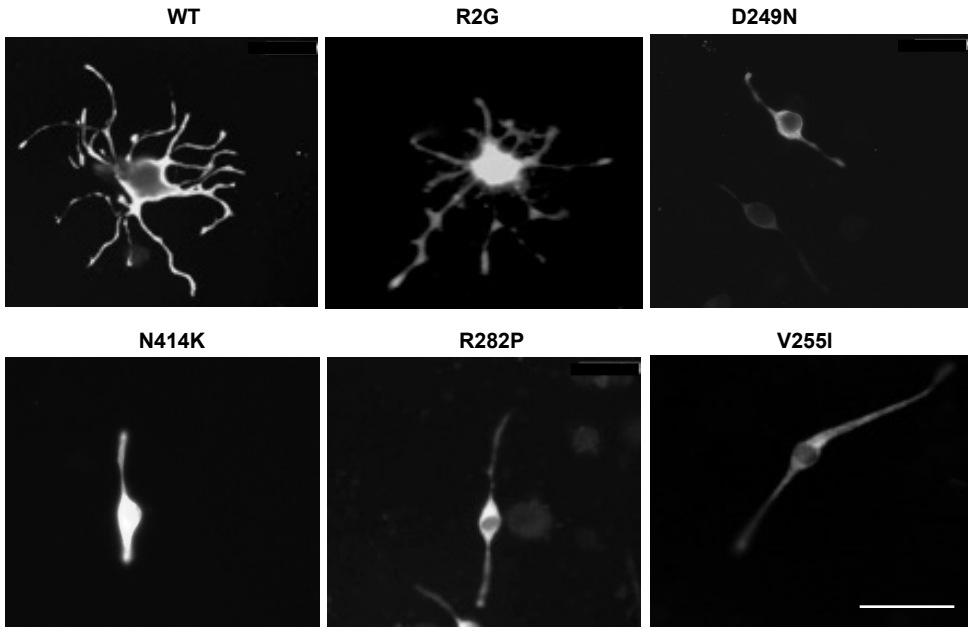
H-ABC: the neuronal phenotype

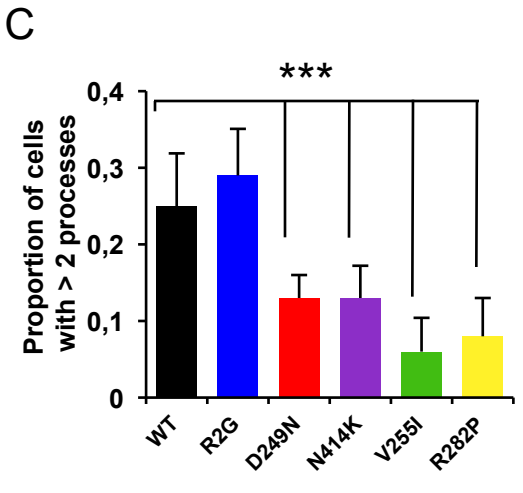


Curiel, … Bugiani, 2017

H-ABC: the oligodendrocytic phenotype

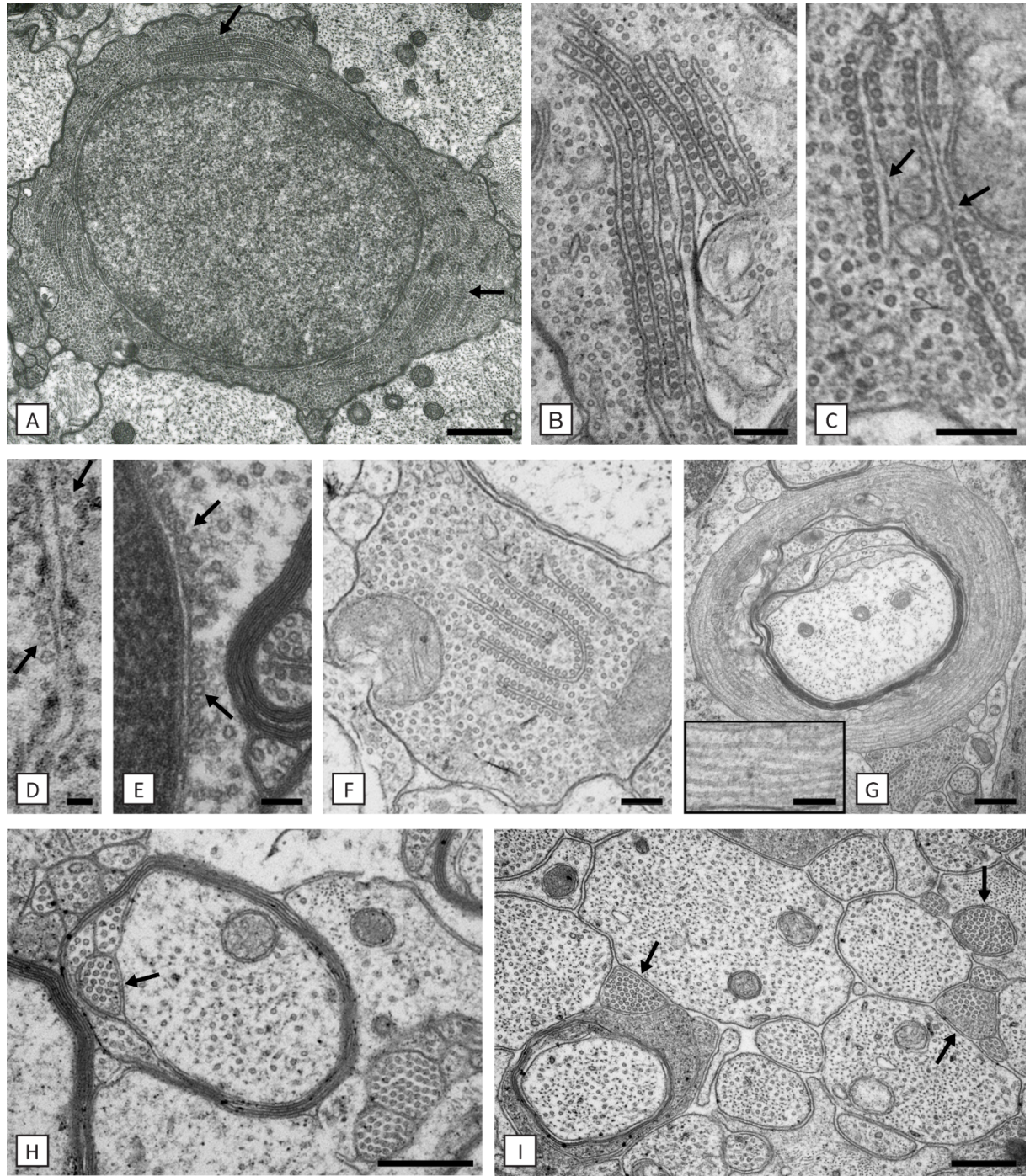






Curiel, … Bugiani, 2017

Figure 3



Duncan, Bugiani…, 2017

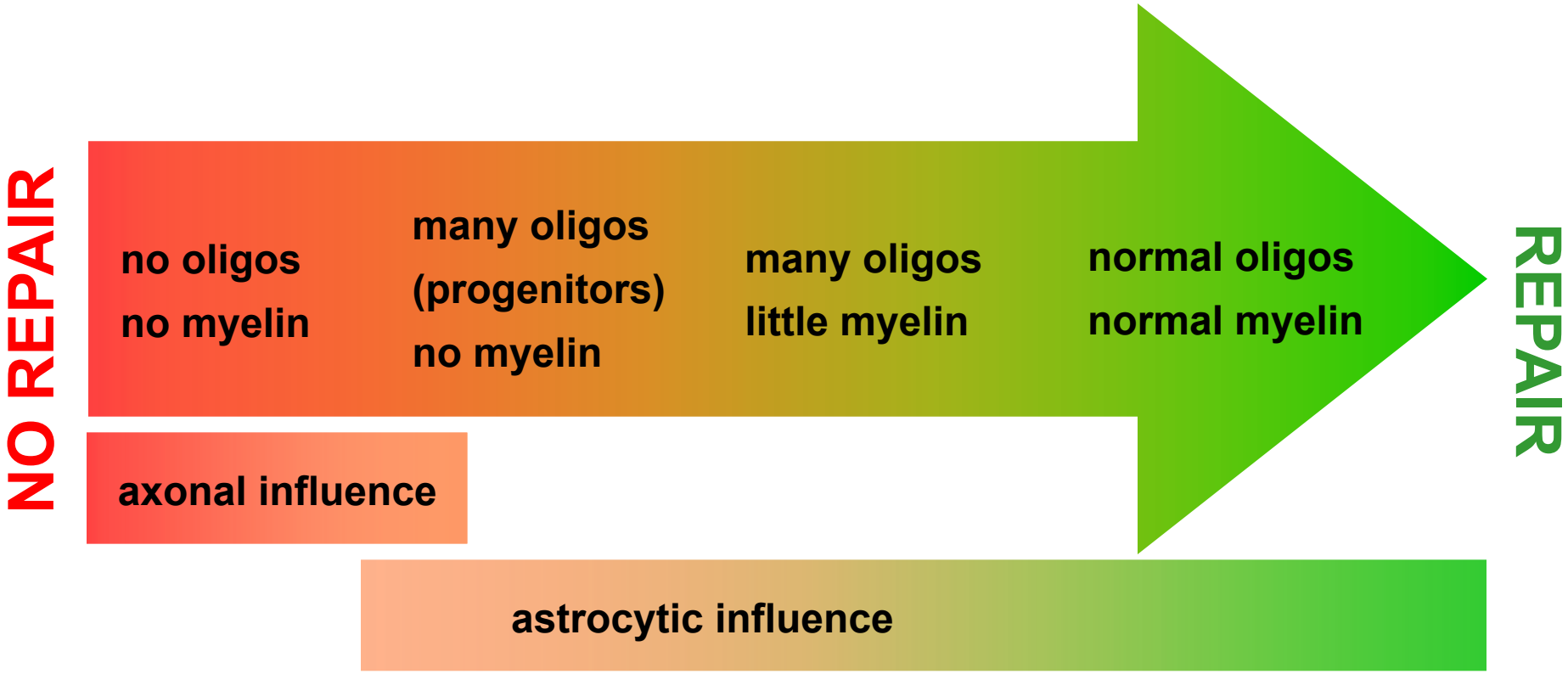
Conclusions

- The definition of leukodystrophies had to be revised
- Genetic disorders in which *any* white matter structural component is primarily affected

Importance of a new definition

- Better understanding of the complexity of the brain white matter
- When treating patients with leukodystrophies, we need to repair more than myelin alone

The intrinsic repair potential of leukodystrophies



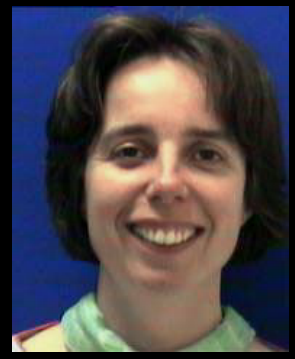
The Amsterdam leukodystrophy center: the PIs


Marjo van der Knaap


Marianna Bugiani


Nicole Wolf


Niek van Til


Truus Abbink


Rogier Min

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