Joint webinar series

Hypomyelinating Leukodystrophies

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DG 'Leukodystrophies'
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Emma Children's Hospital Amsterdam UMC

Amsterdam Leukodystrophy Center

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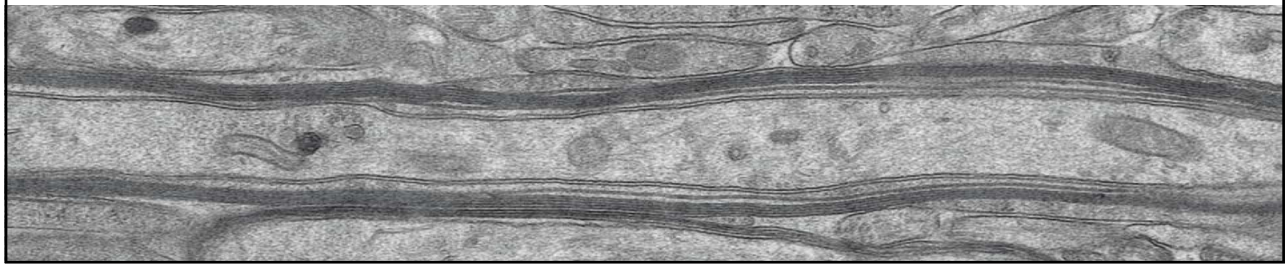
Outline

- What is myelin and what is myelination?
- Definition of hypomyelination
- Different MRI patterns in hypomyelination
- What kind of proteins are involved in hypomyelination (= what proteins are essential for normal myelination)?
- Why is a genetic diagnosis important?



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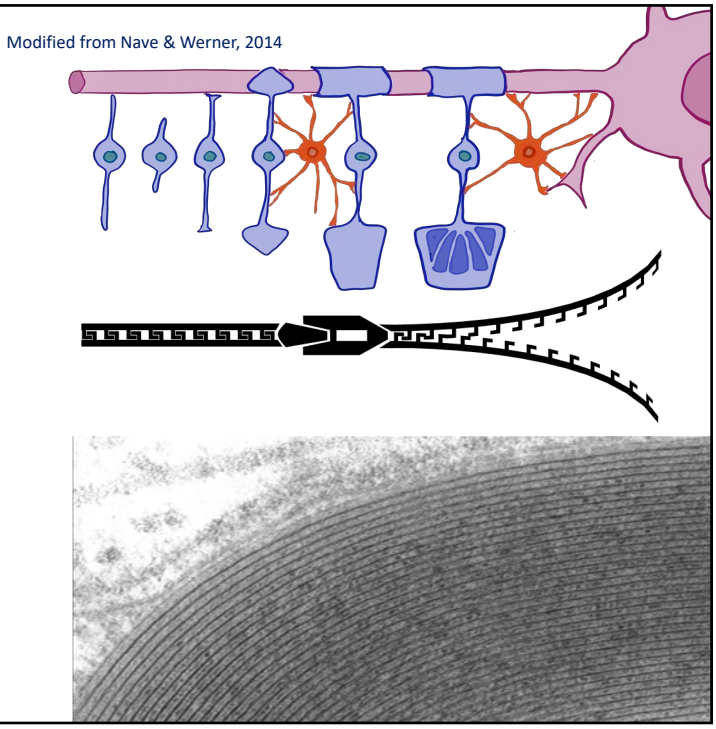
Myelin

- Produced by oligodendrocytes
- Membrane wrappings
- 70% fat (26% cholesterol, galactolipids 31%, cerebroside 14-26%, sulfatides 2-7%), plasmalogens
- Most important myelin proteins: Proteolipid protein 1 (PLP1 – about 50%), myelin basic protein (MBP), myelin-associated glycoprotein
- Maturation (compaction of myelin sheaths)



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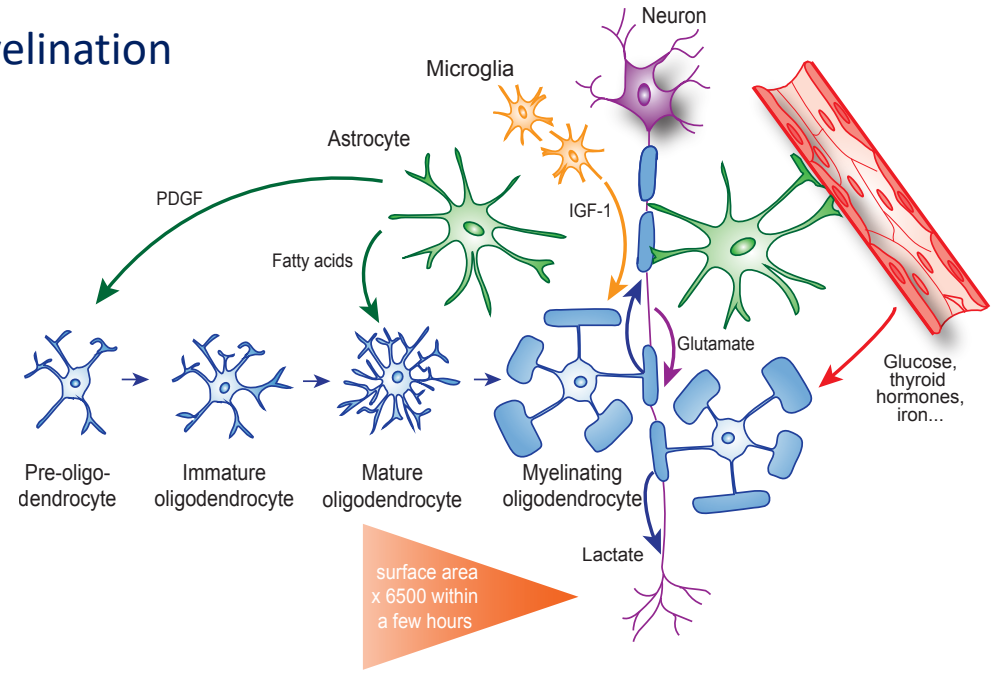
Myelination



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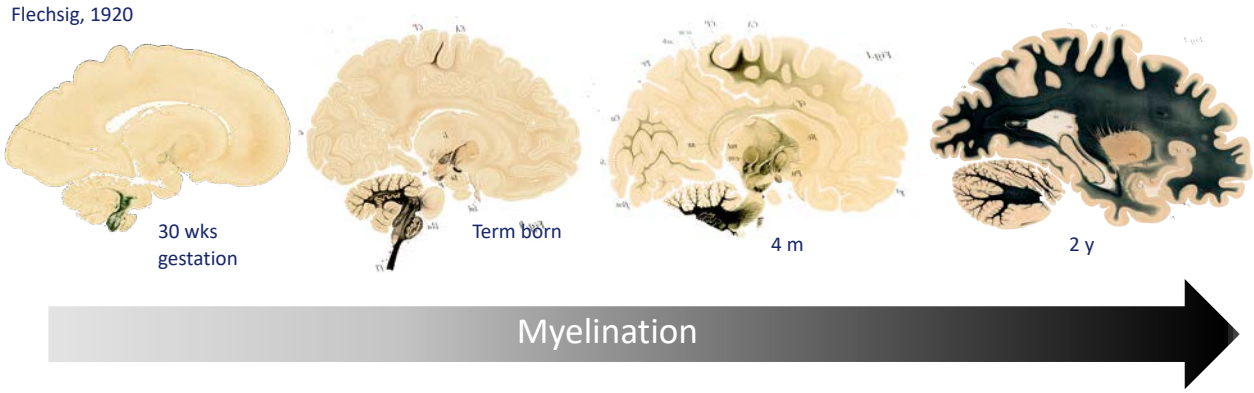
Normal myelination



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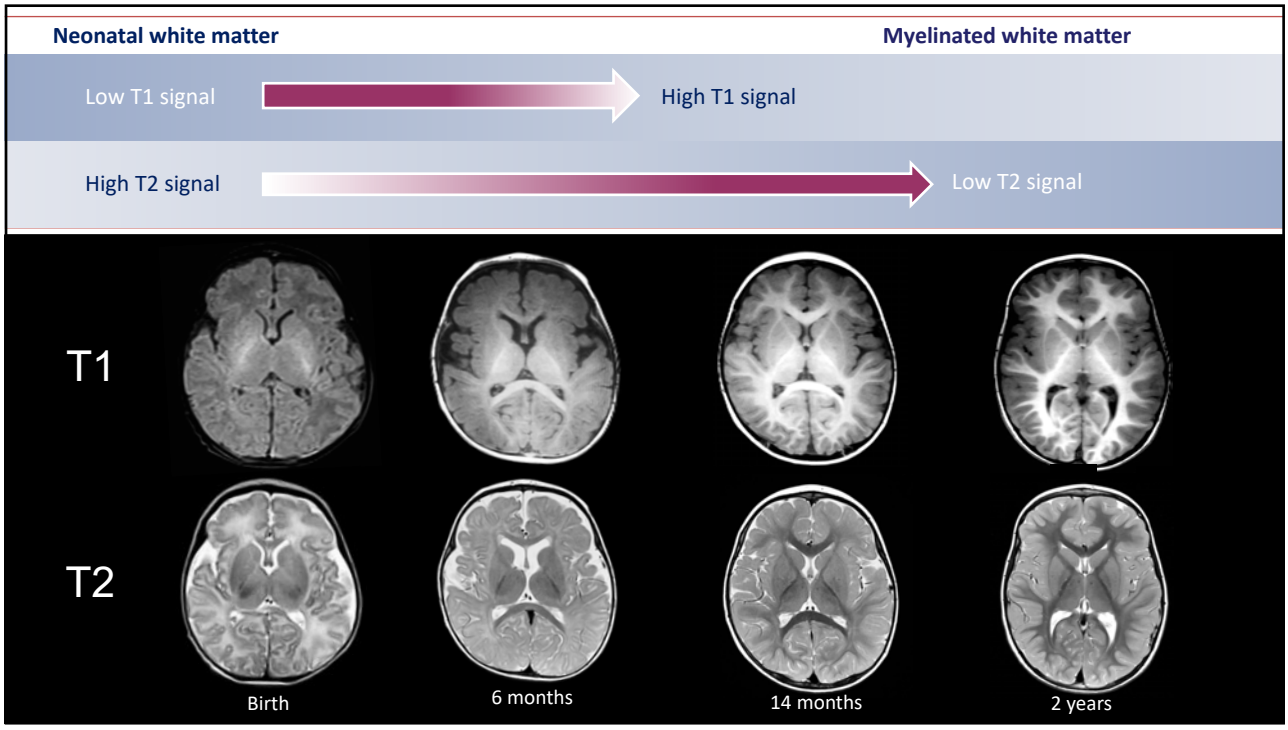

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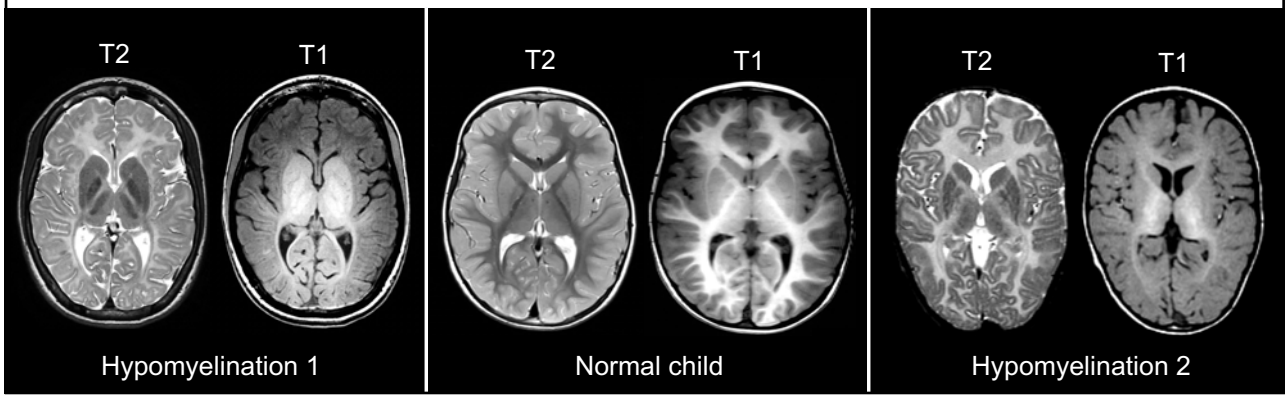
Disorders of myelination

- **Disorders of myelination**: hypomyelination (hypomyelinating leukodystrophies)
- **Definition**: „significant permanent deficit in myelin deposited“ (van der Knaap & Valk)
- **Diagnosis**: by MRI (T2 hyperintensity of white matter (but less bright than in other leukodystrophies), T1 may be hypointense, isointense or hyperintense, depending on the amount of myelin deposited



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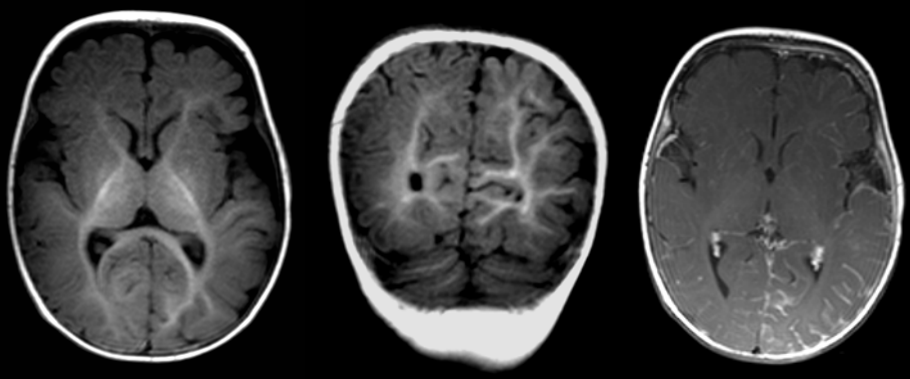
Accelerated myelination



Sturge-Weber syndrome in a 5 month-old girl

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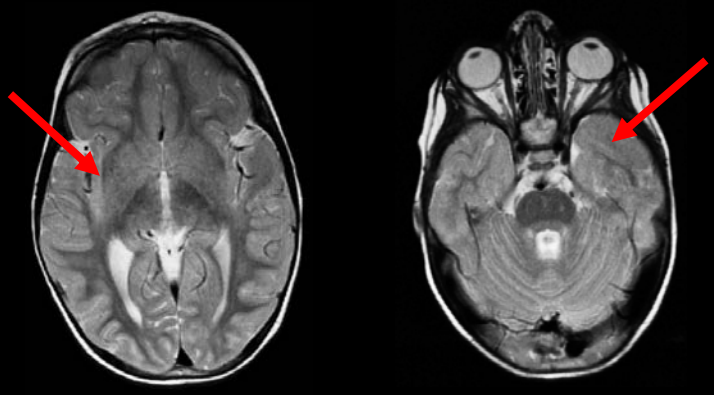
Incomplete myelination



3 year-old child

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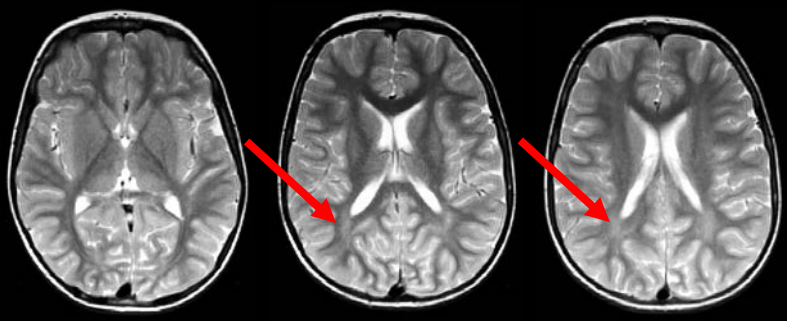
“Terminal zones” of myelination



3 year-old child

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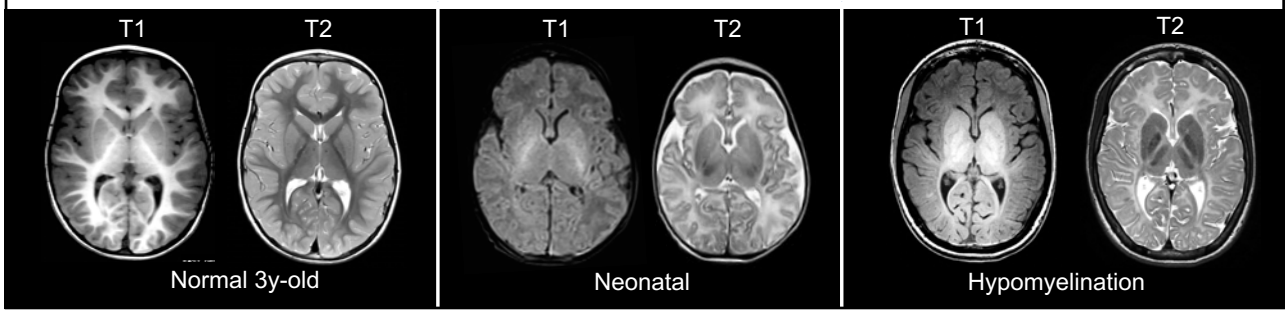
MRI in hypomyelination: Pitfalls

- Hypomyelinating disorders: „**significant permanent deficit** in myelin deposited“ (van der Knaap & Valk)
- → In young children < 2 years, the radiological diagnosis of hypomyelination cannot be made with 1 single MRI.
- → But: with suggestive clinical presentation, hypomyelination can be suspected and appropriate diagnostic workup initiated.



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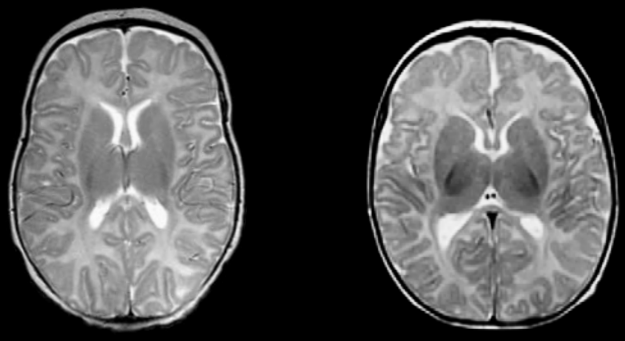
Young infants: hypomyelination?



Publication in *Molecular Genetics and Metabolism*: 10 wk-old child with “central hypomyelination”

10 weeks - normal

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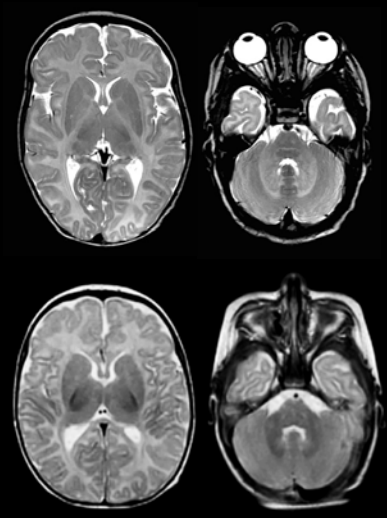
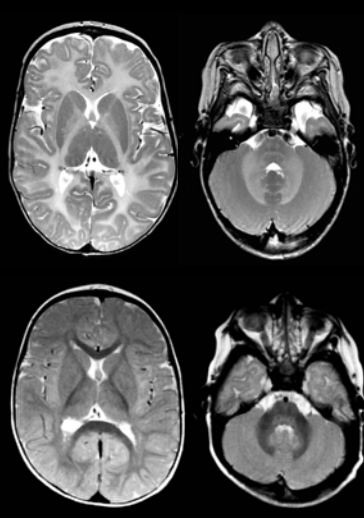
Young infants: hypomyelination?





Pelizaeus-Merzbacher disease

Normal baby

Age 10 weeks

Age 12 months

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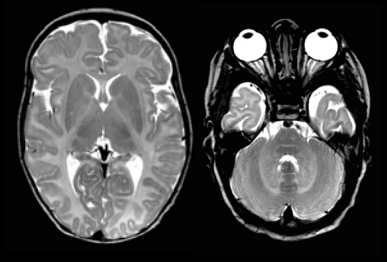
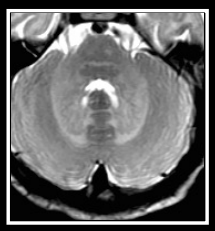
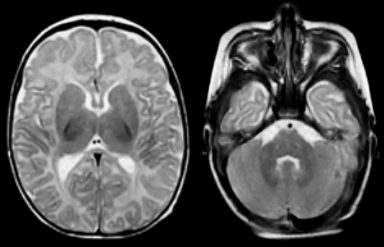
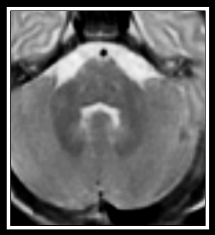
Young infants: cerebellum and brainstem as clues for hypomyelination





Pelizaeus-Merzbacher disease





Normal baby

Age 10 weeks

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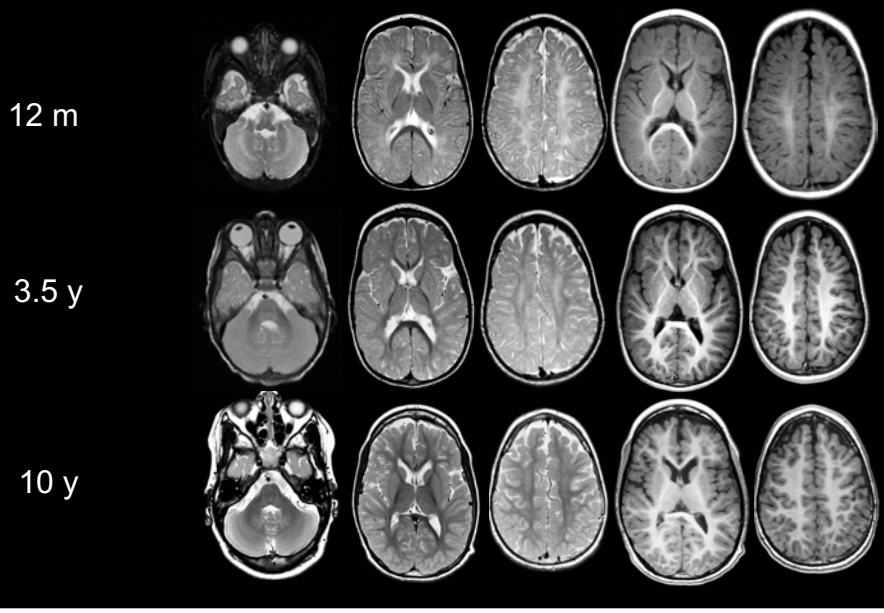
Not hypomyelination



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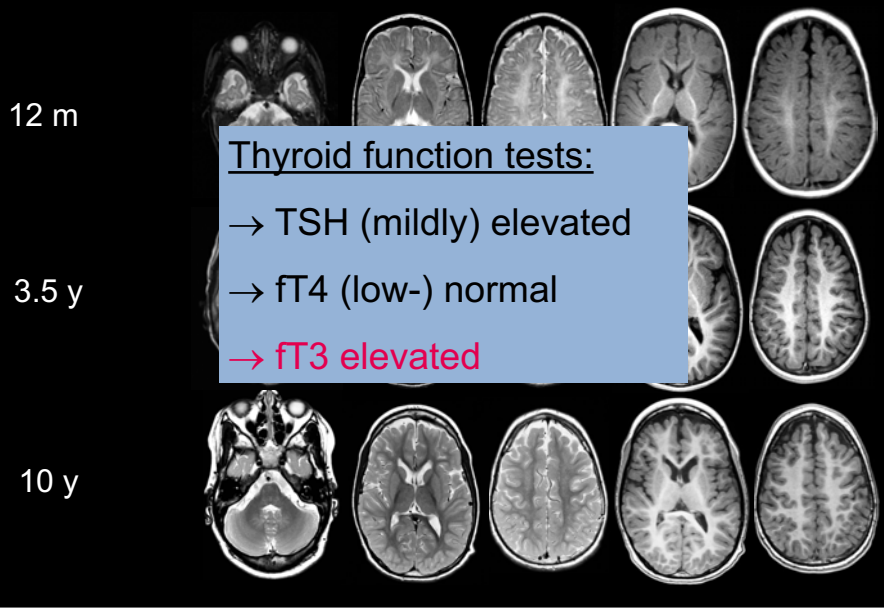
Delayed myelination: e.g. MCT8



Thyroid function tests:

→ TSH (mildly) elevated

→ fT4 (low-) normal

→ fT3 elevated

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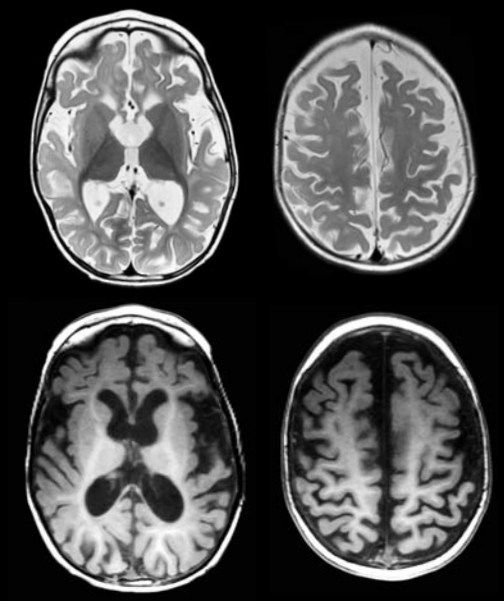
Impaired myelination due to grey matter disease

- Early severe atrophy (supratentorial)
- Thin cortex
- Severely delayed myelination
- Differential diagnosis large

➔ Usually DD for early epileptic encephalopathies



PIGA, 2 years

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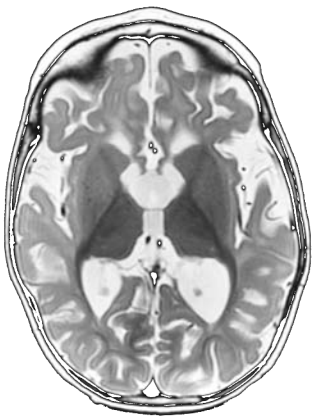
What argues against "primary/true" hypomyelination?

Clinical clues

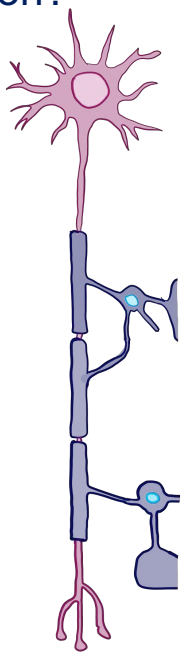
- Bad visual contact
- No milestones reached
- Early severe epilepsy
- Early regression



MRI clues

- Early severe atrophy
- Thin cortex / cortical signal changes
- Signal changes of deep grey matter structures

➔ Different differential diagnosis



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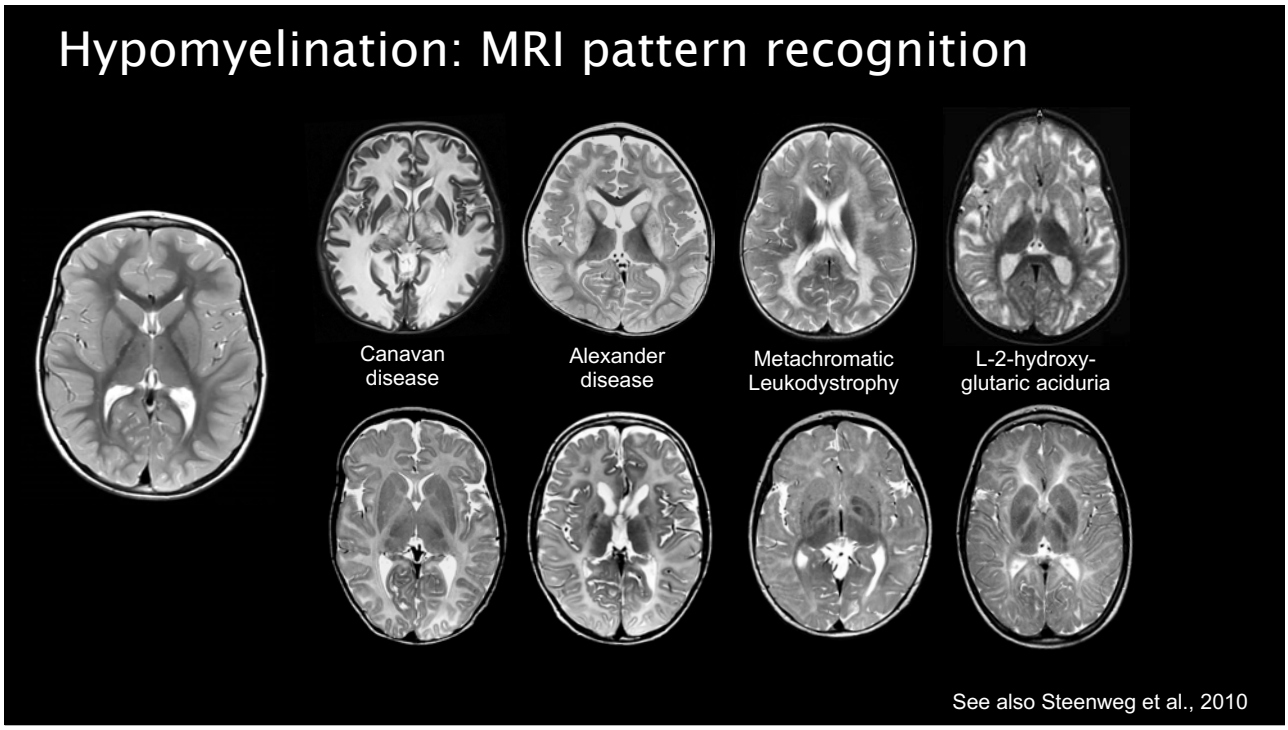
Hypomyelination: MRI pattern recognition
Canavan disease
Alexander disease
Metachromatic Leukodystrophy
L-2-hydroxy-glutaric aciduria
See also Steenweg et al., 2010

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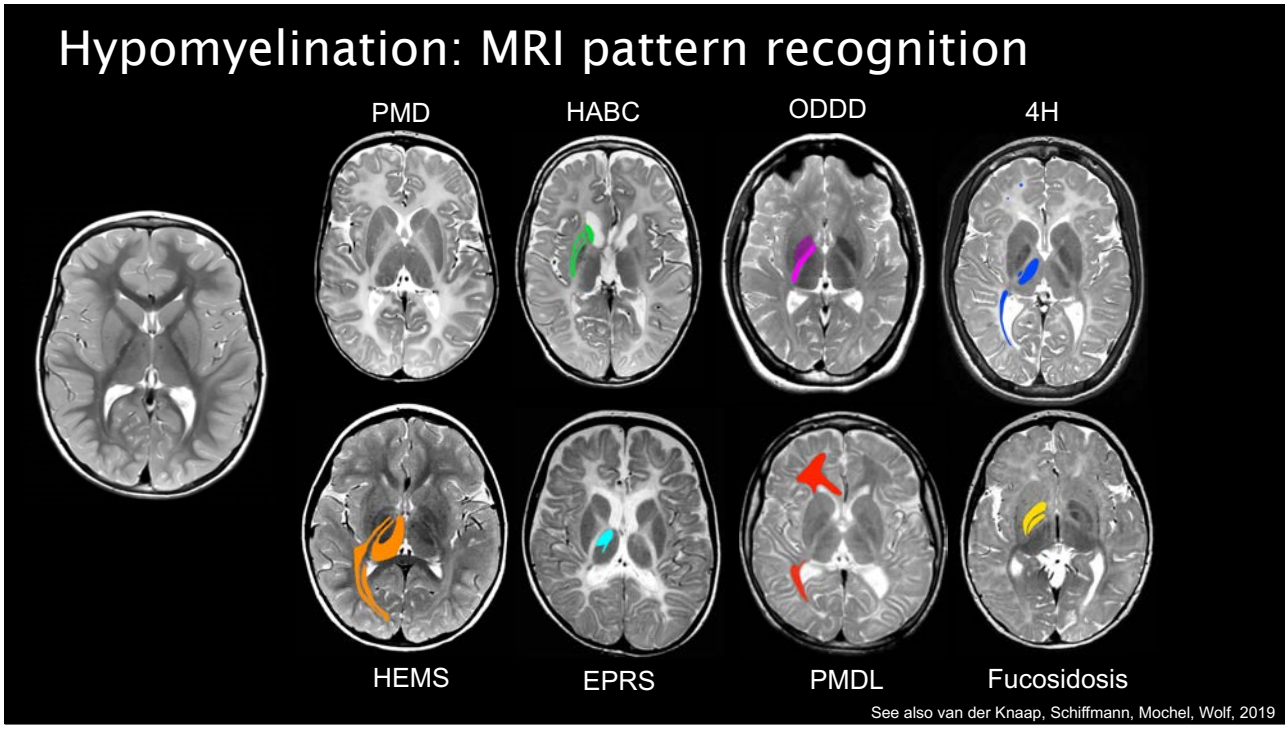
Hypomyelination: MRI pattern recognition
PMD
HABC
ODDD
4H
HEMS
EPRS
PMDL
Fucosidosis
See also van der Knaap, Schiffmann, Mochel, Wolf, 2019

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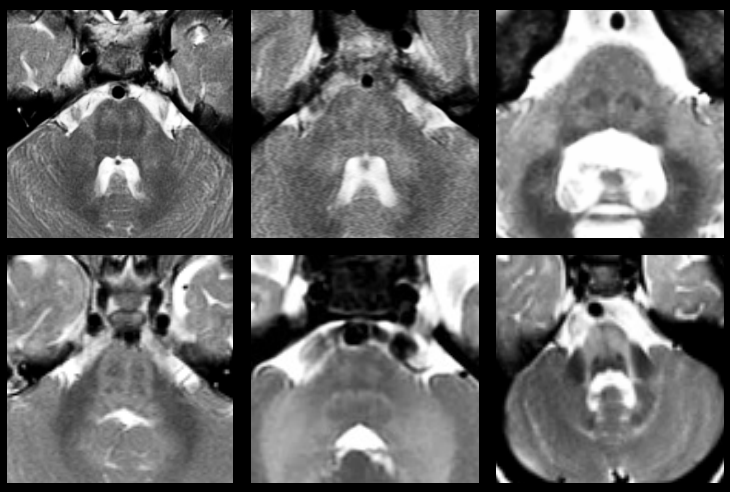
Hypomyelination: the brainstem as a clue



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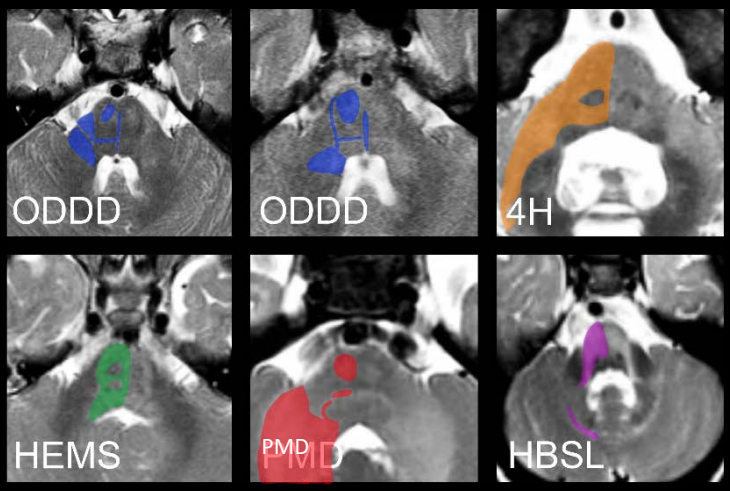
Hypomyelination: the brainstem as a clue



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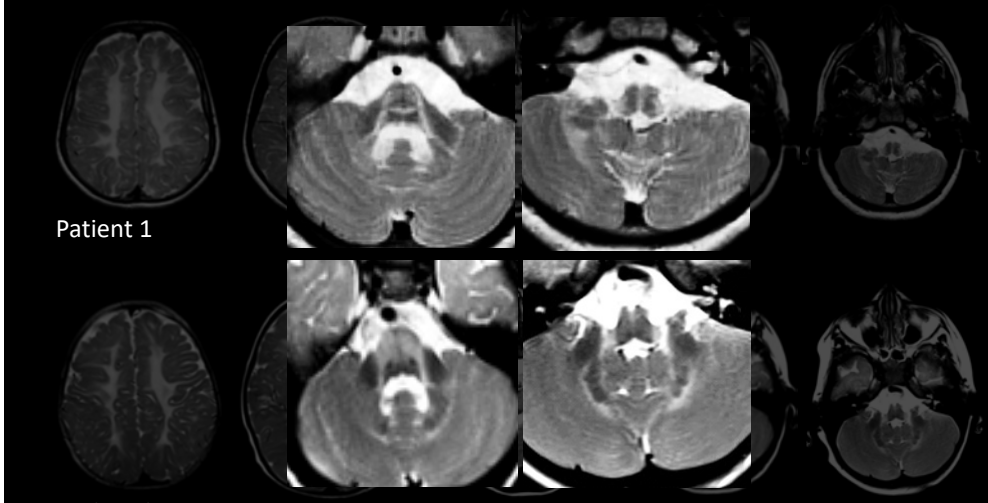
HBSL – hypomyelination with brain stem and spinal cord involvement and leg spasticity



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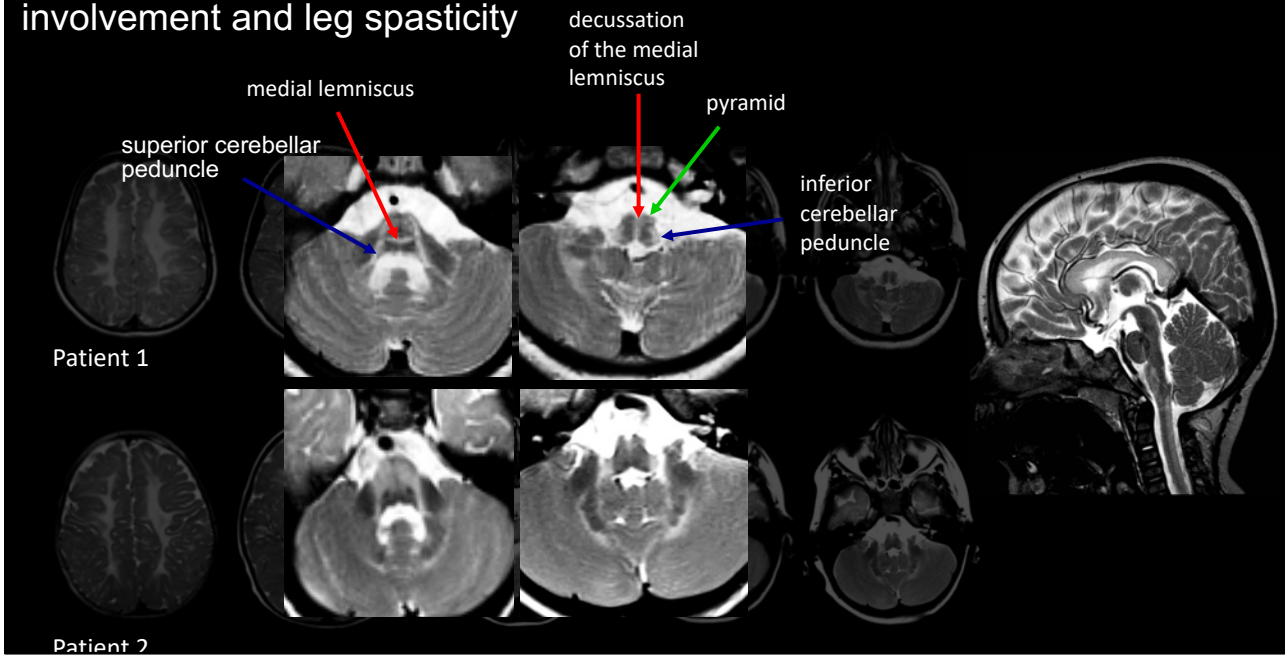
HBSL – hypomyelination with brain stem and spinal cord involvement and leg spasticity



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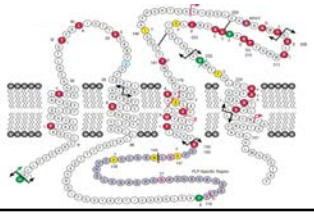
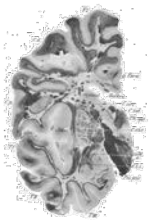
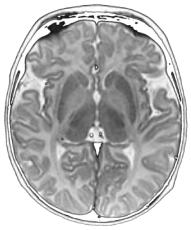
Hypomyelination: Typical presentation

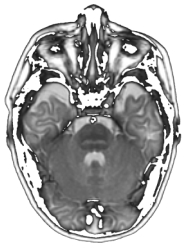
- Nystagmus (congenital, usually pendular)
- Wheelchair dependency
- Spasticity / mixed movement disorder
- Ataxia
- Mental retardation (although much less severe than motor impairment)
- Greatly reduced life expectancy



Prototype: **Pelizaeus-Merzbacher disease** (PMD): Alterations of *PLP1* (encoding the most abundant structural myelin protein)







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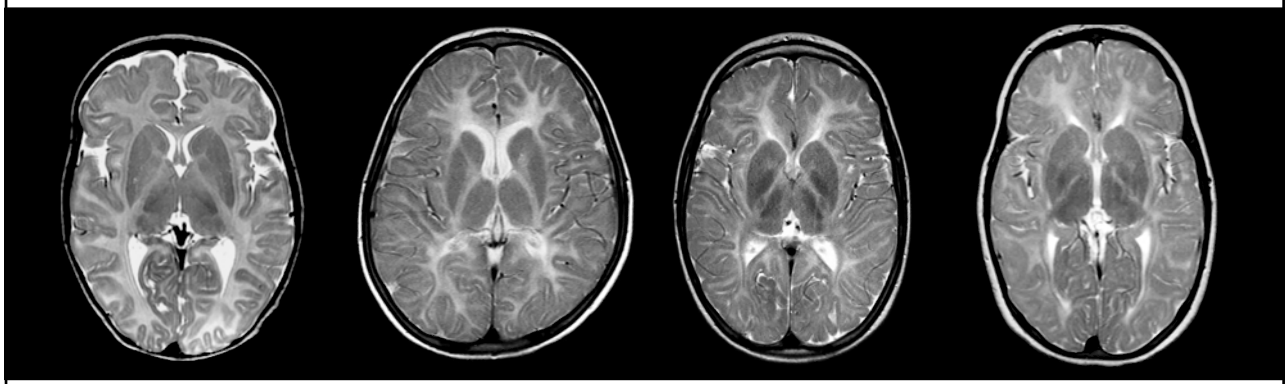
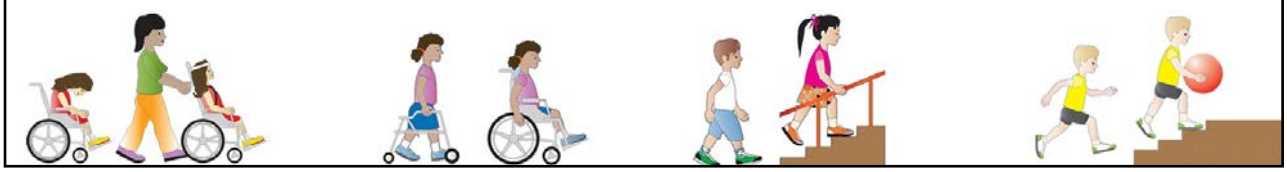
Hypomyelination: Clinical presentation (2)





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Hypomyelination – causes

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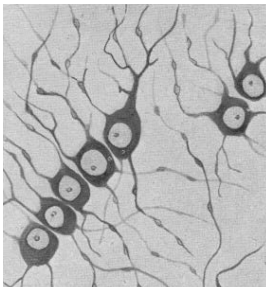
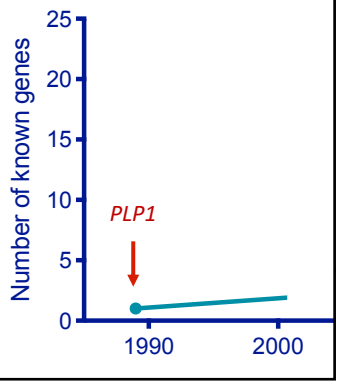
What did we expect?

1. Mutations in structural myelin genes (e.g. MBP)
2. Mutations in genes encoding oligodendrocyte differentiation proteins





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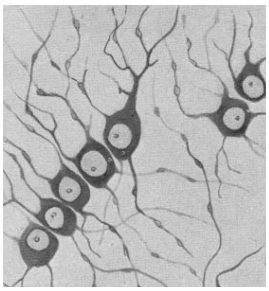
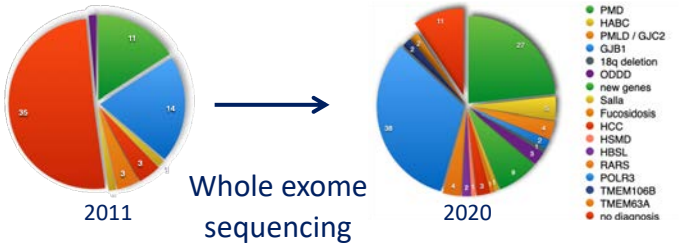
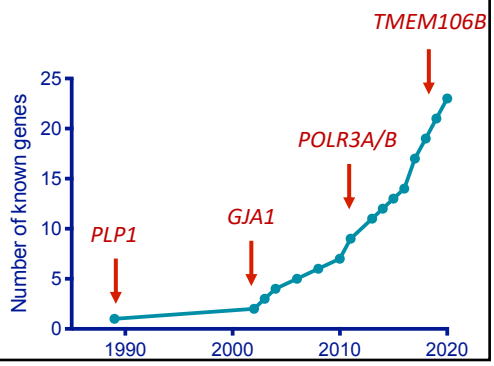
What did we expect?



1. Mutations in structural myelin genes (e.g. MBP)
2. Mutations in genes encoding oligodendrocyte differentiation proteins

→ Large patient cohorts were sequenced for candidate genes, without success





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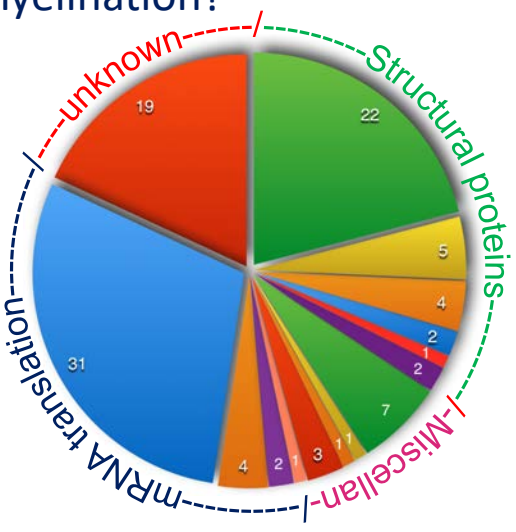
Which genes are involved in hypomyelination?

Genes encoding

- Structural myelin (oligodendrocyte) proteins
- Proteins essential for oligodendrocyte differentiation
- Proteins involved in protein transcription and translation
- Lysosomal proteins
- Proteins involved in membrane lipid synthesis
- Proteins with miscellaneous functions



Genes encoding proteins with very variable functions

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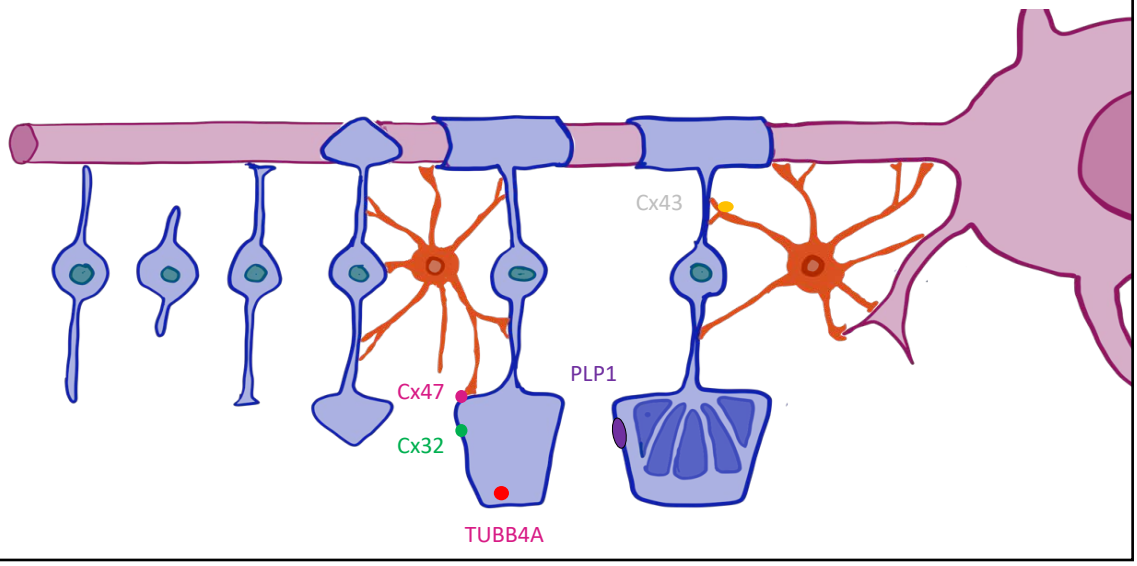
Structural (oligodendrocyte) proteins



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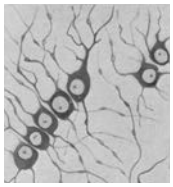
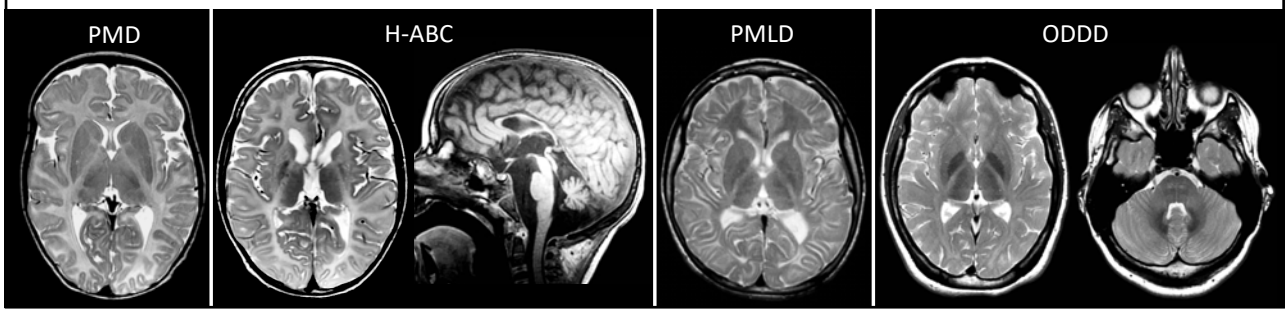
Structural oligodendrocyte proteins



- PLP1: Pelizaeus-Merzbacher disease
- TUBB4A: Hypomyelination with atrophy of the basal ganglia and cerebellum
- GJA1 / Cx43: Oculodentodigital dysplasia (astrocytes)
- GJC2 / Cx47: Pelizaeus-Merzbacher like disase
- GJB1 Cx32: X-linked hypomyelination (oligodendrocytes)



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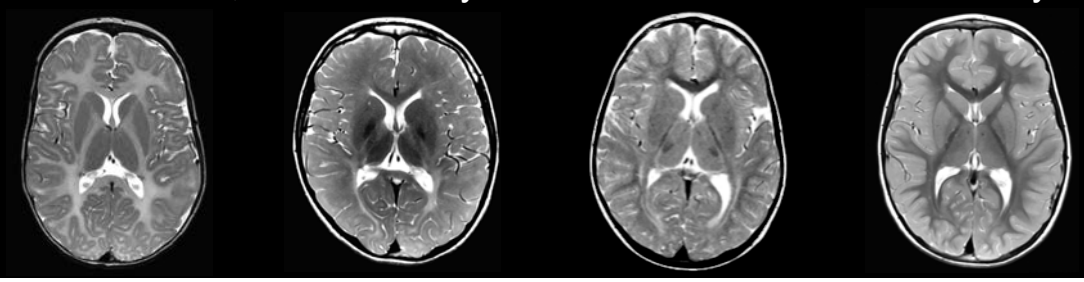
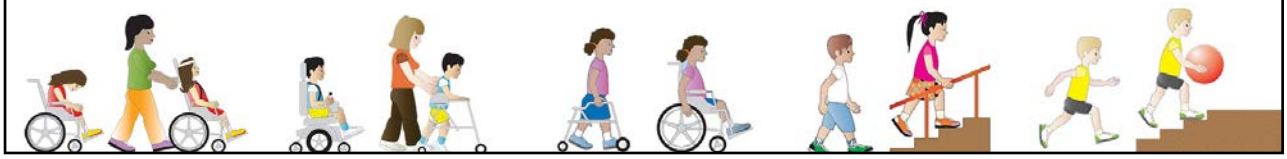
Clinical spectrum of PMD:
within one disease, amount of myelin correlates with clinical severity



Severe presentation — Mild presentation (pure HSP)

PLP1



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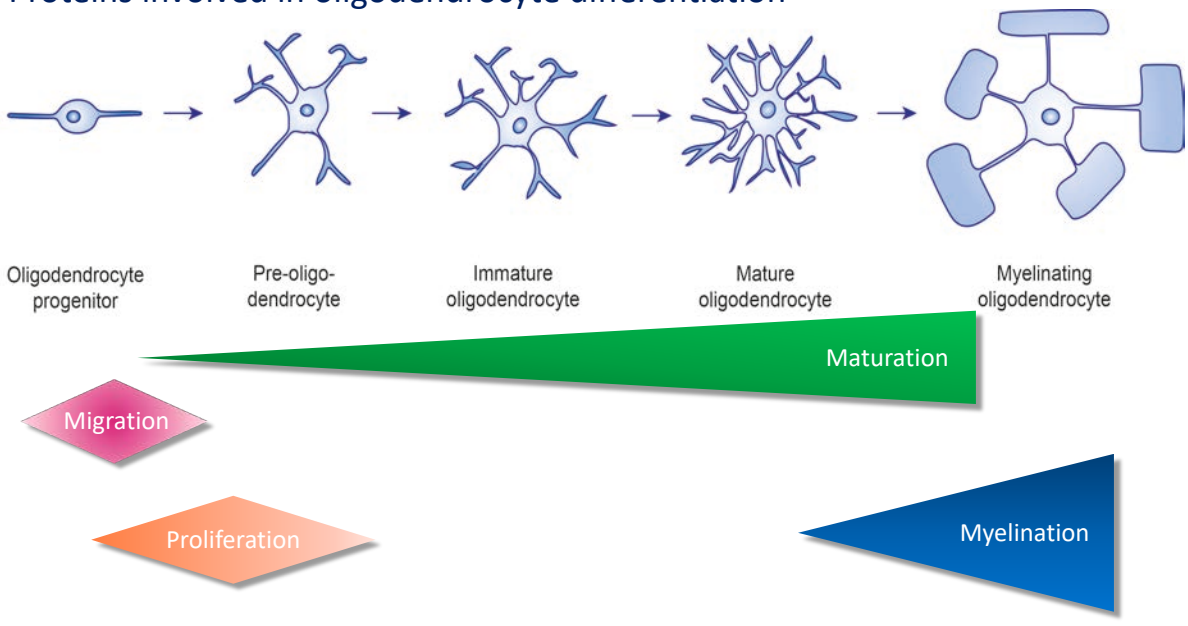
Proteins involved in oligodendrocyte differentiation



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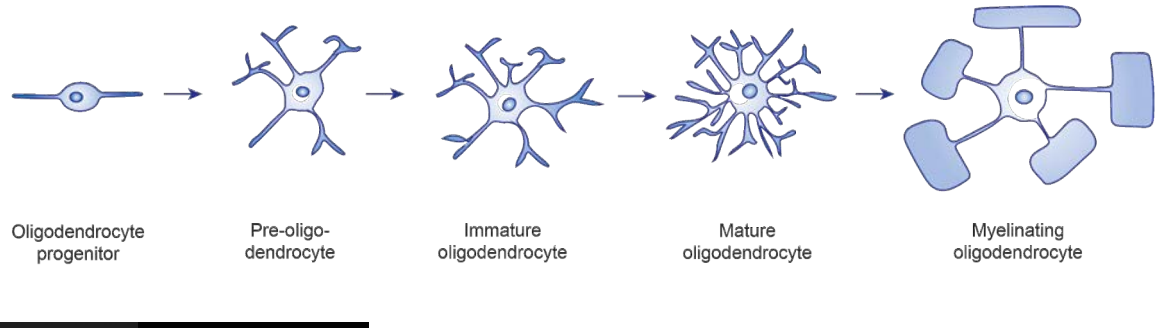

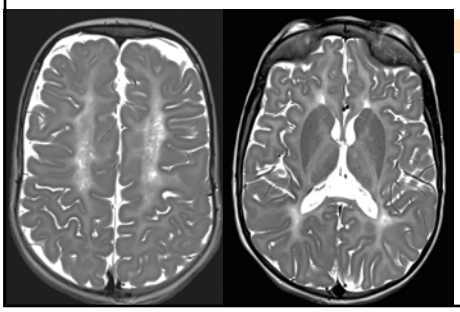

MRI: dr. Bertini, Rome

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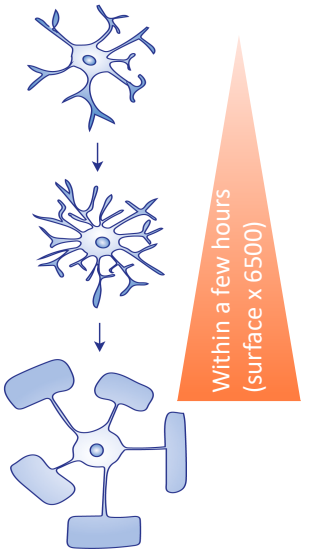
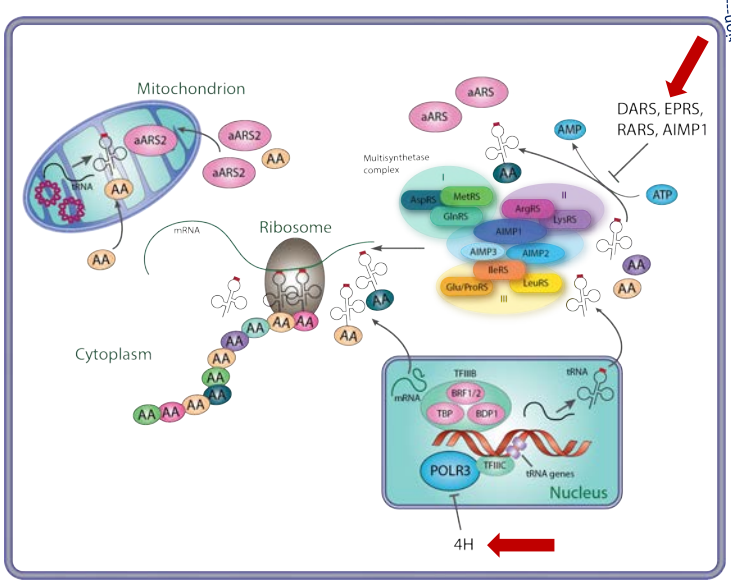
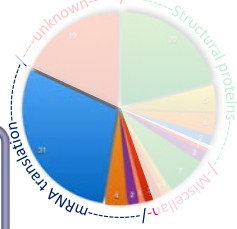
Proteins involved in protein synthesis (transcription and translation)



Within a few hours (surface x 6500)





- *DARS1*
- *RARS1*
- *EPRS1*
- *AIMP1*
- *POLR3A*
- *POLR3B*
- *POLR1C*
- *POLR1A*

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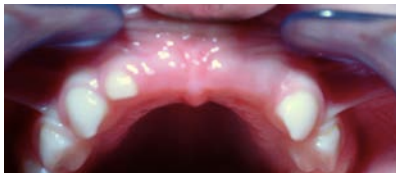
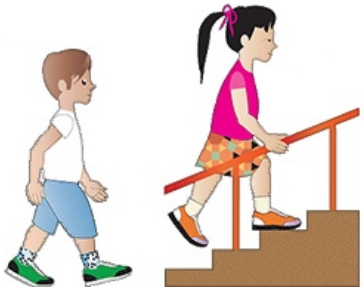
4H Leukodystrophy





Cause: recessive mutations in *POLR3A*, *POLR3B* , POLR3K or *POLR1C* (RNA Polymerase 3)

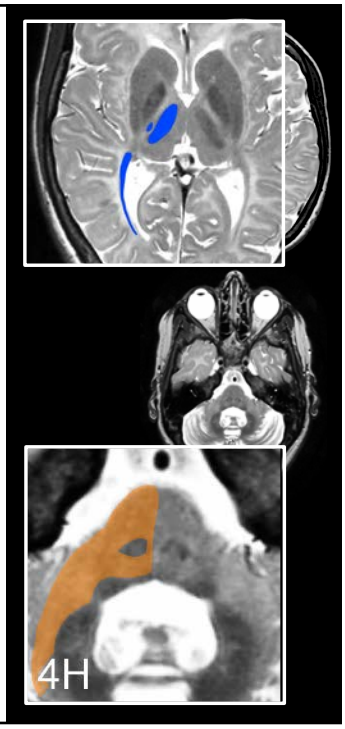
Classic form

- **H**ypomyelination
- **H**ypodontia
- **H**ypogonadotropic **H**ypogonadism

Additional frequent symptoms

- Myopia (severe)
- Small stature
- Other endocrine abnormalities possible

Broad spectrum of severity (depending on mutations?)



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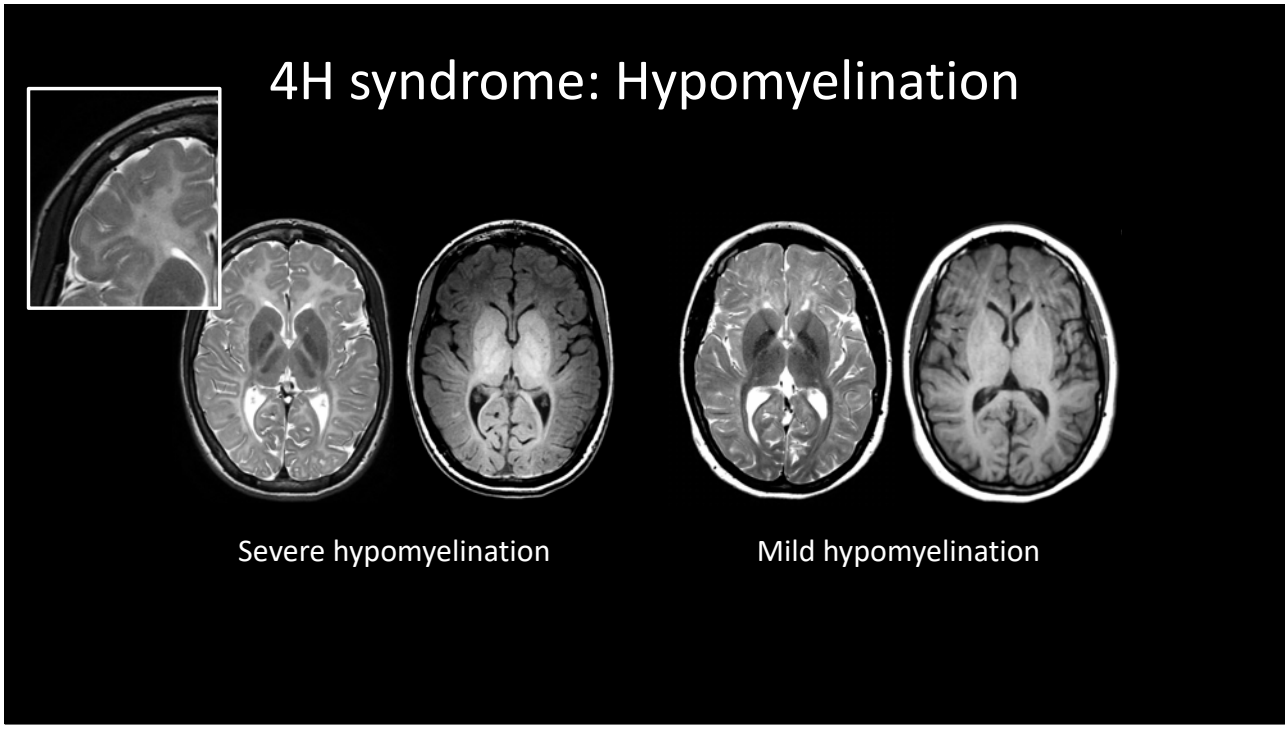

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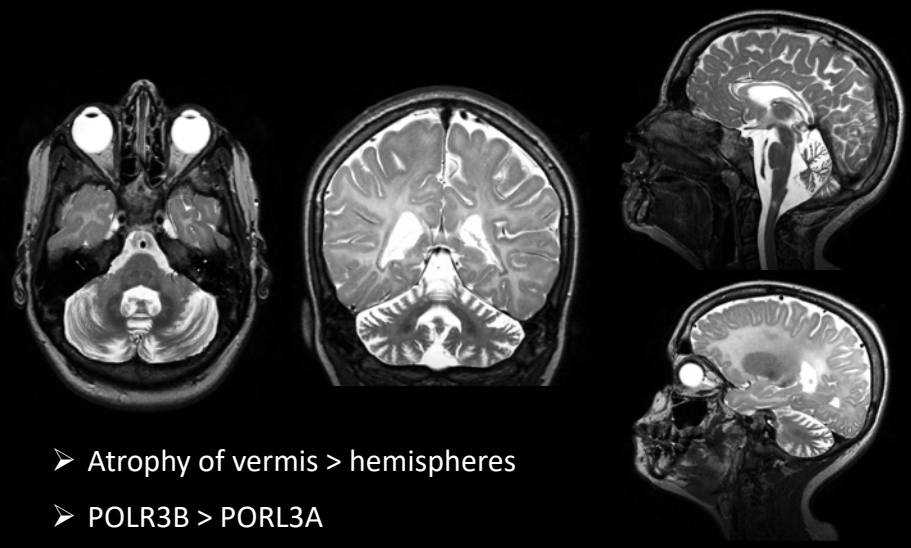
4H syndrome: Cerebellar atrophy



- Atrophy of vermis > hemispheres
- POLR3B > PORL3A

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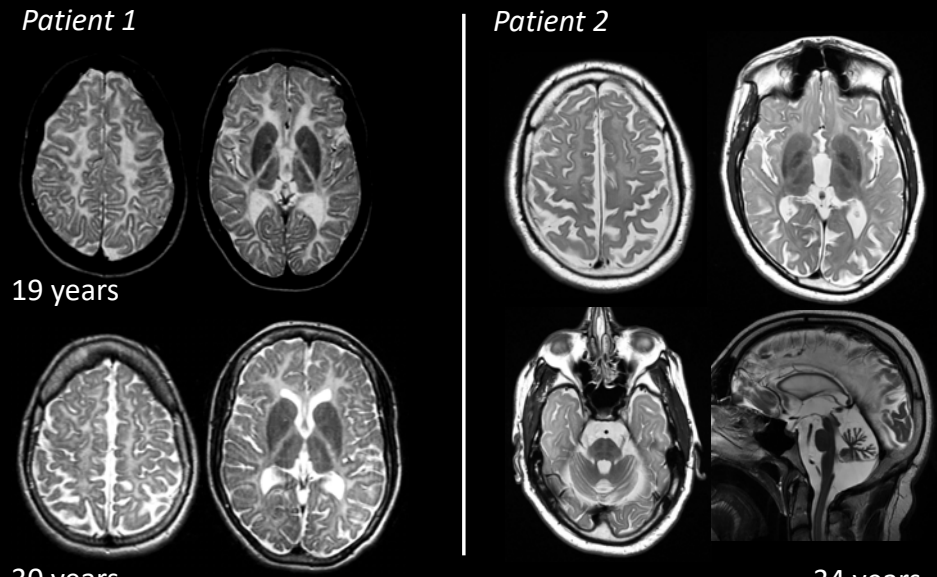
4H syndrome: MRI evolution



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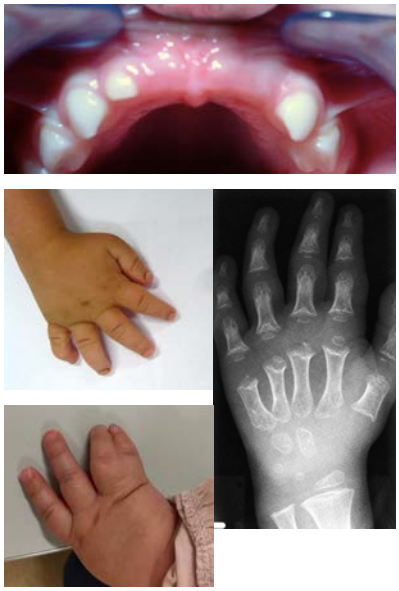
Clinical clues in hypomyelination

- Hypodontia – 4H
- Hypogonadotropic hypogonadism – 4H
- Congenital cataract – HCC
- Peripheral neuropathy – PMD-L and others
- Short stature, broad wrists and knees – H-SMD
- Hirschsprung disease and white lock of hair – Waardenburg syndrome type 2E / PCWH
- Severe overactive bladder – ODDD
- Syndactyly of 4th and 5th fingers – ODDD
- …



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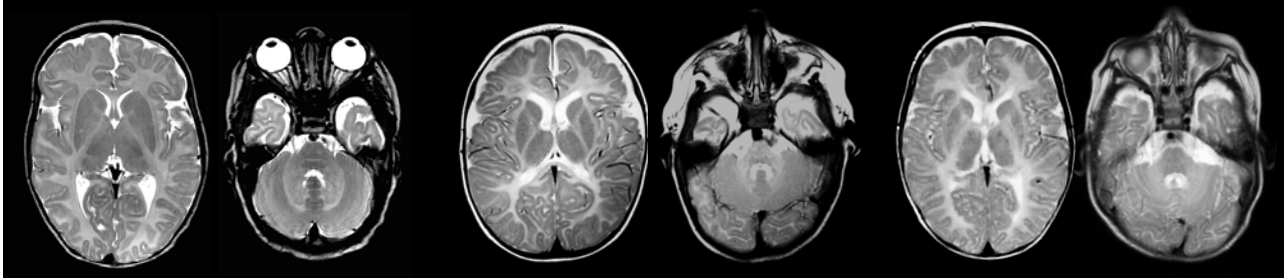
Genetic diagnosis: Impact

Patient 1 *Patient 2* *Patient 3*



3 boys, all 3-6 months old.

Clinical presentation: pendular nystagmus, axial hypotonia, lack of head control

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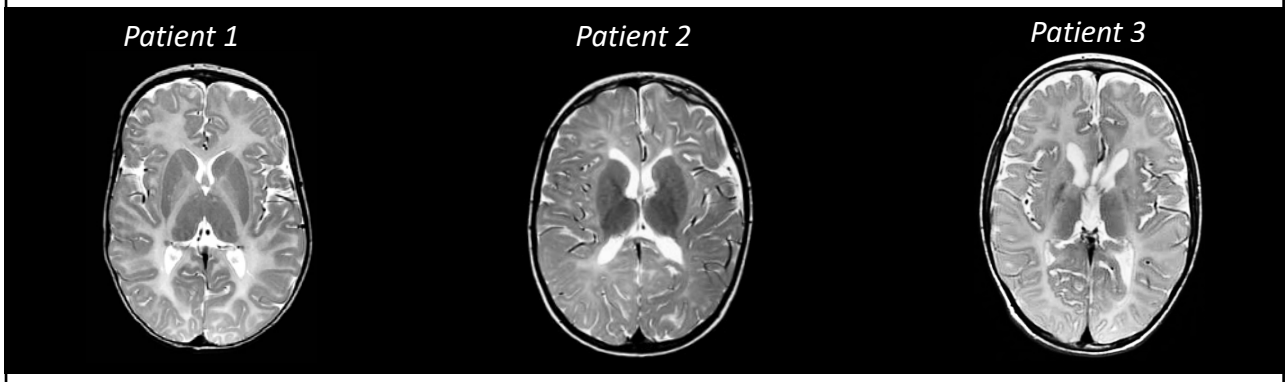
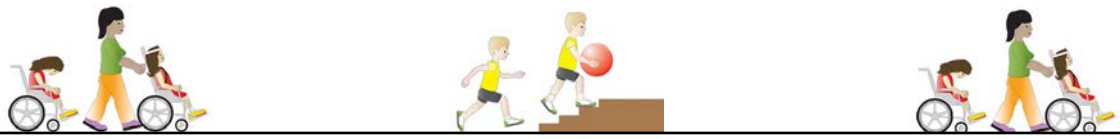
4 years later…



Pelizaeus-Merzbacher (*PLP1* duplication)	de novo *TMEM106B* mutation	HABC (de novo *TUBB4A* mutation)



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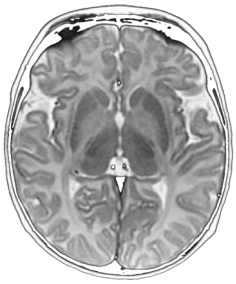
What have we learnt?



- Hypomyelination are many different disorders.
- MRI pattern recognition is possible for quite a few.
- Extra-neurological involvement may help in finding a diagnosis.

Implications for normal brain development

- Myelination is an intricate and tightly controlled process.
- Normal protein translation and synthesis seem essential for myelination.
- Lysosomal proteins play a role in myelination.

Implications for treatment

- The process of myelination can start later than normal and still proceed.

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Suggested reading

- van der Knaap MS, Bugiani M. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. *Acta Neuropathol*. 2017;134(3):351–382. doi:10.1007/s00401-017-1739-1
- van der Knaap MS, Schiffmann R, Mochel F, Wolf NI. Diagnosis, prognosis, and treatment of leukodystrophies. Lancet Neurol. 2019;18(10):962–972. doi:10.1016/S1474-4422(19)30143-7
- Cayami FK, Bugiani M, Pouwels PJW, Bernard G, van der Knaap MS, Wolf NI. 4H Leukodystrophy: Lessons from 3T Imaging. Neuropediatrics. 2018;49(2):112–117. doi:10.1055/s-0037-160878010):962–972. doi:10.1016/S1474-4422(19)30143-7
- Pouwels PJ, Vanderver A, Bernard G, et al. Hypomyelinating leukodystrophies: translational research progress and prospects. Ann Neurol. 2014;76(1):5–19. doi:10.1002/ana.24194
- Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders [published correction appears in Brain. 2013 Sep;136(Pt 9):2923]. Brain. 2010;133(10):2971–2982. doi:10.1093/brain/awq257

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Joint webinar series

THANK YOU

Next Webinar: ‚Exercise and Neuromuscular Disorders‘
April 23, 2020, 15-16h CET

Amsterdam Leukodystrophy Center

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