Joint webinar series

MRI Pattern Recognition in Leukodystrophies

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DG 'Leukodystrophies'
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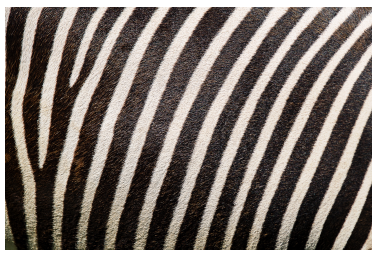
MRI pattern recognition in leukodystrophies

Most helpful for a diagnosis: MRI pattern recognition (MS van der Knaap).



But:

- May be normal in a presymptomatic patient
- May improve or even normalize
- May be non-characteristic, certainly in adult patients

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MRI pattern recognition in leukodystrophies

Why is it still important (in the time of next generation sequencing)?

- Ultrafast diagnosis, confirmation needs usually less time than NGS (think of implications for treatment)
- Interpretation of variants found in primary genetic testing
- Looking for variants in non-coding parts of DNA

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Contents

- Pattern recognition step by step
- The importance of disease stage and age of onset
- Some examples
- Why pattern recognition is still important

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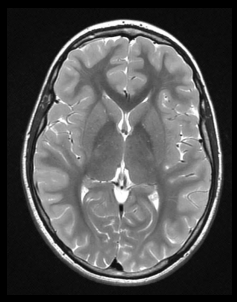
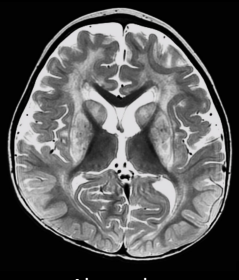
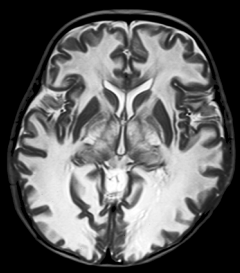
Pattern recognition

Normal MRI

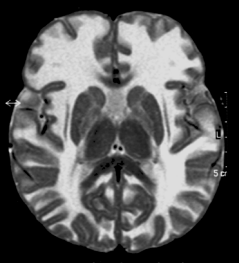




Alexander disease



Canavan disease



Megalencephalic leukodystrophy with subcortical cysts (MLC)

T2

Macrocephaly

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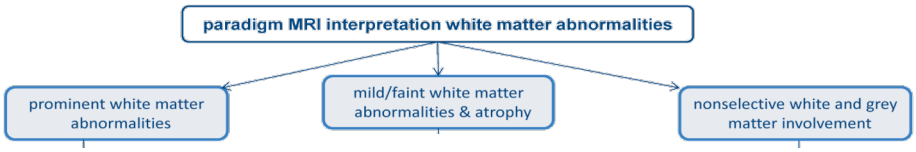
How to analyse MRI images?



Van der Knaap Schiffmann, Mochel, Wolf; Lancet Neurology 2019

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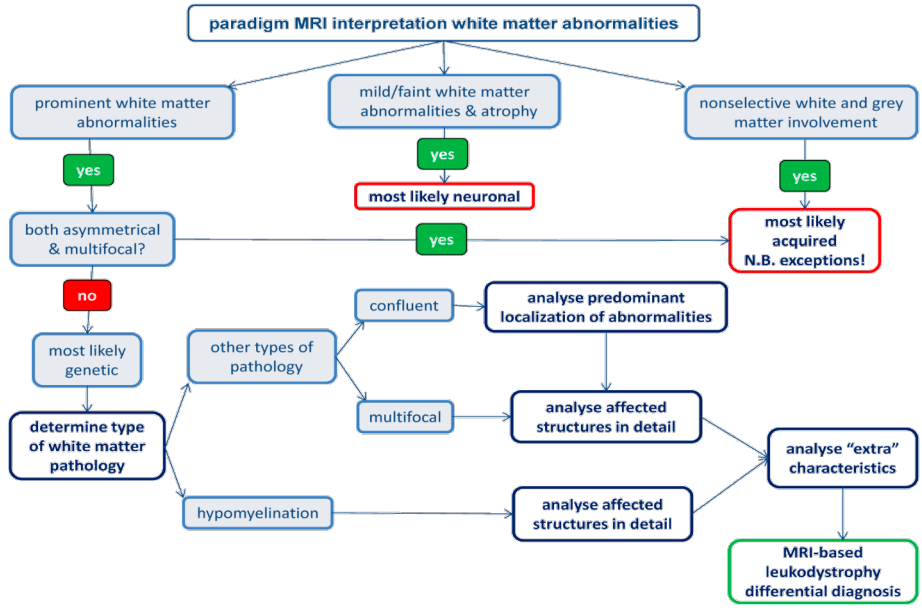
How to analyse MRI images?



Van der Knaap Schiffmann, Mochel, Wolf; Lancet Neurology 2019

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MRI paradigm for other pathologies

multifocal cerebral

L-2-HGA
Hyperhomocystinuria/ homocystein remethylation defects
HMG-CoA lyase deficiency
LBSL
Mitochondrial LDs
Genetic vasculopathies
Mucopolysaccharidoses
Lowe
Galactosemia
ALSP
Chromosomal mosaicism and other abnormalities

DD
Non-genetic vasculopathies
Infections
Inflammatory disorders

confluent cerebral

extensive / diffuse cerebral

VWM
MLC
Merosin deficiency
CLCN2-related LD
Mitochondrial LDs
ADLD

Endstage of most LDs

DD
(Sub)acute cortex degeneration in neonates
Toxins

anterior cerebral

MLD (later onset forms)
Alexander
Cerebral ALD
AARS2-related LD
HDLS

posterior cerebral

Cerebral ALD
ALD variants
MLD (late-infantile form)
Krabbe
AARS2-related LD
APBD

DD
(Sub)acute cortex degeneration due to hypoglycemia in neonates

periventricular cerebral

MLD
Krabbe
Cerebral ALD
SLS
LAMB1-related LD
LBSL
PKU

subcortical cerebral

L-2-HGA
Canavan
KSS
LTBL

brain stem + cerebellum + spinal cord

brain stem

LBSL
LTBL
Genetic vasculopathies
Mitochondrial LDs
AMACR deficiency
ALD variants
Alexander
APBD
ADLD
CLCN2-related LD
DRPLA

DD
Non-genetic vasculopathies
Pontine myelinolysis

cerebellar white matter + middle cerebellar peduncles

CTX
ALD variants
LBSL
LTBL
Alexander
Giant axonal neuropathy
FXTAS
ADLD
CLCN2-related LD
MSUD

DD
Paramalignant, histiocytosis

spinal cord

LBSL
Mitochondrial LDs
Alexander
APBD
ADLD

DD
Inflammatory diseases
Infections

Van der Knaap Schiffmann, Mochel, Wolf; Lancet Neurology 2019

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"special" characteristics of leukodystrophies

WM swelling + megalencephaly	myelin micro-vacuolization	cystic WM degeneration	anterior temporal cysts	contrast enhancement	calcium deposits	micro-bleeds	central nuclei	cortex
MLC Alexander Canavan L-2-HGA Merosin deficiency	*CLCN2*-related LD X-linked CMT *MYRF*-related LD MSUD LBSL LTBL Mitochondrial LDs GABA transaminase deficiency **DD** Mild Encephalopahty with Reversible Splenial lesion Toxins	Mitochondrial LDs VWM Alexander (Sub)acute cortex degeneration in neonates (e.g. molybdenum cofactor deficiency) Incontinentia pigmenti in neonates **DD** Periventricular leukomalacia (Sub)acute cortex degeneration in neonates	MLC *RNASET2*-related LD Aicardi-Goutières, severe VWM, severe Merosin deficiency *RMND1*-related disorder **DD** Congenital CMV infection	Alexander Mitochondrial LDs Cerebral ALD LCC Coates Plus **DD** Infections Inflammatory disorders Vasculitis Vascular/perivascular malignancies Haemophagocytic lymphohistiocytosis	Aicardi-Goutières *RNASET2*-related LD LCC Coates Plus Cockayne ALSP Genetic vasculopthies Mitochondrial LDs **DD** Congenital CMV infection Other congenital infections Periventricular leukomalacia Vasculopathies	Genetic vasculopathies **DD** Periventricular leukomalacia Vasculopathies	Genetic vasculopathies LCC Coates Plus LTBL Mitochondrial LDs Canavan L-2-HGA MSUD DRPLA Porphyria-related LD AMACR deficiency CTX **DD** Extrapontine myelinolysis	**cerebral, lesion** Mitochondrial LDs **DD** (Sub)acute cortex degeneration in neonates (e.g. molybdenum cofactor deficiency, asphyxia) Infections Inflammatory disorders **cerebellar, lesion** *NUPBL*-related LD **DD** Parainfectious **cerebral, dysplasia** early onset peroxisomal defects *LAMB1*-related LD *GPR56*-related LD Congenital muscular dystrophies **DD** Congenital CMV infection **cerebellar, dysplasia** Congenital muscular dystrophies *LAMB1*-related LD *GPR56*-related LD **DD** Congenital CMV infection

Van der Knaap Schiffmann, Mochel, Wolf; Lancet Neurology 2019

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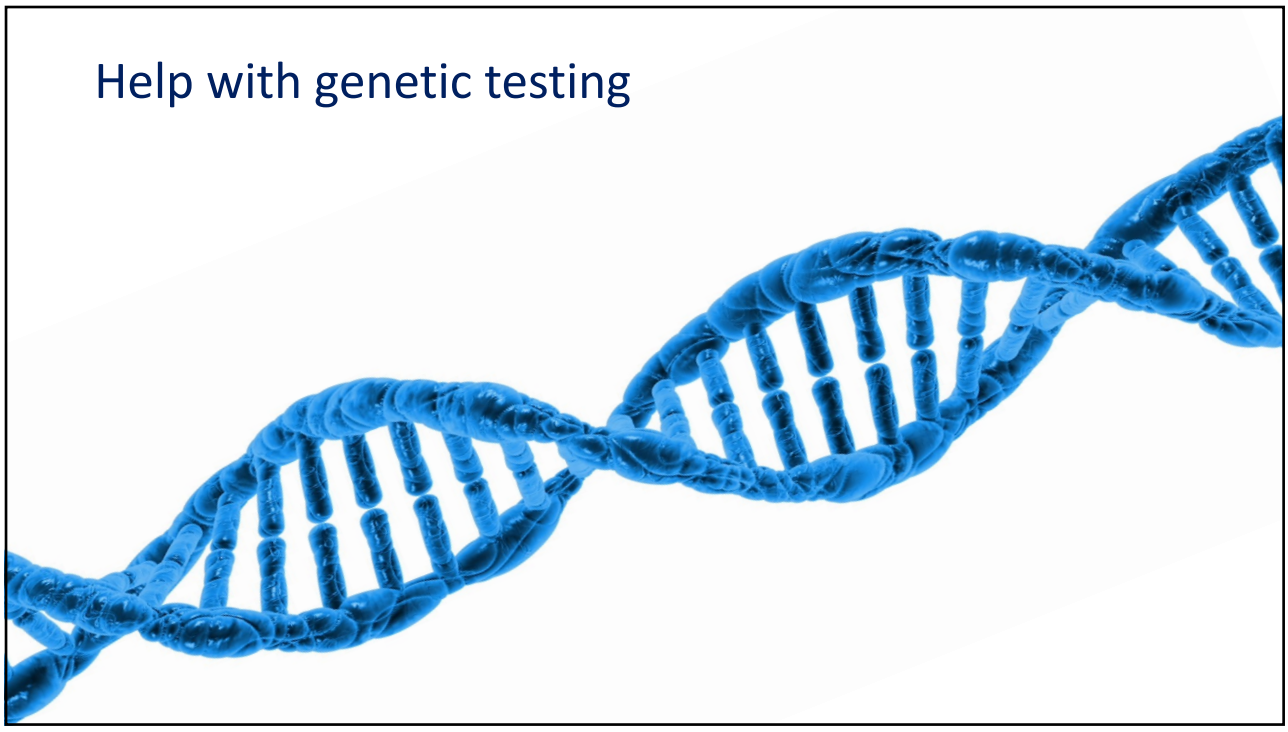
Help with genetic testing



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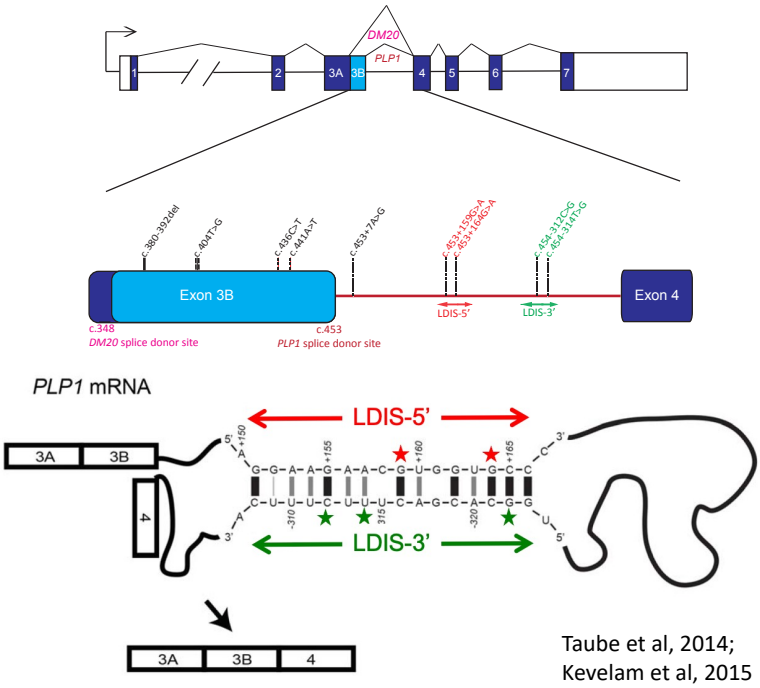
HEMS – genetics

- Variants in exon 3B (including synonymous variants)
- Variants deep in intron 3
- Splicing affected with higher ratio DM20/PLP1 than normal
- Typical MRI pattern – hypomyelination of early myelinating structures
- Clinically, complicated spastic paraplegia
- Intron 3 not covered by WES



Taube et al, 2014;
Kevelam et al, 2015

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Another case

- Several seizures round age 7 months
- Clumsy child, attention deficit
- Chromosome analysis and fragile X normal

→ Leukoencephalopathy with calcifications and cysts (LCC)

→ Pathogenic variants in the 3' region of the non-coding *SNORD118* gene

→ Usually missed by WES

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Key points

- Leukodystrophies are heterogeneous genetic disorders primarily affecting brain white matter.
- Brain MRI analysis very often helps to make a diagnosis („pattern recognition“).
- Diagnosis with pattern recognition is fast.
- Diagnosis with pattern recognition is still important.

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Background reading

Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. *Neurology*. 2009;72(8):750–759. doi:10.1212/01.wnl.0000343049.00540.c8.

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.

Roosendaal SD, van de Brug T, Alves CAPF, Blaser S, Vanderver A, Wolf NI, van der Knaap MS. Imaging Patterns Characterizing Mitochondrial Leukodystrophies. *Am J Neuroradiol* April 2021, DOI: https://doi.org/10.3174/ajnr.A7097.

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.

Wolf NI, ffrench-Constant C, van der Knaap MS. Hypomyelinating leukodystrophies - unravelling myelin biology. Nat Rev Neurol. 2021;17(2):88-103. doi: 10.1038/s41582-020-00432-1.

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