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Institut-Hôpital neurologique de Montréal
Montreal Neurological Institute-Hospital

Lésions de la matière blanche : quand soupçonner un problème génétique

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McGill
Centre universitaire de santé McGill
McGill University Health Centre

Conflicts of Interest

No conflicts of interest to be declared for this presentation

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- Rare Disease Foundation

Speaking Honoraria

- Novartis

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Outline of the presentation

1. Review of hereditary vascular white matter diseases
2. Useful hints for the diagnosis in the clinical practice
3. The challenge of identifying new entities

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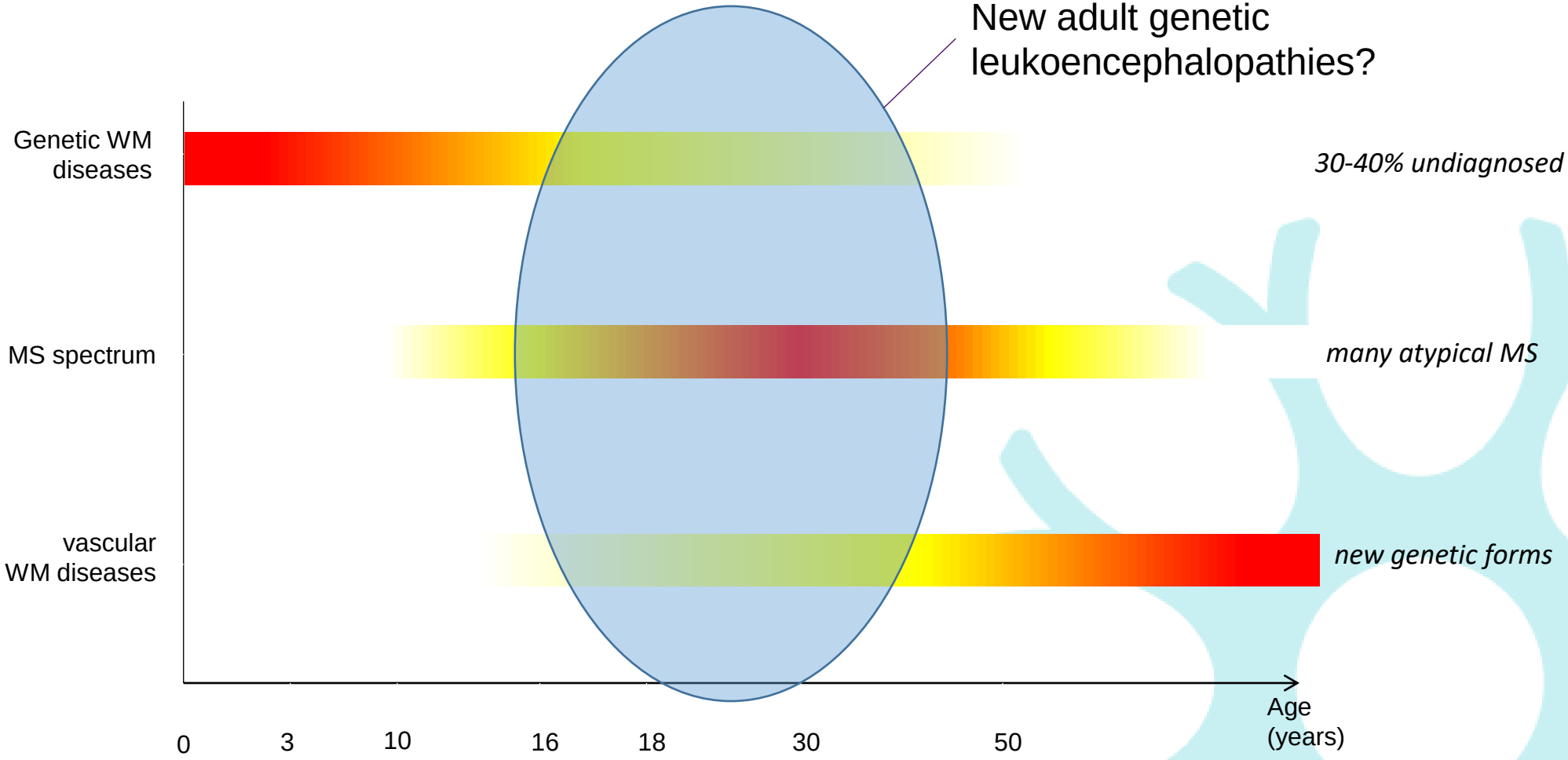
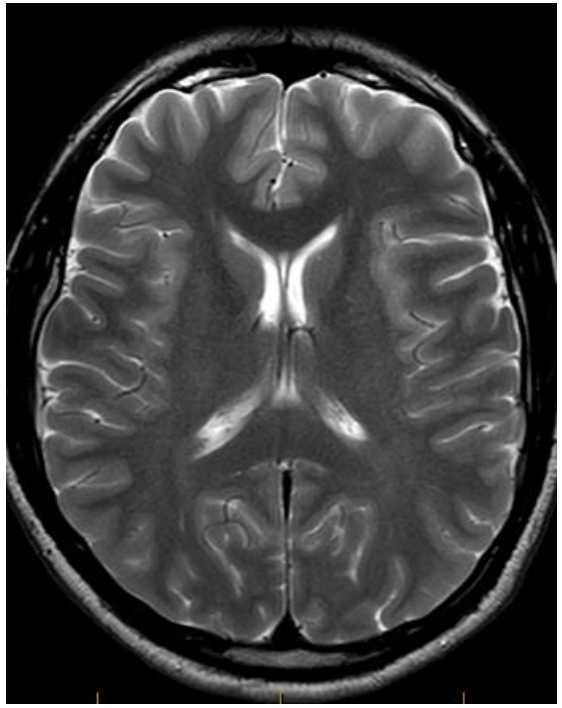
The Problem

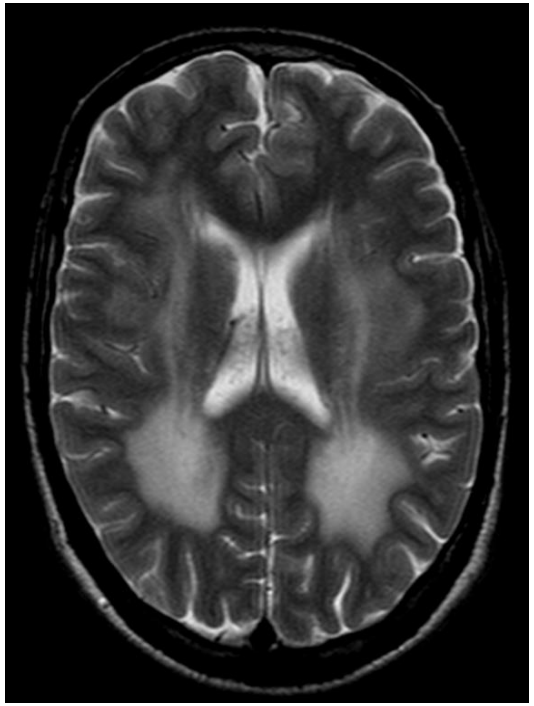


Bonkowsky et al., Neurology 2010
Vanderver et al., Semin Pediatr Neurol 2012
Kohler et al., Nature Reviews 2018
Jeong et al., J Child Neurol 2019
www.nationalmssociety.org

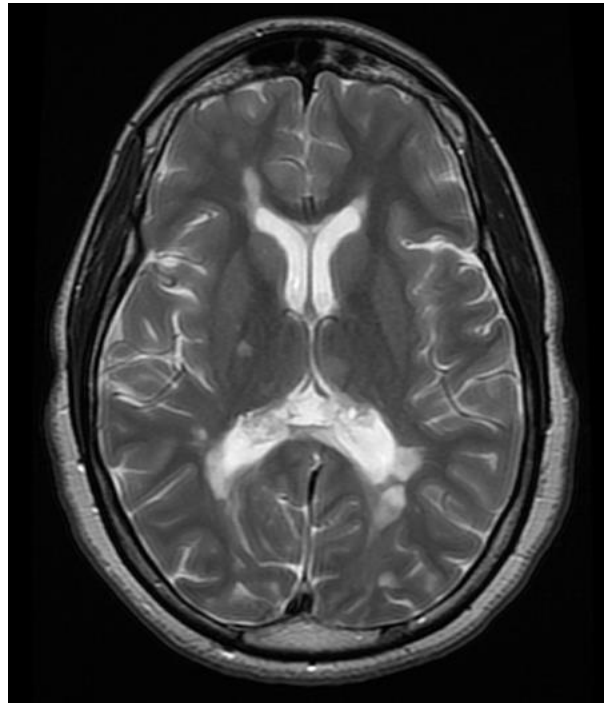
Misinterpretation of **MRI** abnormalities is the most frequent cause of misdiagnosis and delayed diagnosis of a genetic white matter disorder



normal WM



diffuse and symmetric
=
genetic



multifocal and asymmetric
=
acquired

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Images from our cohort

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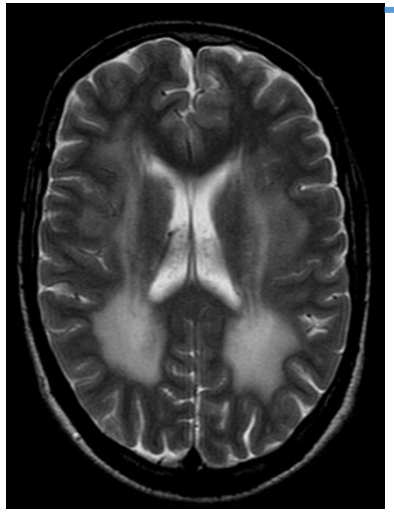
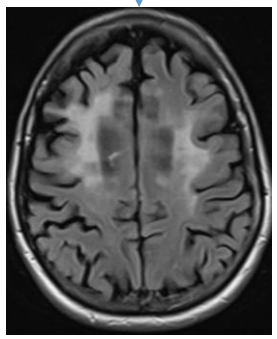
The interpretation of **MRI** abnormalities is crucial to correctly classify white matter diseases

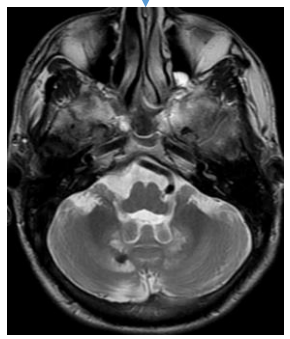


diffuse and symmetric = genetic



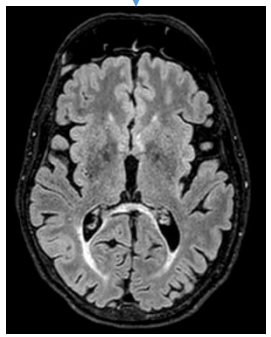
Frontal predominance

-Alexander disease
-Metachromatic leukodystrophy



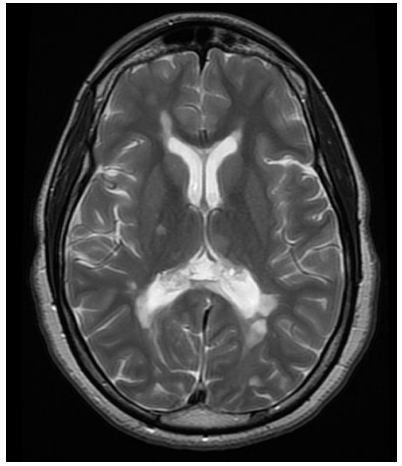
Infratentorial predominance

-Cerebrotendineous xanthomatosis
-Adult-Autosomal Dominant Leukodystrophy

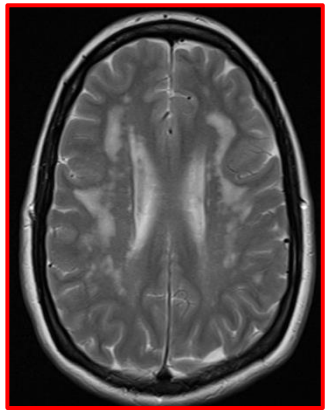


Occipital predominance

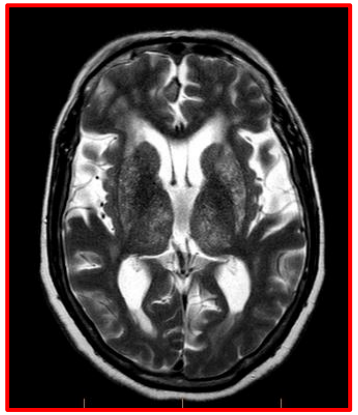
-Krabbe Disease
-X-linked adrenoleukodystrophy



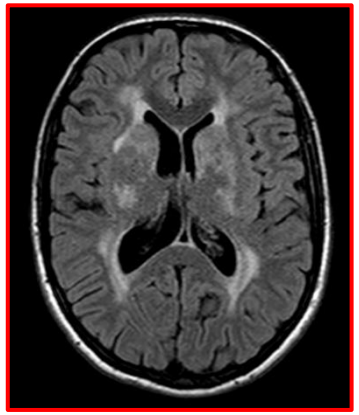
multifocal and asymmetric = acquired



CADASIL



CARASIL



COL4A1-related

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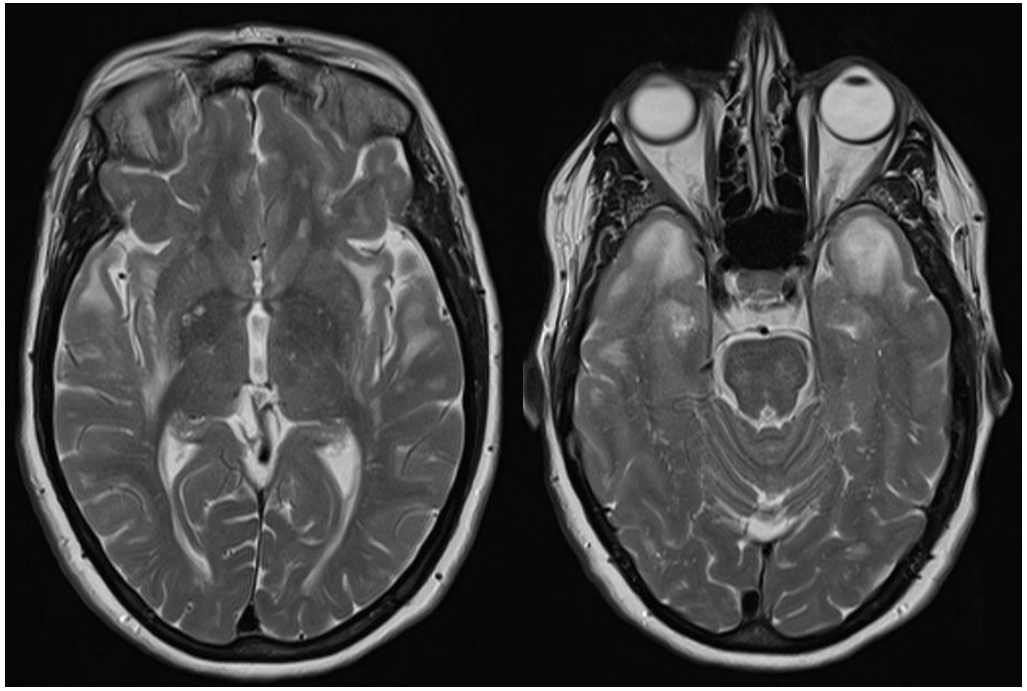
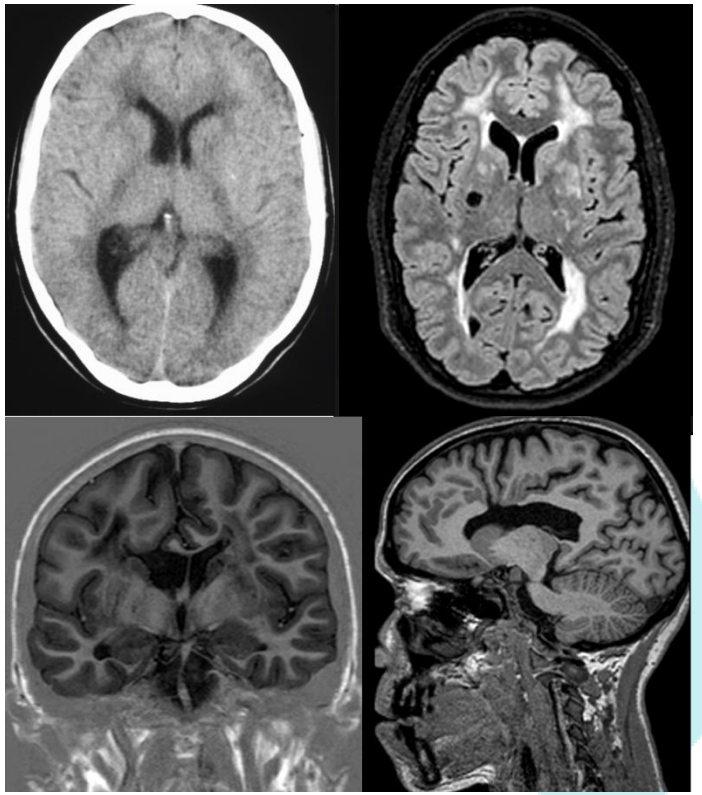
When to suspect a vascular white matter disease of genetic origin

1. Absence of risk factors for acquired cerebrovascular disorders
2. MRI findings can suggest specific forms

MRI Pattern Recognition



CADASIL
Involvement of temporal poles and external capsules



COL4A1-related disorders
Calcifications
Cortical malformations
Enlarged perivascular spaces

Tonduti, La Piana et al., 2012

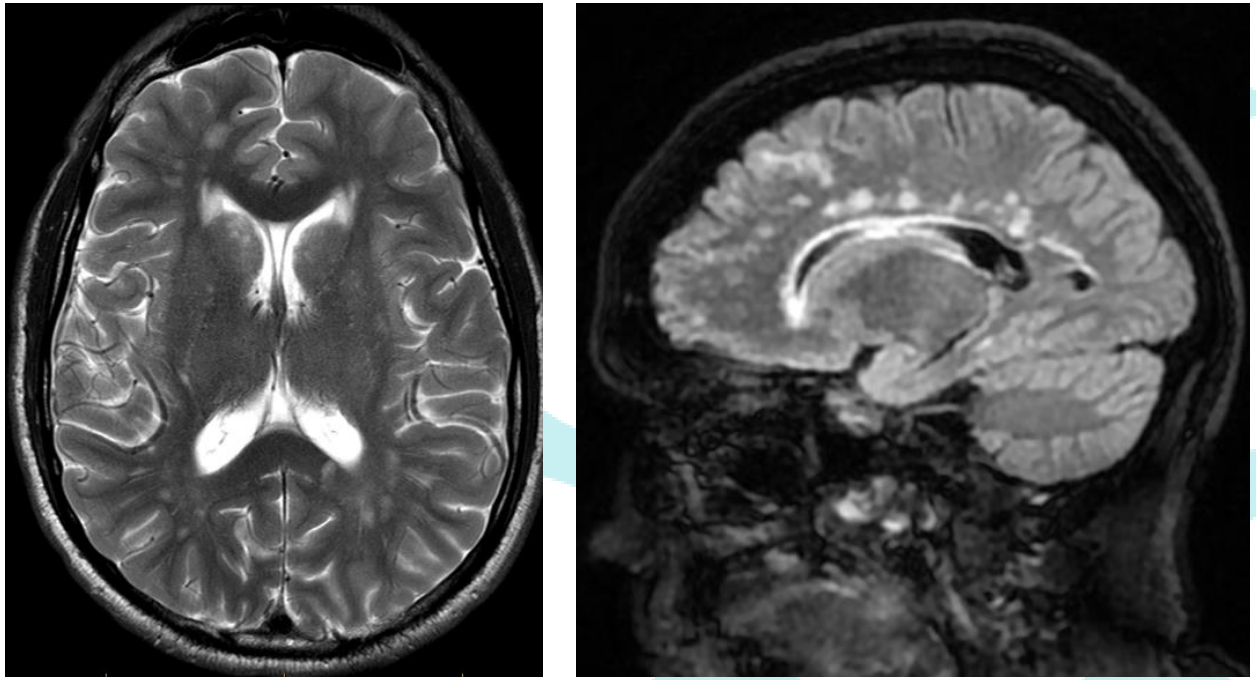
CADASIL

Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy

- Autosomal dominant
- Mutations in the *NOTCH3* gene

Diagnostic challenges

- Relapsing course
- No migraine
- No psychiatric symptoms
- No family history



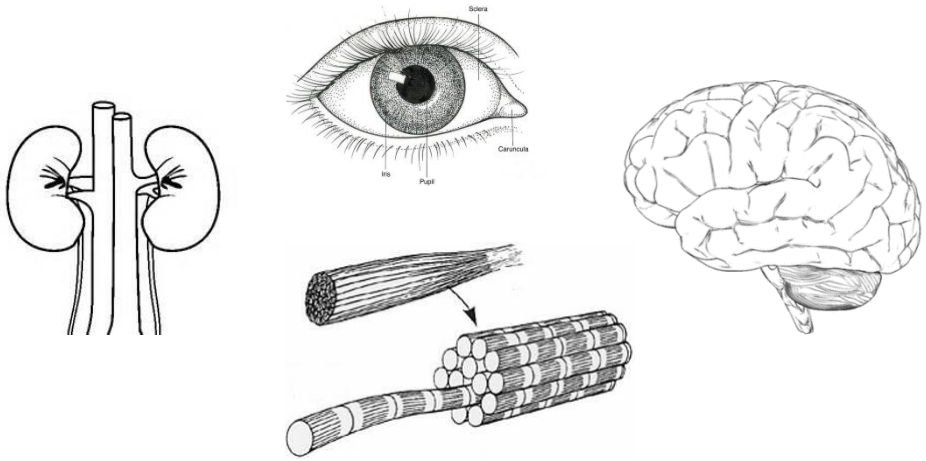
Images from our cohort

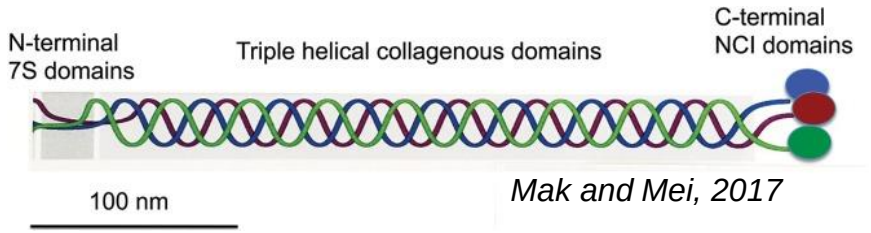
When to suspect a vascular white matter disease of genetic origin

1. Absence of risk factors for acquired cerebrovascular disorders
2. MRI findings suggests specific forms
3. Extraneurological involvement can orient the diagnosis

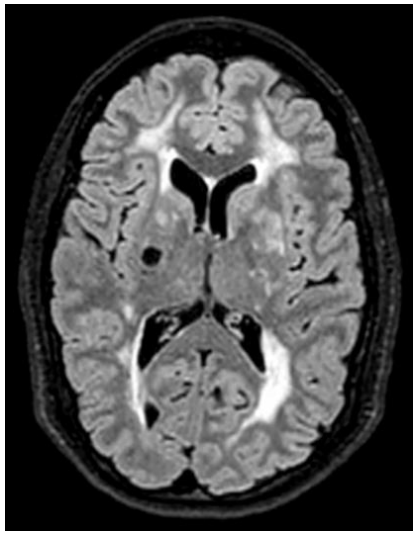
COL4A1-related disorders

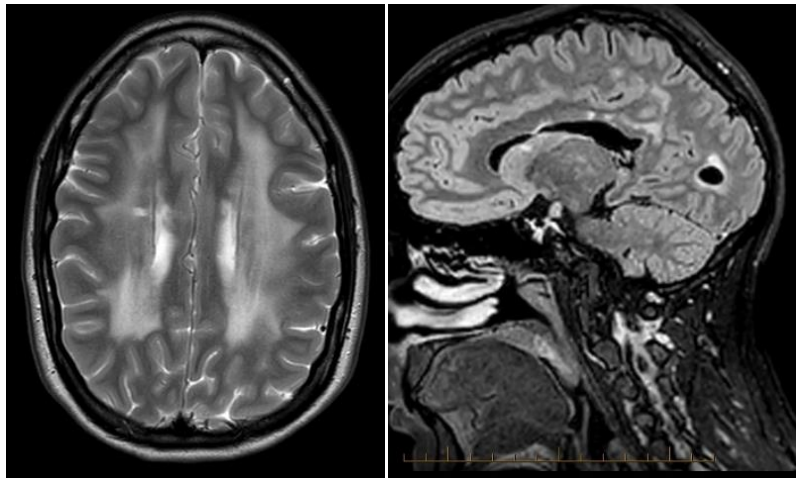
-Autosomal dominant (*de novo* in 27%)
-Clinically heterogeneous
-High intrafamilial variability in age of onset and presentation





Mak and Mei, 2017



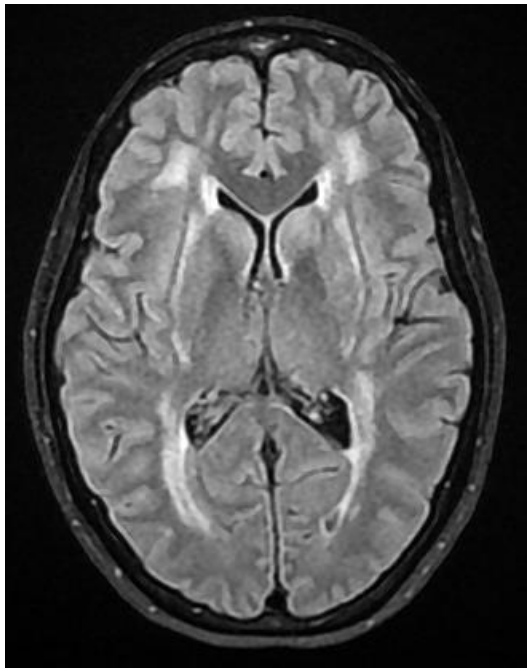


COL4A2-related disorders

Woman with cranial pain syndrome
Low QI
Cramps

Family history
Negative
Six younger siblings with higher cognitive functioning

Heterozygous *COL4A2* mutation



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Kim et al., in preparation

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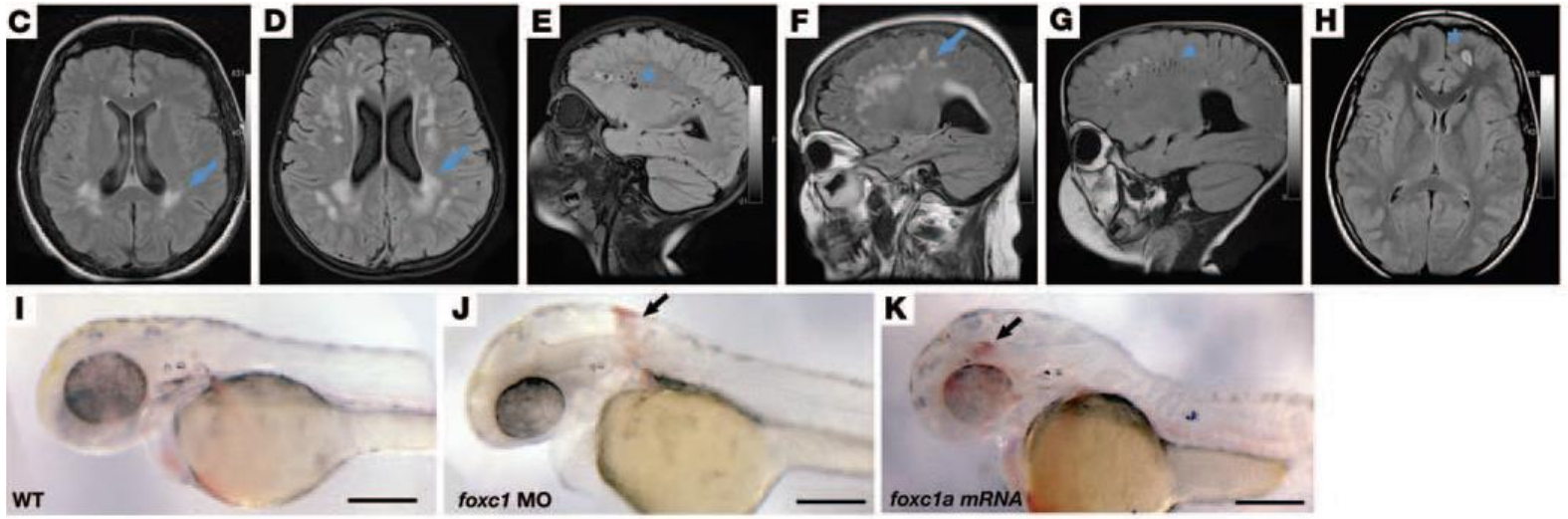
The Journal of Clinical Investigation BRIEF REPORT

Mutation of *FOXC1* and *PITX2* induces cerebral small-vessel disease

Curtis R. French,[1] Sudha Seshadri,[2] Anita L. Destefano,[3] Myriam Fornage,[4] Corey R. Arnold,[5] Philip J. Gage,[6] Jonathan M. Skarie,[7] William B. Dobyns,[8] Kathleen J. Millen,[8] Ting Liu,[9] William Dietz,[9] Tsutomu Kume,[9] Marten Hofker,[10] Derek J. Emery,[11] Sarah J. Childs,[5] Andrew J. Waskiewicz,[12] and Ordan J. Lehmann[1,13]

[1]Department of Ophthalmology, University of Alberta, Edmonton, Alberta, Canada. [2]Department of Neurology and [3]School of Public Health, Boston University, Boston, Massachusetts, USA. [4]Institute of Molecular Medicine and School of Public Health, University of Texas Health Sciences Center, Houston, Texas, USA. [5]Department of Biochemistry and Molecular Biology, University of Calgary, Calgary, Alberta, Canada. [6]Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, Michigan, USA. [7]Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, Wisconsin, USA. [8]Department of Pediatrics and the Center for Integrative Brain Research, University of Washington, Seattle, Washington, USA. [9]Feinberg Cardiovascular Research Institute, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA. [10]Department of Genetics, University of Groningen, Groningen, The Netherlands. [11]Department of Radiology and Diagnostic Imaging, [12]Department of Biological Sciences, and [13]Department of Medical Genetics, University of Alberta, Edmonton, Alberta, Canada.



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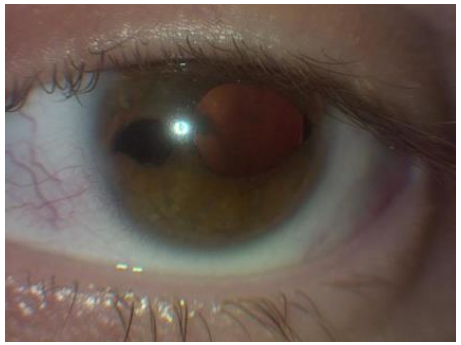
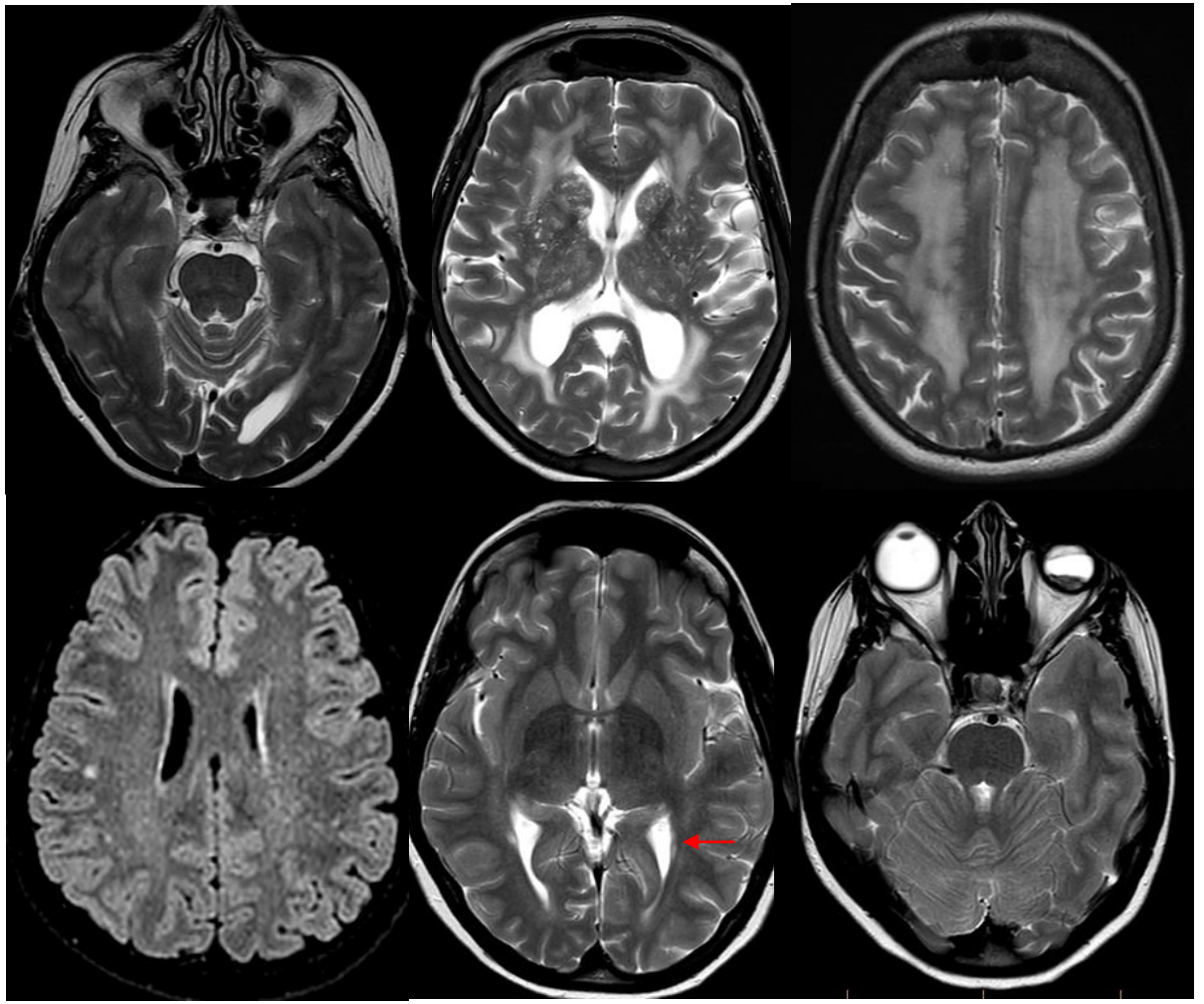
FOXC1-related disorders

- Progressive hearing loss
- Eye abnormalities
- Cerebral small vessel disease



Axenfeld-Rieger Anomaly



Tabassum et al. to be submitted

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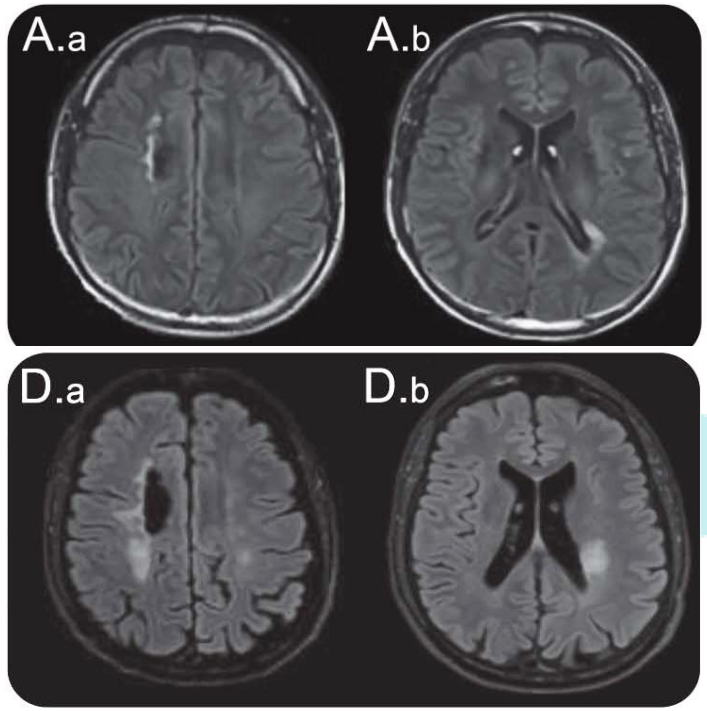
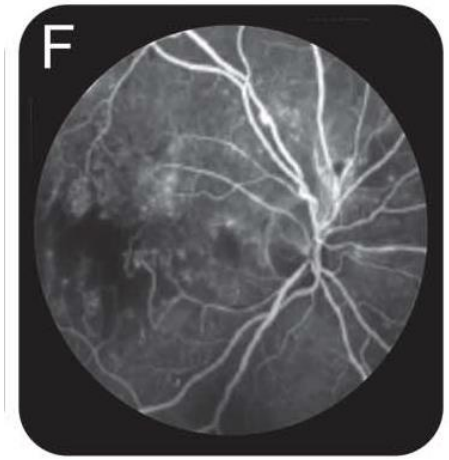
Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)

Autosomal dominant mutations in *TREX1*

Retinal microangiopathy

Genetic endotheliopathy affecting multiple organs: eye, kidney, brain





Schuh et al., Neurology 2015

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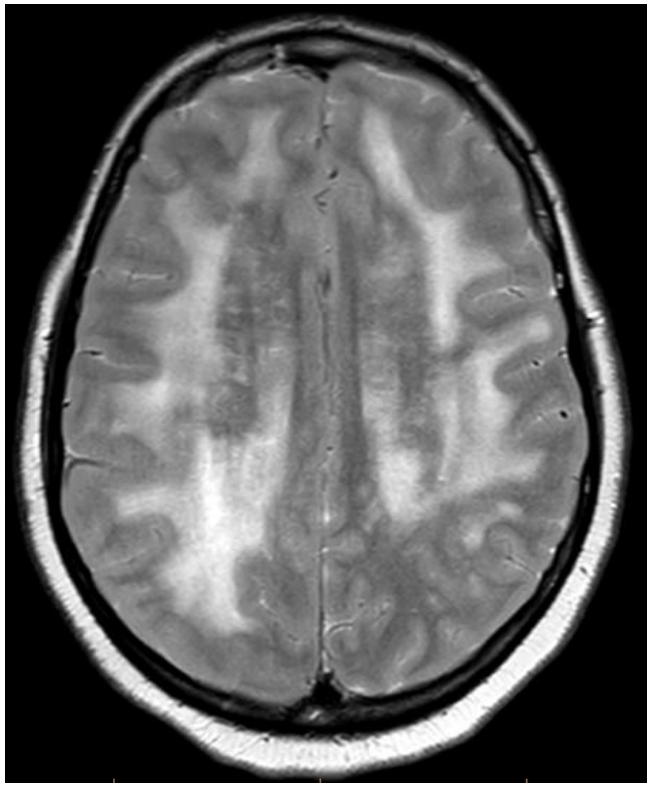
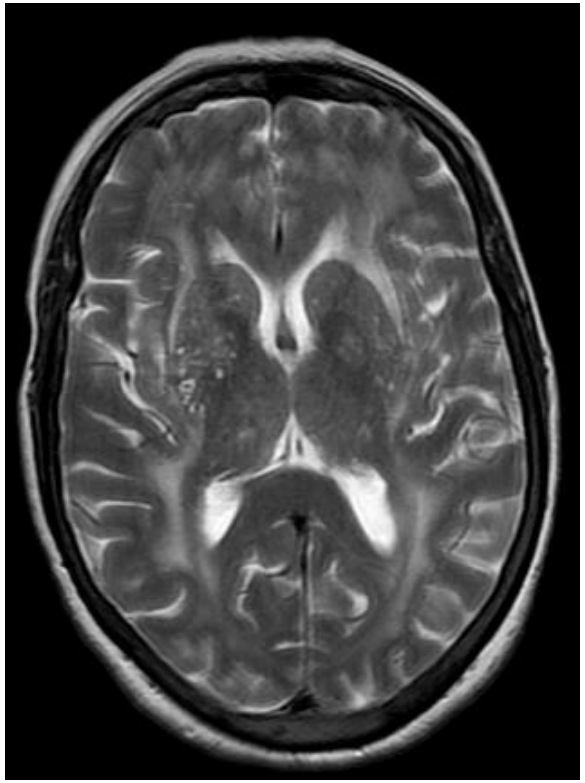
Useful reminders for the clinical practice

- Hereditary CSVD are underrecognized
- MRI features and patterns can narrow down the differential genetic diagnosis
- MRI alone may not be sufficient in identifying all genetic CSVD and there is a need to integrate genetic and clinical datasets

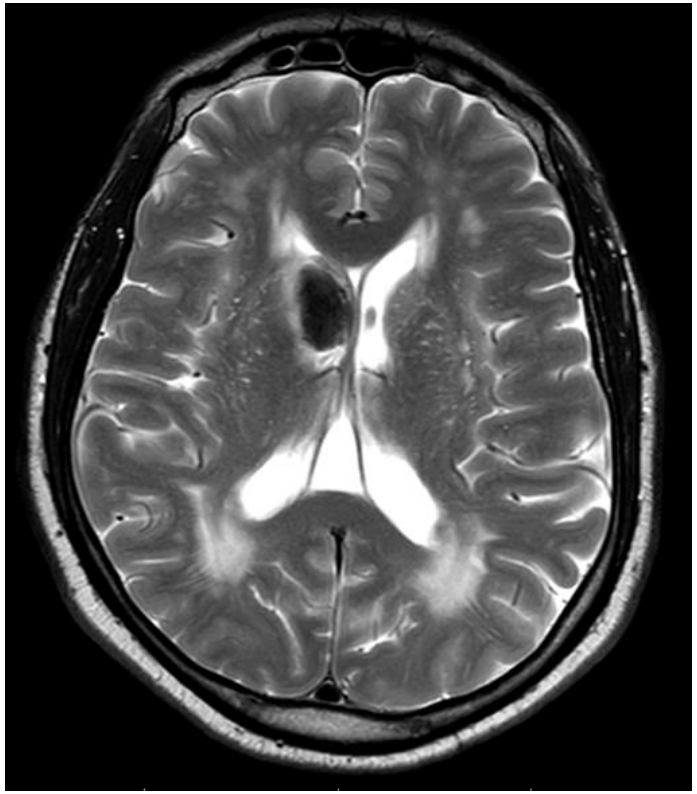
Undiagnosed vascular white matter diseases of genetic origin



32-year-old woman, migraine



67-year-old woman, ataxia and vertigo.
Same symptoms and MRI findings in the sister



47-year-old man, episodes of intracranial hemorrhage.
Important family history for “sudden death”.

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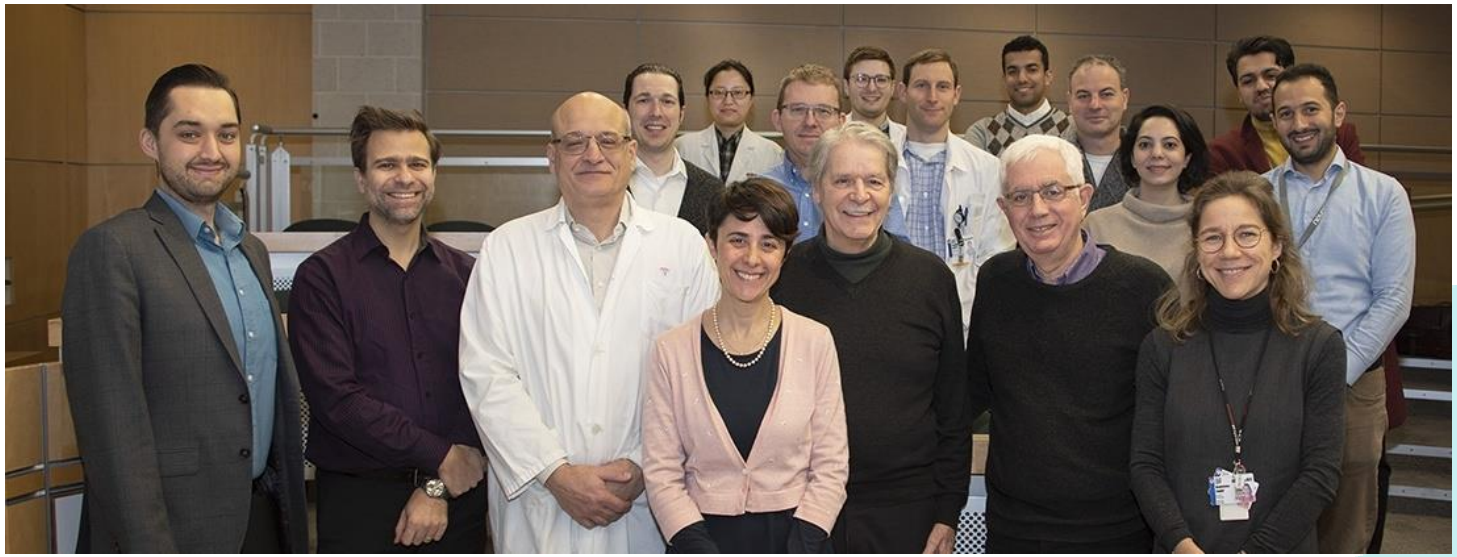
White Matter Rounds

- Created in 2013
- Now an established monthly meeting
- Multidisciplinary team including MS clinicians and scientists, neurogeneticists, imaging experts



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frontiers | Frontiers in Neurology

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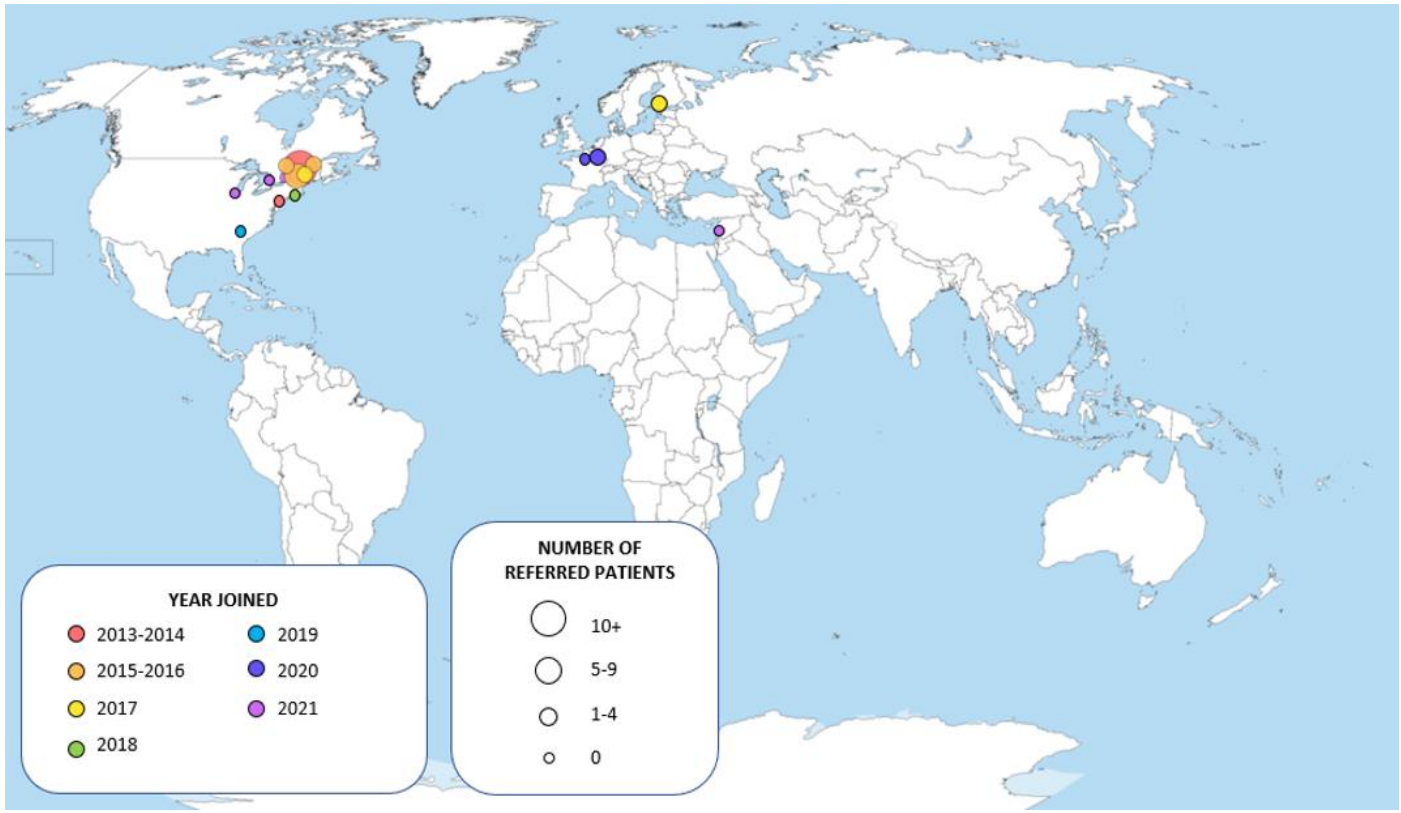
The White Matter Rounds experience: The importance of a multidisciplinary network to accelerate the diagnostic process for adult patients with rare white matter disorders

Yu Tong Huang[1], Paul S. Giacomini[1], Rami Massie[1], Sunita Venkateswaran[2], Anne-Marie Trudelle[3], Giulia Fadda[1], Maryam Sharifian-Dorche[1], Hayet Boudjani[4], Laurence Poliquin-Lasnier[5], Laura Airas[6], Alexander W. Saveriano[1], Matthias Georg Ziller[1,7], Elka Miller[8], Claudia Martinez-Rios[8], Nagwa Wilson[8], Jorge Davila[8], Carolina Rush[9], Erin E. Longbrake[10], Giulia Longoni[11], Gabrielle Macaron[12], Geneviève Bernard[1,13,14,15], Donatella Tampieri[16], Jack Antel[1], Bernard Brais[1] and Roberta La Piana[1,17]* on behalf of the White Matter Rounds Network



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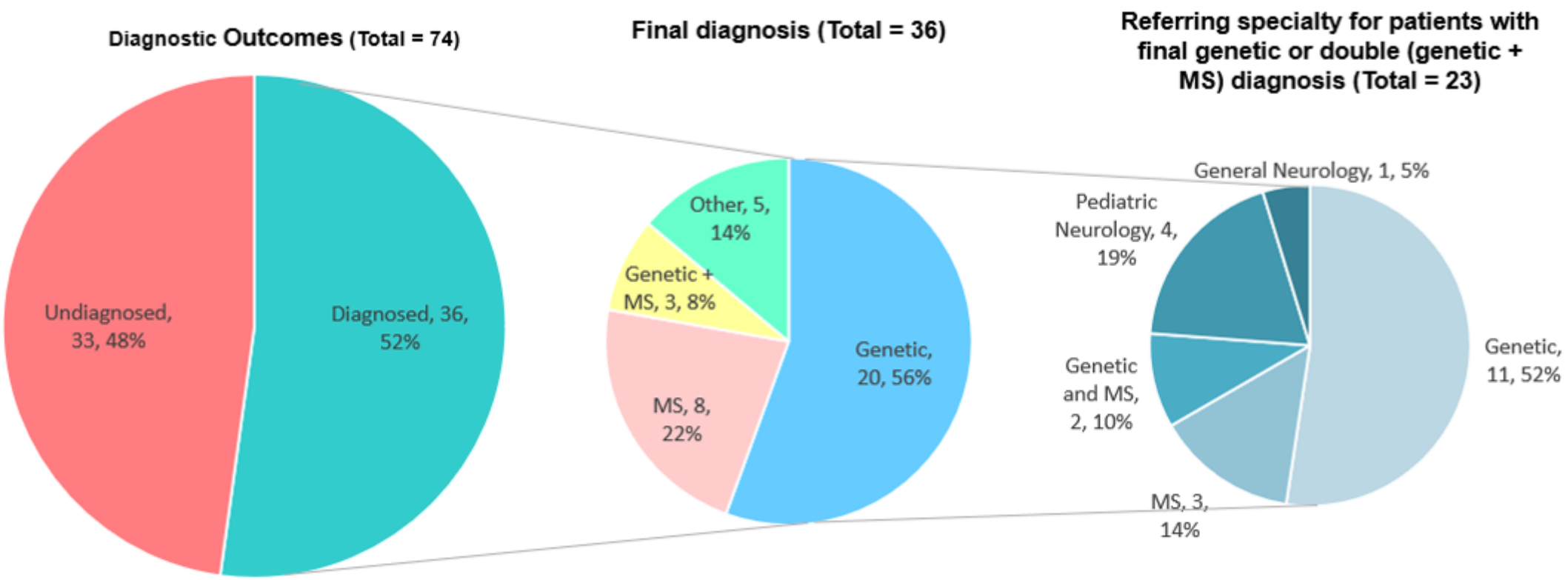

Huang et al., Front Neurol 2022

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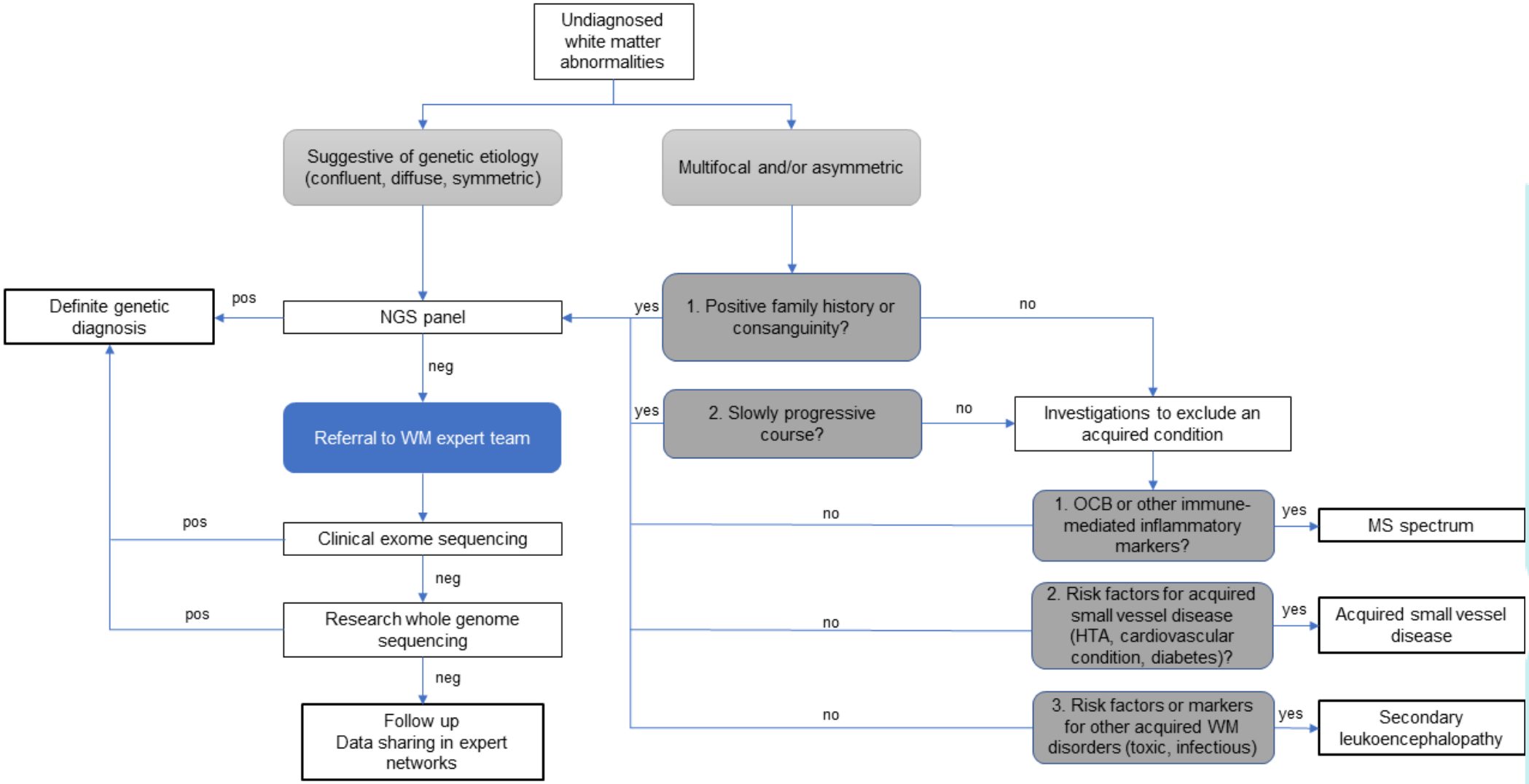
Diagnostic Algorithm



Huang et al., Front Neurol 2022

Aims

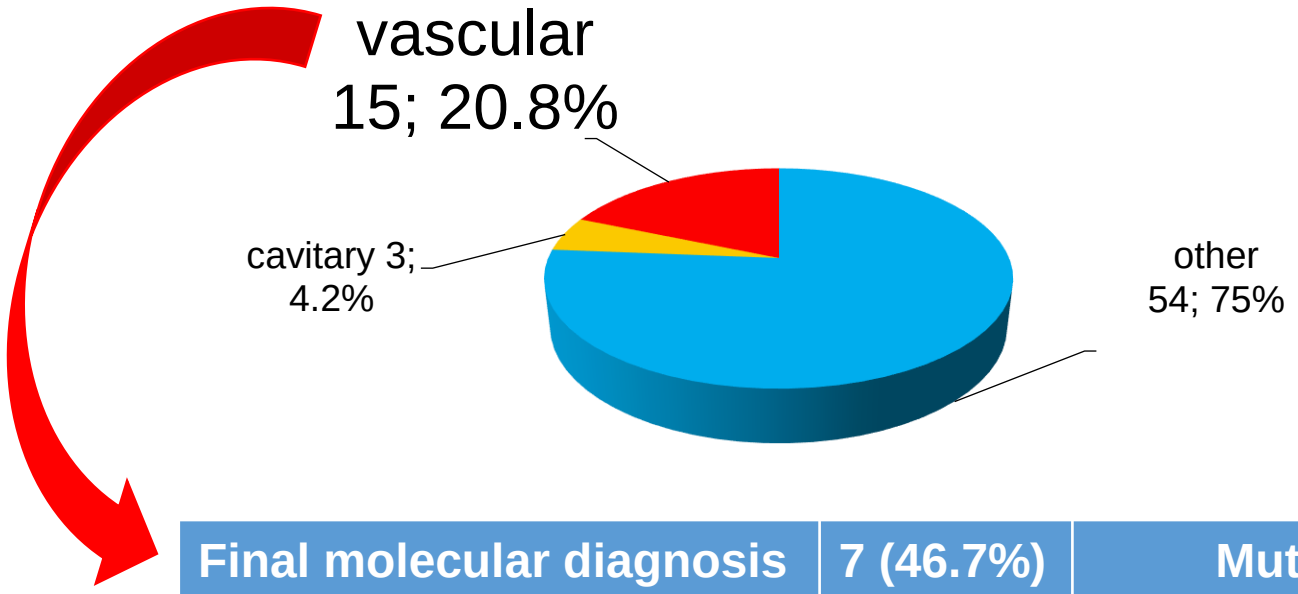
1) To assess the **rate** of subjects with leukoencephalopathy of vascular origin in our cohort of genetic leukoencephalopathies

2) To identify **specific MRI patterns** that

a. will orient the diagnosis

b. will guide the genetic analysis in undiagnosed forms

Prevalence of vascular MRI patterns in our cohort



Final molecular diagnosis	7 (46.7%)	Mutated Gene and Mutation
CADASIL	4	NOTCH3, c.323G>T; p.Cys108Phe NOTCH3, c.1337G>A; p.Cys446Tyr
CARASIL	1	HTRA1 c.83_93 del; pGly28Alafs*137
COL4A1-related disorder	1	COL4A c.3734G>T (p.Gly1245Val)
FOXC1-related disorder	1	FOXC1 c.331delC, p.Arg111AlafsX70

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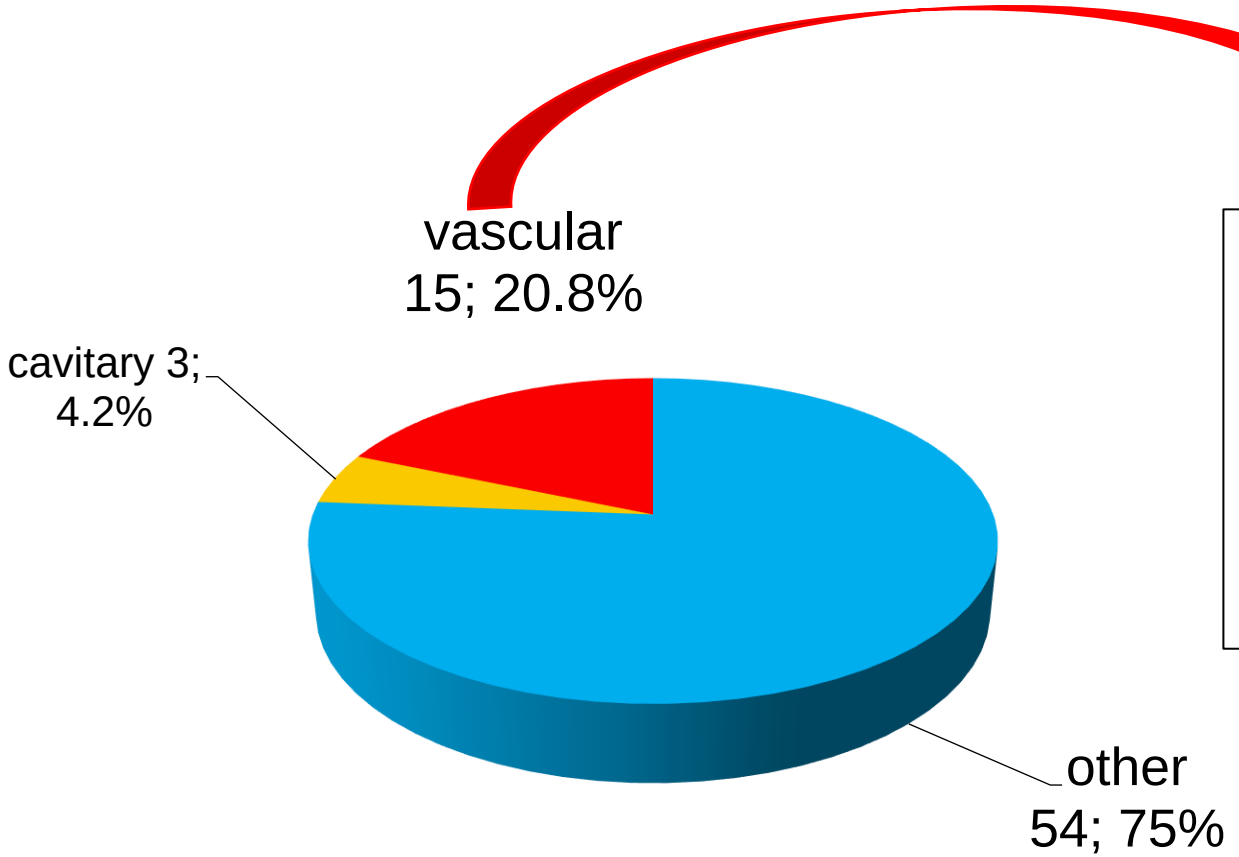
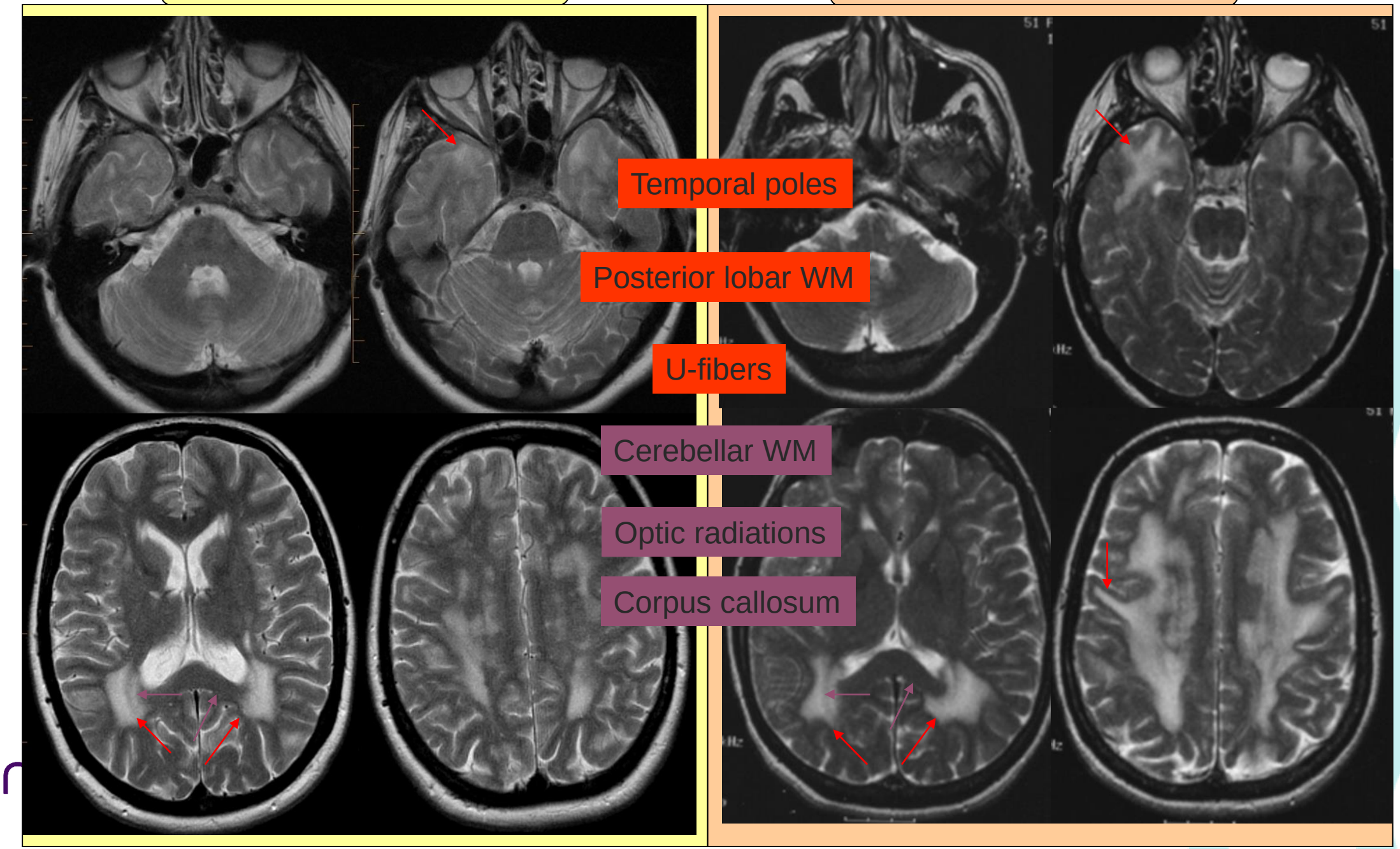


No variants in genes associated with known genetic small vessel diseases in 8 subjects*
53.3%

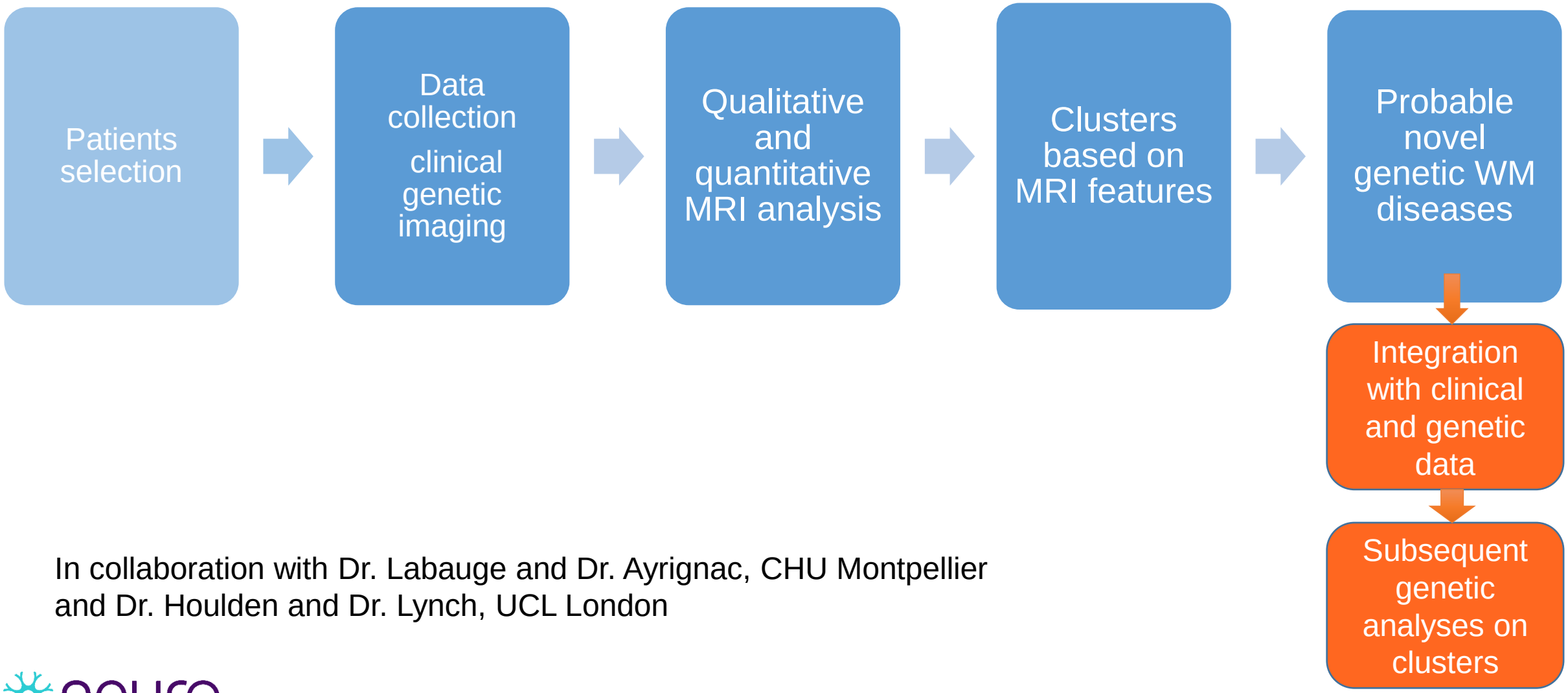
*candidate genes identified by WES in 2 subjects to be validated in other cohorts

Case 1

Case 2


Temporal poles
Posterior lobar WM
U-fibers
Cerebellar WM
Optic radiations
Corpus callosum

Project Outline and Future Directions



In collaboration with Dr. Labauge and Dr. Ayrignac, CHU Montpellier and Dr. Houlden and Dr. Lynch, UCL London

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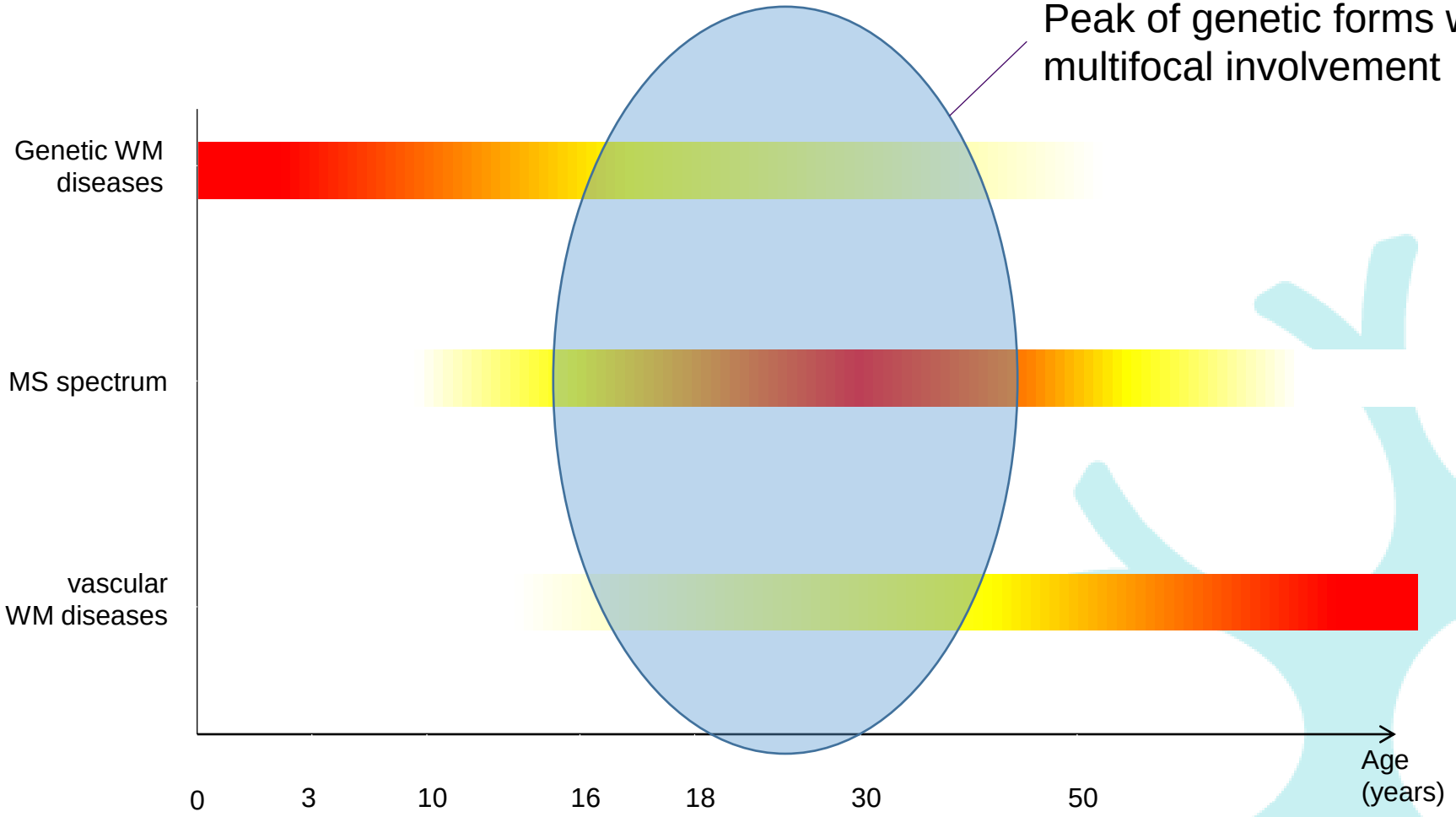
Conclusions

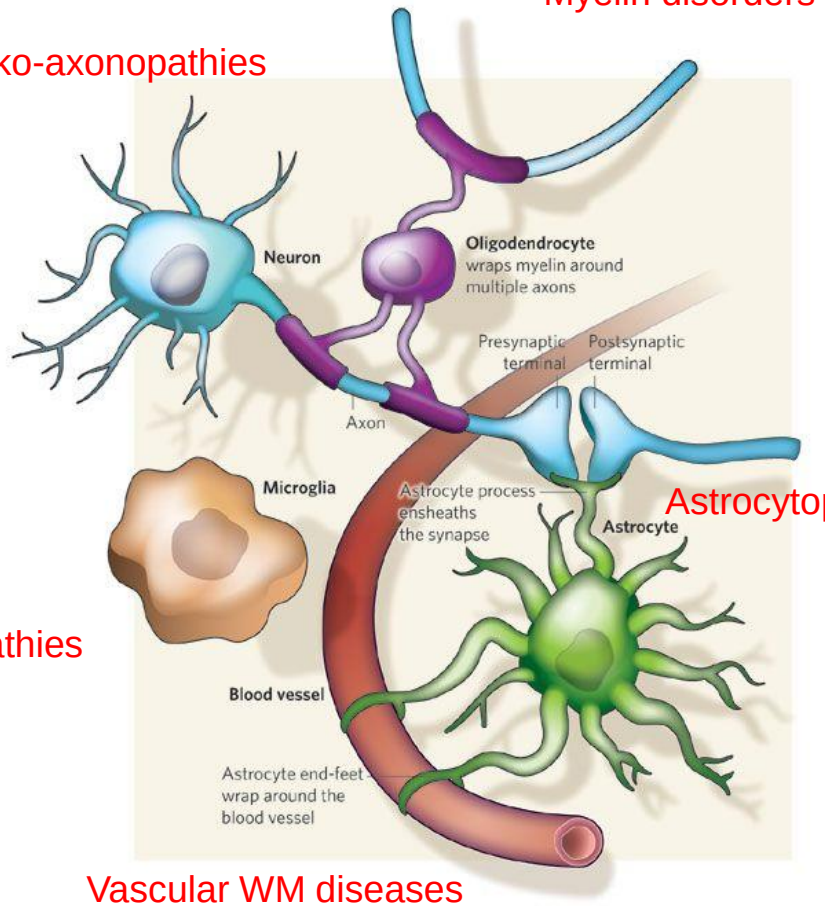


Bonkowsky et al., Neurology 2010
Vanderver et al., Semin Pediatr Neurol 2012
Kohler et al., Nature Reviews 2018
Jeong et al., J Child Neurol 2019
www.nationalmssociety.org

Conclusions

Myelin disorders

Leuko-axonopathies



Astrocytopathies

Microgliopathies

Vascular WM diseases

van der Knaap & Bugiani, Acta Pathol 2017

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