Update on Leukodystrophies: A Historical Perspective and Adapted Definition

Sietske H. Kevelam[1,2,*] Marjan E. Steenweg[1,2,*] Siddharth Srivastava[3] Guy Helman[4] Sakkubai Naidu[3] Raphael Schiffmann[5] Susan Blaser[6] Adeline Vanderver[4] Nicole I. Wolf[1,2] Marjo S. van der Knaap[1,2,7]

[1] Department of Child Neurology, VU University Medical Centre, Amsterdam, The Netherlands
[2] Amsterdam Neuroscience, VU University, Amsterdam, The Netherlands
[3] Department of Neurogenetics, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States
[4] Department of Neurology, Children's National Health System, Washington, District of Columbia, United States
[5] Institute of Metabolic Disease, Baylor Research Institute, Dallas, Texas, United States
[6] Division of Neuroradiology, The Hospital for Sick Children, Toronto, Ontario, Canada
[7] Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, VU University, Amsterdam, The Netherlands

Address for correspondence Marjo S. van der Knaap, MD, PhD, Department of Child Neurology, VU Medical Center, de Boelelaan 1117, 1081 HV Amsterdam, The Netherlands (e-mail: ms.vanderknaap@vumc.nl).

Neuropediatrics 2016;47:349–354.

Abstract

Leukodystrophies were defined in the 1980s as progressive genetic disorders primarily affecting myelin of the central nervous system. At that time, a limited number of such disorders and no associated gene defects were known. The majority of the leukodystrophy patients remained without a specific diagnosis. In the following two decades, magnetic resonance imaging pattern recognition revolutionized the field, allowing the definition of numerous novel leukodystrophies. Their genetic defects were usually identified through genetic linkage studies. This process required substantial numbers of cases and many rare disorders remained unclarified. As recently as 2010, 50% of the leukodystrophy patients remained unclassified. Since 2011, whole-exome sequencing has resulted in an exponential increase in numbers of known, distinct, genetically determined, ultrarare leukodystrophies. We performed a retrospective study concerning three historical cohorts of unclassified leukodystrophy patients and found that currently at least 80% of the patients can be molecularly classified. Based on the original definition of the leukodystrophies, numerous defects in proteins important in myelin structure, maintenance, and function were expected. By contrast, a high percentage of the newly identified gene defects affect the housekeeping process of mRNA translation, shedding new light on white matter pathobiology and requiring adaptation of the leukodystrophy definition.

Keywords
- leukodystrophy
- genetics
- myelin

* *These authors contributed equally to the study.*

received
July 9, 2016
accepted
July 13, 2016
published online
August 26, 2016

© 2016 Georg Thieme Verlag KG Stuttgart · New York

DOI http://dx.doi.org/10.1055/s-0036-1588020.
ISSN 0174-304X.

Downloaded by: Johns Hopkins University. Copyrighted material.

Introduction

Leukodystrophies have a history of just over a 100 years. For long, the field has been dominated by the problem of unclassified and unclassifiable cases. Over the years, multiple different techniques have been applied to address this problem depending on technological developments, with limited success. Since a few years, however, an exponential increase in numbers of ultrarare cases with novel genetic defects is seen. In this update, we address the proportion of classified leukodystrophies and discuss the impact of the insights gained from all newly detected genetic defects on what we define as a leukodystrophy.

Pathology

Research on brain white matter disorders started in the 1830s, when the first pathology descriptions appeared. In the subsequent 150 years, their diagnosis and classification remained almost exclusively based on pathology. "Multiple sclerosis" was first defined,[1,2] after 60 years, followed by the definition of "diffuse sclerosis" to distinguish disorders with a diffuse abnormality of the brain white matter from those with multifocal abnormalities.[3] The word "leukodystrophy" was introduced in 1928 for metachromatic leukodystrophy (MLD)[4]. "Leukodystrophy" comes from the Greek roots leuko = white, dys = lack of, and trophy = growth. Consensus on the definition of "leukodystrophies" as a disease category emerged in the 1980s. In two papers in this journal, they were defined as disorders primarily affecting myelin, either directly or through the involvement of oligodendrocytes, caused by a genetic defect, and clinically progressive.[5,6] So, the initial definition of leukodystrophy was myelin focused. As of today, it is this definition that most physicians have in mind when using the word. "Leukoencephalopathy" is a more neutral term for any brain white matter disorder, genetic or acquired.

Magnetic Resonance Imaging

In the 1970s, the advent of computed tomography (CT) scanning provided the first opportunity to visualize leukoencephalopathies in vivo, but due to the low sensitivity and tissue differentiation, CT was unable to distinguish between most different disorders.[7] In the early 1980s, the advent of magnetic resonance imaging (MRI) had a major impact on the leukoencephalopathy field. It was immediately clear that MRI had a very high sensitivity for white matter abnormalities,[8] but the specificity of these findings was initially considered as low.[9,10]

When we started to study leukoencephalopathies in the late 1980s, a limited number of disorders and no genes associated with a leukodystrophy were known. The diagnosis depended on metabolic investigations (metabolites in body fluids and enzyme activities) for most disorders[11] and pathology findings for a few.[12,13] MRI changed the diagnostic approach entirely. We noticed that patients with a diagnosis that was verifiable by laboratory testing presented with distinct patterns of MRI abnormalities, shared by patients with the same diagnosis, but different from the patterns observed in patients with other diagnoses.[14] This observation prompted the development of MRI pattern recognition to enhance the specificity of MRI interpretation.[15]

For the diagnosis of leukoencephalopathies known at that time, MRI pattern recognition worked well.[16] In the 90s, it became, however, clear that in substantial numbers of leukoencephalopathy cases no specific diagnosis could be established. We estimated that over 60% of the leukoencephalopathy cases remained unsolved.[17] The heavy load of unclassified leukoencephalopathies impelled us and others to work on them and define novel disorders by their distinct MRI patterns.[17] In this way, new disease entities as megalencephalic leukoencephalopathy with subcortical cysts (MLC),[18] vanishing white matter (VWM),[19–21] hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC),[22] leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation,[23] hypomyelination, hypodontia, and hypogonadotropic hypogonadism (4H syndrome),[24–26] leukoencephalopathy and thalamus and brainstem involvement and high lactate (LTBL),[27] and hypomyelination of early myelinating structures (HEMS)[28] were defined and criteria were drafted for MRI-based diagnoses.

Genetic Linkage

The first genes associated with known leukodystrophies were identified at the end of the 1980s, initially mainly by a candidate gene approach directed at the likely genetic defect. Examples are *PLP1* for Pelizaeus–Merzbacher disease,[29] *ARSA* for MLD,[30] *ASPA* for Canavan disease,[31] and *GALC* for Krabbe disease.[32] Later, genes were identified by genetic linkage, for example, *ABCD1* for X-linked adrenoleukodystrophy.[33]

Validation of the concept that novel leukodystrophies could be defined by their MRI pattern came in 2001, when the first genes mutated in MRI-defined disorders were identified: *EIF2B1–5* for VWM[34,35] and *MLC1* for MLC.[36] Over the following years, several genes mutated in new, MRI-defined disorders were identified.[37–41] Linkage analysis using positional cloning to pinpoint the chromosomal location of the candidate gene and subsequent narrowing of the candidate region, followed by sequential analysis of candidate genes in the region by Sanger sequencing were the main techniques used. This approach required substantial numbers of patients at all stages. Several patients with the same MRI pattern were necessary to define the disease and multiple genetically informative families were needed for genetic linkage. For most patients with an unclassified or defined, but molecularly undetermined leukodystrophy, this technique did not succeed, mainly due to the rarity of the disorders or dominant de novo inheritance.

Despite the fact that the most prevalent novel leukodystrophies had been identified between 1990 and 2010 and their gene defect had been elucidated, it was found that 50% of leukodystrophy patients still remained without a specific diagnosis in 2010.[42]

Exome Sequencing

The advent of next-generation-sequencing technology in 2005 had a major impact on the leukodystrophy field. It

Downloaded by: Johns Hopkins University. Copyrighted material.

created a paradigm shift in the approach of gene discovery for rare Mendelian disorders.[43] Massive parallel sequencing of the protein-coding part of the genome is referred to as whole-exome sequencing (WES).[43] In 2011, the first genetic defect for a leukodystrophy without known molecular cause, "hereditary diffuse leukoencephalopathy with spheroids (HDLS)," was identified using WES, which revealed dominant mutations in *CSF1R*.[44] Soon thereafter WES revealed recessive mutations in *EARS2* in patients with LTBL,[45] and dominant de novo mutations in *TUBB4A* in the sporadic disease H-ABC.[46] The number of novel genes associated with new or previously defined Mendelian disorders identified between 2011 and 2016 using WES has been enormous and illustrates the high potential of this technique for gene finding.[47,48] In addition, WES has proven to greatly facilitate a molecular diagnosis for disorders associated with numerous different gene defects, such as hypomyelination and respiratory chain defects, in which sequential gene analysis is costly and time consuming.

Although extremely successful, one of the biggest challenges of WES still is an interpretation of the data. From approximately 20,000 to 25,000 variants identified in each individual exome, a single candidate gene has to be selected. WES approaches using small groups of patients with presumably the same MRI-defined novel leukodystrophy are quite successful in gene identification[45,46,49–56] and appear much more powerful than WES in large, unselected patient groups. We have had a success rate of 80 to 90% for gene identification by WES in small, homogeneous patient groups from our database of unclassified leukoencephalopathies, whereas several larger WES studies have reported success rates of 42% for mixed leukodystrophy cases[57] and 16 to 53% for unselected patients.[58–60] The most important advantage of WES in homogeneous patient groups is that the patients validate each other in that the conclusion on the pathogenicity of the identified variants does not only depend on knowledge of gene function or predicted effect of the variant, but also on whether variants in the same gene are observed in other patients.

Percentage of Unsolved Cases

In 2010, 50% of the leukodystrophy cases were still unclassified.[42] We suspected that with WES the percentage has decreased substantially. To confirm this, we conducted a retrospective study of three different historical cohorts, including a total of 430 patients with an unclassified leukoencephalopathy despite extensive available diagnostic workup.

The first and oldest cohort, cohort 1, was published in 1999 and contains 92 leukoencephalopathy patients from 82 families, including both inherited and acquired disorders, evaluated at the Kennedy Krieger Institute in Baltimore during 1990 to 1996.[17] Follow-up of outcomes was executed in October 2015. A specific diagnosis had been established in 40 of the 82 families: 27 through DNA confirmation, 10 based on established MRI criteria (four MLC and six Alexander disease), and three based on pathology (Alexander disease and HDLS). For the latter 13 patients, the diagnosis could not be confirmed molecularly because of lack of available DNA. The percentage of almost 50% of the cases with a specific diagnosis is an underestimation. As expected for such an old cohort, many cases were lost to follow-up and most cases never had the genetic workup that would now be state-of-the-art. In addition, part of the patients may not have a genetic disease.[17]

The second and third cohorts consist of cases from the MRI database of the Center for Childhood White Matter Disorders in Amsterdam that contains over 3,000 unclassified leukoencephalopathy cases. In 2011, cases from this database were entered on lists if they presumably had a leukodystrophy, but no molecular diagnosis, and had hypomyelination (cohort 2) or were suspected of a mitochondrial defect (cohort 3). Hypomyelination was defined as evidence of stable lack of myelin on two successive MRIs with an interval of at least 6 months and the second MRI after 1 year of age.[61] A "suspected mitochondrial leukodystrophy" was determined by the MRI pattern, showing features as cystic lesions in the abnormal white matter, additional gray matter lesions, restricted diffusion, contrast enhancement, and elevated lactate on magnetic resonance spectroscopy of the brain.[62,63] Outcomes were assessed in December 2015 and exclusively based on the presence or absence of a molecular diagnosis. Counting siblings as one, 181 cases were present in cohort 2 and 167 in cohort 3. For cohorts 2 and 3, 67 (37%) and 61 (37%) of the cases were lost to follow-up leaving 114 and 106 cases, respectively (►**Table 1**). For these remaining cases, a molecular diagnosis was established in 60/114 (53%) for cohort 2, 69/106 (65%) for cohort 3, and 129/220 (59%) for the overall group (►**Table 1**).

Table 1 Outcome for cohorts 2 and 3

	Cohort 2 : Hypomyelination	Cohort 3: Suspected mitochondrial leukodystrophy
	Number of cases (%)	
Informative cases	114 (100%)	106 (100%)
Diagnosis	60/114 (53%)	69/106 (65%)
No diagnosis, WES unrevealing	4/114 (4%)	3/106 (3%)
No diagnosis, no WES performed	50/114 (43%)	34/106 (32%)
Lost to follow-up	67	61
Total cases	181	167

Abbreviation: WES, whole-exome sequencing.

Downloaded by: Johns Hopkins University. Copyrighted material.

It is important to realize that the patients included in the present retrospective study represent the 60% (cohort 1) or 50% (cohorts 2 and 3) patients in whom no diagnosis could be established 16 or 5 years before, respectively. A positive molecular diagnosis in these cases results in an estimated decrease of the unclassified group to approximately 20%. This is still an underestimation of the percentage of classifiable leukodystrophy cases. Most of the remaining unclassified leukodystrophy patients did not undergo WES (50/54 cases for cohort 2 and 34/37 cases for cohort 3). With WES applied in all patients, the percentage of unclassified cases would be even lower.

Genetic Defects and Leukodystrophy Concepts

►**Fig. 1** presents the reported diagnoses in the cohorts. An intriguing finding is that only three myelin- or oligodendrocyte-specific protein defects were found: *PLP1* for HEMS,[55] *GJC2* for Pelizaeus–Merzbacher like disease[64] and *GJB1* for brain manifestations of X-linked Charcot–Marie–Tooth disease.[50] Based on the original definition of the leukodystrophies, numerous defects in proteins important in the myelin build-up, maintenance, structure, and function would be expected, but instead a high percentage of the newly identified gene defects affect the housekeeping process of mRNA translation, both in the hypomyelination and in the suspected mitochondrial leukodystrophy groups (►**Fig. 1**).

mRNA translation is a highly complex process and numerous proteins are involved, including proteins mediating activation, initiation, elongation or termination of mRNA translation; aminoacyl-tRNA synthetases; ribosomal proteins; as well as cofactors and modifying proteins.[65] VWM was the first example of a leukodystrophy caused by a defect in mRNA translation.[34,66] In cohorts 2 and 3 many patients had a defect in one of the mitochondrial or cytosolic aminoacyl-tRNA synthetases. These are housekeeping enzymes that attach amino acids to their cognate tRNA molecules as an essential step in protein synthesis.[67] Furthermore, a large group of patients had mutations in genes encoding subunits of RNA polymerase POLR3 (*POLR3A*, *POLR3B*, and *POLR1C*). Strikingly, POLR3-related disorders prove to be among the most prevalent hypomyelinating leukodystrophies.[68] In line with the housekeeping function in the mRNA translation of the affected proteins, patients never have two mutations that would cause complete function loss, because the absence of the housekeeping function would not be compatible with life. In fact, we suspect that the housekeeping function of the mutated proteins is still guaranteed and that it is not the hampered housekeeping function that causes the disease. We hypothesize that noncanonical functions of the affected proteins play a role in the pathogenesis of mRNA translation-related leukodystrophies.[69–71]

For some disorders accepted as leukodystrophies, WES revealed defects in proteins specifically expressed in unexpected cell types. The *CSF1R* gene, mutated in HDLS, encodes a growth factor specific for microglia, macrophages, and monocytes,[72] while pathology suggests a white matter axonopathy.[13] *TUBB4A*, mutated in H-ABC, encodes a β-tubulin protein, a building block of microtubules. Microtubules are an essential component of the cytoskeleton and allow cell organelles and vesicles to move. In H-ABC, in which pathology points at the primary axonal damage, the defective microtubule system may hamper axonal transport, leading to axonal dysfunction and loss and secondary myelin deficit.[73]

The findings of the last 5 years have major implications for how we understand leukodystrophies. The original definition was focused on myelin and required a progressive disease course. With the information on newly identified defects underlying leukodystrophies, there is no justification for a myelin focused definition of the leukodystrophies. In addition, molecular progress has made clear that there are also nonprogressive or even improving leukodystrophy variants. MLC, widely accepted as a leukodystrophy,[74] was found to have an improving variant along with only transient abnormalities on MRI.[40,75] Another example is LTBL, which is typically characterized by a single episode of deterioration early in life, followed by improvement. The timing and severity of the episode determine the outcome, which varies from no or almost no handicap to severe dysfunction or death.[45,76] The conclusion based on these observations is that progression should not be regarded as a prerequisite for inclusion in the category of the leukodystrophies.

Definitions reflect the state of knowledge at the time and should be regularly updated to incorporate new insights. Recently the GLIA consortium suggested a modified leukodystrophy definition to include heritable disorders affecting

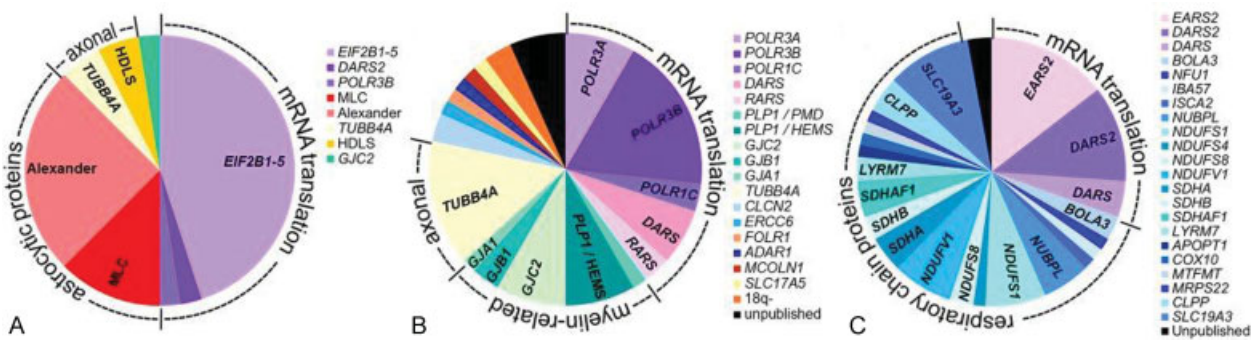

Fig. 1 Overview of diagnoses established (**A**) Diagnoses in cohort 1. (**B**) Genes mutated in cohort 2, hypomyelination. (**C**) Genes mutated in cohort 3, suspected mitochondrial leukodystrophies.

Downloaded by: Johns Hopkins University. Copyrighted material.

the central nervous system white matter with abnormalities involving myelin or all macroglial cell types, both oligodendrocytes and astrocytes.[74] The progressive disease course was no longer a criterion. Weighing all new information, we propose to take the next step and define leukodystrophies as all genetically determined disorders primarily affecting central nervous system white matter, irrespective of the structural white matter component involved, the molecular process affected and the disease course. Leukodystrophy definitions are, although necessarily imperfect, of fundamental importance, because they determine how we understand white matter physiology and pathophysiology and how we approach treatment. Not only do remyelination and glia restoration need to be achieved for leukodystrophies, but a complex tissue that contains many more components needs to be repaired.

Funding
The study received financial support from ZonMw TOP grant 91211005. G. H. and A. V. are supported by the Myelin Disorders Bioregistry Project.

Acknowledgments
The authors thank all the colleagues for referring patients and families and helping to retrieve information on the molecular diagnosis. Without their help this study would not have been feasible.

References

1 Carswell R. Pathological Anatomy. Illustrations of the Elementary Forms of Disease. London, United Kingdom: Longman, Orme, Brown, Green and Longman; 1838
2 Cruveilhier J. Anatomie pathologique du corps humain. Vol II. Fasc XXXII. Paris, France: Bailliere; 1835–1842
3 Heubner O. Über diffuse Hirnsclerose. Charité Ann 1897;22:298–310
4 Bielschowsky M, Henneberg R. Über familiäre diffuse sklerose (Leukodystrophia cerebri progressiva hereditaria). J Psychol Neurol 1928;36:131–181
5 Morell P. A correlative synopsis of the leukodystrophies. Neuropediatrics 1984;15(Suppl):62–65
6 Seitelberger F. Structural manifestations of leukodystrophies. Neuropediatrics 1984;15(Suppl):53–61
7 Barnes DM, Enzmann DR. The evolution of white matter disease as seen on computed tomography. Radiology 1981;138(2):379–383
8 Young IR, Hall AS, Pallis CA, Legg NJ, Bydder GM, Steiner RE. Nuclear magnetic resonance imaging of the brain in multiple sclerosis. Lancet 1981;2(8255):1063–1066
9 Dietrich RB, Vining EP, Taira RK, Hall TR, Phillipart M. Myelin disorders of childhood: correlation of MR findings and severity of neurological impairment. J Comput Assist Tomogr 1990;14(5): 693–698
10 Demaerel P, Faubert C, Wilms G, Casaer P, Piepgras U, Baert AL. MR findings in leukodystrophy. Neuroradiology 1991;33(4):368–371
11 Valle D, Beaudet AL, Vogelstein B, et al. The Online Metabolic and Molecular Bases of Inherited Disease. New York, NY: The McGraw-Hill Companies; 2016. Available at: http://ommbid.mhmedical.com/book.aspx?bookid=971. Accessed August 17, 2016
12 Alexander WS. Progressive fibrinoid degeneration of fibrillary astrocytes associated with mental retardation in a hydrocephalic infant. Brain 1949;72(3):373–381, 3
13 van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, Kamphorst W, Weinstein HC. Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. Neurology 2000;54(2): 463–468
14 Valk J, van der Knaap MS. Magnetic Resonance of Myelin, Myelination and Myelin Disorders. Berlin, Germany: Springer; 1989
15 van der Knaap MS, Valk J, de Neeling N, Nauta JJ. Pattern recognition in magnetic resonance imaging of white matter disorders in children and young adults. Neuroradiology 1991;33(6):478–493
16 van der Knaap MS, Valk J. Magnetic Resonance of Myelin, Myelination and Myelin Disorders. Berlin, Germany: Springer; 1995
17 van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology 1999;213(1):121–133
18 van der Knaap MS, Barth PG, Stroink H, et al. Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. Ann Neurol 1995;37(3):324–334
19 Hanefeld F, Holzbach U, Kruse B, Wilichowski E, Christen HJ, Frahm J. Diffuse white matter disease in three children: an encephalopathy with unique features on magnetic resonance imaging and proton magnetic resonance spectroscopy. Neuropediatrics 1993; 24(5):244–248
20 Schiffmann R, Moller JR, Trapp BD, et al. Childhood ataxia with diffuse central nervous system hypomyelination. Ann Neurol 1994;35(3):331–340
21 van der Knaap MS, Barth PG, Gabreëls FJ, et al. A new leukoencephalopathy with vanishing white matter. Neurology 1997;48(4): 845–855
22 van der Knaap MS, Naidu S, Pouwels PJ, et al. New syndrome characterized by hypomyelination with atrophy of the basal ganglia and cerebellum. AJNR Am J Neuroradiol 2002b;23(9):1466–1474
23 van der Knaap MS, van der Voorn P, Barkhof F, et al. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. Ann Neurol 2003;53(2):252–258
24 Wolf NI, Harting I, Boltshauser E, et al. Leukoencephalopathy with ataxia, hypodontia, and hypomyelination. Neurology 2005;64(8): 1461–1464
25 Timmons M, Tsokos M, Asab MA, et al. Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia. Neurology 2006;67(11):2066–2069
26 Bernard G, Thiffault I, Tetreault M, et al. Tremor-ataxia with central hypomyelination (TACH) leukodystrophy maps to chromosome 10q22.3-10q23.31. Neurogenetics 2010;11(4):457–464
27 Steenweg ME, Vanderver A, Ceulemans B, et al. Novel infantile-onset leukoencephalopathy with high lactate level and slow improvement. Arch Neurol 2012b;69(6):718–722
28 Steenweg ME, Wolf NI, Schieving JH, et al. Novel hypomyelinating leukoencephalopathy affecting early myelinating structures. Arch Neurol 2012;69(1):125–128
29 Hudson LD, Puckett C, Berndt J, Chan J, Gencic S. Mutation of the proteolipid protein gene PLP in a human X chromosome-linked myelin disorder. Proc Natl Acad Sci U S A 1989;86(20):8128–8131
30 Polten A, Fluharty AL, Fluharty CB, Kappler J, von Figura K, Gieselmann V. Molecular basis of different forms of metachromatic leukodystrophy. N Engl J Med 1991;324(1):18–22
31 Kaul R, Gao GP, Balamurugan K, Matalon R. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. Nat Genet 1993;5(2):118–123
32 Sakai N, Inui K, Fujii N, et al. Krabbe disease: isolation and characterization of a full-length cDNA for human galactocerebrosidase. Biochem Biophys Res Commun 1994;198(2):485–491
33 Mosser J, Douar AM, Sarde CO, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature 1993;361(6414):726–730
34 Leegwater PA, Vermeulen G, Könst AA, et al. Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. Nat Genet 2001;29(4): 383–388

Downloaded by: Johns Hopkins University. Copyrighted material.

35 van der Knaap MS, Leegwater PA, Könst AA, et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. Ann Neurol 2002;51(2):264–270

36 Leegwater PA, Yuan BQ, van der Steen J, et al. Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 2001;68(4):831–838

37 Zara F, Biancheri R, Bruno C, et al. Deficiency of hyccin, a newly identified membrane protein, causes hypomyelination and congenital cataract. Nat Genet 2006;38(10):1111–1113

38 Scheper GC, van der Klok T, van Andel RJ, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. Nat Genet 2007;39(4):534–539

39 Bernard G, Chouery E, Putorti ML, et al. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. Am J Hum Genet 2011;89(3):415–423

40 López-Hernández T, Ridder MC, Montolio M, et al. Mutant GlialCAM causes megalencephalic leukoencephalopathy with subcortical cysts, benign familial macrocephaly, and macrocephaly with retardation and autism. Am J Hum Genet 2011;88(4):422–432

41 Tétreault M, Choquet K, Orcesi S, et al. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. Am J Hum Genet 2011;89(5):652–655

42 Bonkowsky JL, Nelson C, Kingston JL, Filloux FM, Mundorff MB, Srivastava R. The burden of inherited leukodystrophies in children. Neurology 2010;75(8):718–725

43 Ng SB, Turner EH, Robertson PD, et al. Targeted capture and massively parallel sequencing of 12 human exomes. Nature 2009;461(7261):272–276

44 Rademakers R, Baker M, Nicholson AM, et al. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet 2012; 44(2):200–205

45 Steenweg ME, Ghezzi D, Haack T, et al. Leukoencephalopathy with thalamus and brainstem involvement and high lactate 'LTBL' caused by EARS2 mutations. Brain 2012;135(Pt 5): 1387–1394

46 Simons C, Wolf NI, McNeil N, et al. A de novo mutation in the β-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. Am J Hum Genet 2013;92(5):767–773

47 Boycott KM, Dyment DA, Sawyer SL, Vanstone MR, Beaulieu CL. Identification of genes for childhood heritable diseases. Annu Rev Med 2014;65:19–31

48 Vissers LE, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet 2016;17(1):9–18

49 Kevelam SH, Rodenburg RJ, Wolf NI, et al. NUBPL mutations in patients with complex I deficiency and a distinct MRI pattern. Neurology 2013;80(17):1577–1583

50 Depienne C, Bugiani M, Dupuits C, et al. Brain white matter oedema due to ClC-2 chloride channel deficiency: an observational analytical study. Lancet Neurol 2013;12(7):659–668

51 Taft RJ, Vanderver A, Leventer RJ, et al. Mutations in DARS cause hypomyelination with brain stem and spinal cord involvement Dallabona C, Diodato D, Kevelam SH, et al. Novel (ovario) leukodystrophy related to AARS2 mutations. Neurology 2014;82(23): 2063–2071

53 Melchionda L, Haack TB, Hardy S, et al. Mutations in APOPT1, encoding a mitochondrial protein, cause cavitating leukoencephalopathy with cytochrome c oxidase deficiency. Am J Hum Genet 2014;95(3):315–325

54 Wolf NI, Salomons GS, Rodenburg RJ, et al. Mutations in RARS cause hypomyelination. Ann Neurol 2014a;76(1):134–139

55 Kevelam SH, Taube JR, van Spaendonk RM, et al. Altered PLP1 splicing causes hypomyelination of early myelinating structures. Ann Clin Transl Neurol 2015;2(6):648–661

56 Dallabona C, Abbink TE, Carrozzo R, et al. LYRM7 mutations cause a multifocal cavitating leukoencephalopathy with distinct MRI appearance. Brain 2016;139(Pt 3):782–794

57 Vanderver A, Simons C, Helman G, et al; Leukodystrophy Study Group. Whole exome sequencing in patients with white matter abnormalities. Ann Neurol 2016;79(6):1031–1037

58 de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med 2012;367(20):1921–1929

59 Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol 2014;76(4): 473–483

60 Taylor RW, Pyle A, Griffin H, et al. Use of whole-exome sequencing to determine the genetic basis of multiple mitochondrial respiratory chain complex deficiencies. JAMA 2014;312(1):68–77

61 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

62 van der Knaap MS, Valk J. Magnetic Resonance of Myelination and Myelin Disorders. Heidelberg, Germany: Springer; 2005

63 Naidu S, Bibat G, Lin D, et al. Progressive cavitating leukoencephalopathy: a novel childhood disease. Ann Neurol 2005;58(6): 929–938

64 Uhlenberg B, Schuelke M, Rüschendorf F, et al. Mutations in the gene encoding gap junction protein alpha 12 (connexin 46.6) cause Pelizaeus-Merzbacher-like disease. Am J Hum Genet 2004; 75(2):251–260

65 Scheper GC, van der Knaap MS, Proud CG. Translation matters: protein synthesis defects in inherited disease. Nat Rev Genet 2007b;8(9):711–723

66 Scheper GC, Proud CG, van der Knaap MS. Defective translation initiation causes vanishing of cerebral white matter. Trends Mol Med 2006;12(4):159–166

67 Antonellis A, Green ED. The role of aminoacyl-tRNA synthetases in genetic diseases. Annu Rev Genomics Hum Genet 2008;9:87–107

68 Wolf NI, Vanderver A, van Spaendonk RM, et al; 4H Research Group. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. Neurology 2014b;83(21):1898–1905

69 van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol 2006;5(5):413–423

70 Kim S, You S, Hwang D. Aminoacyl-tRNA synthetases and tumorigenesis: more than housekeeping. Nat Rev Cancer 2011;11(10): 708–718

71 Yao P, Poruri K, Martinis SA, Fox PL. Non-catalytic regulation of gene expression by aminoacyl-tRNA synthetases. Top Curr Chem 2014;344:167–187

72 Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 2010;330(6005):841–845

73 Hamilton EM, Polder E, Vanderver A, et al; H-ABC Research Group. Hypomyelination with atrophy of the basal ganglia and cerebellum: further delineation of the phenotype and genotype-phenotype correlation. Brain 2014;137(Pt 7):1921–1930

74 Vanderver A, Prust M, Tonduti D, et al; GLIA Consortium. Case definition and classification of leukodystrophies and leukoencephalopathies. Mol Genet Metab 2015;114(4):494–500

75 van der Knaap MS, Lai V, Köhler W, et al. Megalencephalic leukoencephalopathy with cysts without MLC1 defect. Ann Neurol 2010;67(6):834–837

76 Kevelam SH, Klouwer FC, Fock JM, Salomons GS, Bugiani M, van der Knaap MS. Absent thalami caused by a homozygous *EARS2* mutation: expanding disease spectrum of LTBL. Neuropediatrics 2016; 47(1):64–67

Downloaded by: Johns Hopkins University. Copyrighted material.