Letter to the Editor

Child Neurology Open
Volume 7: 1-3
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DOI: 10.1177/2329048X20983761
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Classifying Hypomyelination: A Critical (White) Matter

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Keywords
genetics, leukodystrophy, magnetic resonance imaging, MRI, neuroimaging, next-generation sequencing

Received September 14, 2020. Accepted for publication December 06, 2020.

We read with great interest the publication by Urbik et al. titled "Expanded phenotypic definition identifies hundreds of potential causative genes for leukodystrophies and leukoencephalopathies."[1] We commend the authors for their work on this study, and for constructing such an extensive list of causative genes for genetic white matter disorders. With the utmost respect, we acknowledge the importance of this work, and truly appreciate that phenotype-specific gene lists provide guidance to both clinicians and researchers, especially when considering the diagnostic odyssey of rare inherited neurological disorders. We recognize the value of such publication and anticipate that it may inspire others to delve into the literature to create other phenotype-specific gene lists.

In their study, Urbik et al. further delineated a list of genes associated with hypomyelination based on phenotypic descriptions in currently published articles. However, after examining the literature and MRI features associated with these disorders, we noted discrepancies between the observed MRI phenotypes and proper definition of hypomyelination in a number of cases. Based on MRI patterns, hypomyelination is defined as a mild hyperintense signal on T2-weighted sequences, with variable (i.e. iso-, hyper-, or mildly hypo-intense) signal on T1-weighted sequences of white matter compared to gray matter, signifying deficiencies in myelin development, which must persist on two MRI scans at least 6 months apart if taken before age two years.[2,3] The MRI phenotypes of demyelination, dysmyelination, and delayed myelination differ significantly from this definition, and have been described extensively in the literature.[2-4] Additionally, when considering disease evolution on a clinical level, it is imperative to consider its origin, and whether it should be classified as primarily neuronal (i.e. affecting the gray matter with secondary implications on myelin development), or primarily hypomyelinating (i.e. directly associated with a deficiency in the formation of myelin).[5,6] Herein, we aim to highlight the importance of properly identifying and classifying hypomyelination on MRI by providing selected examples of genes that should fall under different classifications, such as delayed myelination or nonspecific leukoencephalopathy.

Classic primary hypomyelination is known to be caused by pathogenic variants in a wide range of genes, many of which were appropriately identified in Urbik et al.'s "genes with hypomyelination" list. Examples span from genes encoding for proteins directly associated with myelin formation, such as the structural myelin protein PLP1 or the myelin paranodal junction cell adhesion protein CNTNAP1, to the newly emerging group of hypomyelination-associated transcription/translation-related genes, such as the amino-acyl tRNA synthetase enzymes DARS1, EPRS1, and RARS1 or the transcription enzyme RNA polymerase III subunits POLR3A, POLR3B, POLR1C, and POLR3K. These disorders have varying systemic manifestations, but a clearly identifiable hypomyelination pattern on MRI.

Progression of myelination is the key distinguishing factor between permanent hypomyelination or delayed

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myelination.[3,4] On a single MRI in early infancy, it can be difficult to conclude whether hypomyelination is indeed present, therefore, it is recommended to evaluate a sequential MRI after 6 months for changes in myelination.[2,3] If myelination improvement is evident, delayed myelination should be diagnosed. We note myelination delay is typical in Allan-Herndon-Dudley Syndrome, caused by pathogenic variants in *SLC16A2*, however, this gene was present on the hypomyelination-associated list by Urbik et al. Another less prominent example is *HIKESHI*, in which pathogenic variants were initially published as causing an "infantile hypomyelinating leukoencephalopathy,"[7] however, upon review of published MRI figures, delayed myelination is in fact evident. We note that incorrect classification of delayed myelination as hypomyelination is a cause for concern in the literature, which has been highlighted in recent reviews.[8]

Additionally, although we recognize Urbik et al.'s "genes with hypomyelination" list intended to identify all genes associated with some degree of hypomyelination, we would like to stress the importance of documenting whether disorders are truly primary hypomyelinating leukodystrophies or primary neuronal diseases with associated hypomyelination or slowly progressing myelination. We do also appreciate that knowledge on disease pathology is limited in many disorders, making classifications difficult.[5] Additionally, in cases of neuronal diseases, severe atrophy can be present, making it difficult to classify the level of myelin progression, such as with the gene *PRKDC*.[9] The "genes with hypomyelination" list included several diseases that are neuronal in origin, including some associated with epileptic encephalopathies (e.g. *SLC25A12* and *SPTAN1*), or lysosomal storage disorders (e.g. *FUCA1, GLB1, NPC1, NPC2, SGSH*). Notably, some genes with a primary neuronal origin are not associated with hypomyelination, but rather nonspecific leukoencephalopathies, such as *NPC1* and *NPC2*. We also identified *TSC1,* associated with the neurocutaneous disease Tuberous Sclerosis, which we would not classify as a genetic white matter disorder. While we appreciate the depth of Urbik et al.'s hypomyelination gene list, we note one gene associated with a neuronal phenotype and hypomyelinating leukodystrophy, *AIMP1*, was mistakenly excluded.[10]

We would also like to note the presence of genes associated with treatable diseases on this list. We emphasize that screening for the genes associated with these diseases, such as folate transporter deficiency (caused by *FOLR1* variants) and phenylketonuria (caused by *PAH* variants), should be prioritized to mitigate disease progression by confirming the diagnosis and proceeding with treatment as soon as possible.

Finally, we note that some genes on this list could not be completely classified as truly associated with hypomyelination due to the lack of published MRI data. For example, several genes only had one published MRI obtained early in life, making it difficult to distinguish between hypomyelination or delayed myelination. We recommend that classifications are approached with caution if limited data are available, and to seek expert opinion when evaluating MRIs at a young age, if necessary.

To conclude, we reiterate the importance of composing phenotype-specific gene lists as demonstrated by Urbik et al. and stress the importance of proper white matter disorder characterization when considering clinical diagnoses and evaluating disease course. Moreover, incorporating genes causing myelination delay or other white matter diseases on a verified list of true hypomyelinating leukodystrophies could pose concerns during the diagnostic process (i.e. when evaluating variants for pathogenicity based on correlation to phenotype). Additionally, proper characterization of MRI features and corresponding disease classification is important in understanding the disease on a pathophysiological level. Future collaborative studies with detailed evaluation of published MRIs for each considered disorder would be extremely beneficial when considering the generation of widespread phenotype-specific gene lists. In conclusion, we thank Urbik et al. for their detailed study and emphasize the importance of proper classification of subcategories of leukodystrophies and genetically determined leukoencephalopathies.

Authors' Note

We would like to thank authors VM Urbik, M Schmiedel, H Soderholm, and JL Bonkowsky for their informative study and continued research on white matter disorders. G Bernard has received the New Investigator Salary Award from the Canadian Institutes of Health Research 2017-2022. S Perrier is supported by the Fonds de Recherche du Québec en Santé (FRQS) Doctoral Scholarship, the Fondation du Grand défi Pierre Lavoie Doctoral Scholarship, the McGill Faculty of Medicine F.S.B. Miller Fellowship, and the Research Institute of the McGill University Health Centre Desjardins Studentship in Child Health Research.

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