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Author's Response to "Classifying Hypomyelination: A Critical (white) Matter" From Perrier et al.

regarding
Expanded Phenotypic Definition Identifies Hundreds of Potential Causative Genes for Leukodystrophies and Leukoencephalopathies

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We thank Perrier, Matovic, and Bernard for their very insightful letter regarding topics identified in our article.[1]

The objective of our work was to identify and include all genes that have been reported to cause T2 white matter abnormalities. We wanted to develop a more complete list of genes associated with leukodystrophies and leukoencephalopathies, which we termed "genetic white matter disorders (GWMD)." Previous publications have taken more restrictive definitions of leukodystrophies and GWMD,[2-4] despite the absence of unambiguous, consistent, defining genetic or biochemical features

Perrier et al. identify several limitations in our article, and we agree with their insights. In particular, they point out that it is essential to differentiate delayed or slow myelination from true hypomyelination; and that for some disorders the MRI images are lacking or with insufficient quality or timepoints. Another great point they raise is that some of the disorders are treatable, such as phenylketonuria, and require prompt identification and therapy.

One item raised by Perrier et al. is "*the importance of documenting whether disorders are truly primary hypomyelinating leukodystrophies or primary neuronal diseases with associated hypomyelination*". We agree with the spirit of this point. However, we believe that at this juncture, for most disorders, we do not understand disease pathophysiology in sufficient detail to make this distinction reliably.

We are extremely fortunate to have such a collegial community studying leukodystrophies and GWMD! Our work, and the valuable additions from Perrier et al., suggest 3 key goals for the field:

– first, continued improvements in the ability to determine a genetic diagnosis for all patients;
– second, development of community-wide standards for MRI imaging (timing, image types, etc.).
– and third, improved understanding of pathophysiology.

Author Contributions

Name	Location	Contributions
VU	University of Utah School of Medicine	Design of study; collection and analysis of data; revised manuscript for intellectual content
MS	Austin, Texas	Collection and analysis of data; revised manuscript for intellectual content
HS	Geisel School of Medicine	Design of study; collection and analysis of data; revised manuscript for intellectual content
JB	University of Utah School of Medicine	Conception of study; Design of study; analysis of data; revised manuscript for intellectual content

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: VMU reports no disclosures. MS is an employee of NXP Semiconductor. HS reports no disclosures. JLB has served as a consultant to Bluebird Bio, Calico Life Sciences., Denali Inc., Enzyvant, and Neurogene; is on the board of directors of wFluidx

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