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

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Abstract

**Background:** The genes responsible for genetic white matter disorders (GWMD; leukodystrophies and leukoencephalopathies) are incompletely known. Our goal was to revise the list of genes considered to cause GWMD. We considered a GWMD to consist of any genetic disease causing T2 signal white matter changes in magnetic resonance images.**Methods and Results:** Using a systematic review of PubMed, Google, published literature reviews, and commercial gene panels, we identified 399 unique genes meeting the GWMD definition. Of this, 87 (22%) genes were hypomyelinating. Only 3 genes had contrast enhancement on magnetic resonance imaging (MRI): ABCD1, GFAP, and UNC13D.**Conclusions:** A significantly greater number of genes than previously recognized, 399, are associated with white matter signal changes on T2 MRI. This expansion of GWMD genes can be useful in analysis and interpretation of next-generation sequencing results for GWMD diagnosis, and for understanding shared pathophysiological mechanisms of GWMDs.

Keywords

leukodystrophy, genes, leukoencephalopathy, classification, diagnosis

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Leukodystrophies are genetic disorders that affect development or maintenance of the white matter of the central nervous system (CNS).1-3 Leukodystrophies have an incidence of almost 1 in 7500 live births, with significant morbidities and death in a third by age 8.4 A confounding feature to understanding leukodystrophies is their apparent genetic and mechanistic heterogeneity.5 Further, even with advanced next-generation sequencing (NGS) approaches, diagnosis rates remain below 70%,6 suggesting that a quarter of disease-causing genes may not even be known.

A variety of approaches to define and categorize leukodystrophies have been pursued. An international committee of experts classified 30 disorders as leukodystrophies.7 They defined leukodystrophies as genetic, with T2 signal abnormality on magnetic resonance imaging (MRI), and including glial or myelin sheath abnormalities in the CNS. Further, they termed “genetic leukoencephalopathies” to describe disorders that are heritable and result in white matter abnormalities but that did not necessarily meet their strict criteria as a leukodystrophy. Also, more recent classification schemes have been proposed for leukodystrophies, for example, recognizing the complex pathology of different cell types8 or emphasizing the sorting of leukodystrophies into different types based on

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disease pathology such as hypomyelination or vasculature involvement. Our objective was to identify and include all genes that have been reported to cause T2 white matter abnormalities. Our hypothesis was that a more complete list of genes associated with leukodystrophies and leukoencephalopathies, which we will term “genetic white matter disorders (GWMD),” would be of utility for improving diagnostic yield in genetic testing, and would reveal unexpected shared mechanistic pathways. We chose not to exclude any apparent genetic cause, even if not historically considered as a leukodystrophy or leukoencephalopathy. A secondary aim was to determine whether there were any common genetic or mechanistic pathways identified by grouping similar disorders.

Methods
We conducted a systematic search using keywords “leukodystrophy” or “leukoencephalopathy,” including of PubMed, Google, published literature reviews, and commercial gene panels (Figure 1). We included for consideration any publication reporting white matter signal changes on MRI in human patients. The timeline for publication was January 1, 1990, through December 31, 2018. Exclusion criteria included any white matter change secondary to nongenetic cause, including traumatic, infectious, or autoimmune etiologies. We excluded any genomic-level structural chromosomal changes (deletion, duplication); we also excluded gray matter pathology without white matter involvement, brain iron disorders, and isolated atrophy, thinning, reduced volume, or absence of structures (eg, absence of the corpus callosum). Following review and manual curation, genes were characterized and grouped. We categorized genes as being hypomyelinating if they were specifically stated as such in published literature. We used the same criteria to identify genes reported to cause contrast enhancement. Each gene was linked with its Ensembl stable gene ID from Ensembl 92.

Seven hundred fifty-one disorders of white matter were identified, including from publications, lists from gene panel testing from GeneDx, the United Kingdom National Health Service, scientific crowdsourcing resource Genomics England PanelApp, Invitae, and the University of Chicago. The 751 disorders were limited to 728 genetic diseases, and then to 613 unique genes. Each gene was then reviewed in Online Mendelian Inheritance of Man, and if necessary searches were performed in PubMed to determine whether published examples of T2 MRI white matter changes were reported. Disorders involving nongenetic causes (eg, HIV, cytomegalovirus, dietary B12 deficiency) and portions of chromosomes (eg, 18q Deletion Syndrome, etc) were excluded. Disorders affecting only peripheral myelin were excluded.

Ensembl gene IDs were used to analyze the data on 2 platforms. To categorize the genes by biologic process and metabolic process, we used the Gene Ontology (GO) PANTHER classification system (PANTHER14.1). To conduct pathway analysis, we used Reactome, a biological pathway and process analysis database and visualization tool. Seventy-six leukodystrophy genes could not be mapped to a gene or process in Reactome.

Results
Using a comprehensive review of PubMed, Google, published literature reviews, and commercial gene panels, we identified 399 unique genes with white matter MRI pathology on T2 sequences (Figure 1; Table 1). Of this, 87 (22%) genes were hypomyelinating. Only 3 genes had contrast enhancement on MRI (ABCD1, GFAP, and UNC13D) (Table 2). Gene Ontology term evaluation showed that the most frequent categories of GWMD genes (Figure 2A) were metabolic processes (n = 161), cellular processes (n = 120), localization (n = 49), biological regulation (n = 34), and response to stimulus (n = 14; Supplemental Table 1). Interestingly, although the overall number of genes was fewer, the distribution and type of GO biological processes was very similar to the canonical leukodystrophy genes (Figure 2B; Supplemental Table 2).
Table 1. List of All Identified Genetic White Matter Disorders (GWMD) Genes.

| Gene name | Ensembl ID       |
|-----------|------------------|
| AARS      | ENSG00000090861  |
| AARS2     | ENSG00000124608  |
| ABAT      | ENSG00000183044  |
| ABCA1     | ENSG00000165029  |
| ABCD1     | ENSG00000101986  |
| ACDH5     | ENSG00000107897  |
| ACER3     | ENSG00000078124  |
| ACOX1     | ENSG00000161533  |
| ACP33     | ENSG00000090487  |
| ACP5      | ENSG00000102575  |
| ACSF3     | ENSG00000176715  |
| ADAR      | ENSG00000160710  |
| ADGRG1    | ENSG00000255336  |
| ADSL      | ENSG00000239900  |
| AGA       | ENSG0000038002   |
| AHDC1     | ENSG00000126705  |
| AIMP1     | ENSG00000164022  |
| AIMP2     | ENSG00000106305  |
| ALDH3A2   | ENSG00000072210  |
| ALDH5A1   | ENSG00000112294  |
| ALDH6A1   | ENSG00000119711  |
| ALDH7A1   | ENSG00000164904  |
| ALG12     | ENSG00000182858  |
| ALG13     | ENSG00000101901  |
| ALG2      | ENSG00000119523  |
| ALG6      | ENSG00000088035  |
| ALG9      | ENSG00000086848  |
| AMACR     | ENSG00000031081  |
| AMPD2     | ENSG00000116337  |
| AP4B1     | ENSG00000134262  |
| AP5Z1     | ENSG00000242802  |
| AP0PT1    | ENSG00000256053  |
| APP       | ENSG00000142192  |
| ARHGAP31  | ENSG00000010728  |
| ARHGEF10  | ENSG00000104728  |
| ARNT2     | ENSG00000172379  |
| ARSA      | ENSG00000100299  |
| ASL       | ENSG00000126522  |
| ASNS       | ENSG000000242802 |
| ASPA      | ENSG00000072210  |
| ASXR1     | ENSG000000107897 |
| ASXL1     | ENSG00000171456  |
| ATN1      | ENSG00000111676  |
| ATRP7B    | ENSG00000085224  |
| ATR5F2    | ENSG00000148090  |
| B3GALNT2  | ENSG00000162885  |
| BCAP31    | ENSG00000185825  |
| BCKDHA    | ENSG000000248098 |
| BCKDHB    | ENSG00000083123  |
| BCS1L     | ENSG00000074582  |
| BOLA3     | ENSG00000163170  |
| BRAT1     | ENSG00000106609  |
| BTD       | ENSG00000169814  |
| CARS2     | ENSG00000134905  |
| CDK5L     | ENSG00000080866  |

(continued)
| Gene name | Ensembl ID |
|-----------|------------|
| ERCC3     | ENSG00000163161 |
| ERCC6     | ENSG000000225830 |
| ERCC8     | ENSG00000049167 |
| ETFDH     | ENSG00000171503 |
| ETHE1     | ENSG00000105755 |
| FA2H      | ENSG00000103089 |
| FAM126A   | ENSG00000122591 |
| FARS2     | ENSG00000145982 |
| FASTKD2   | ENSG00000118246 |
| FBXL4     | ENSG00000112234 |
| FH        | ENSG00000091483 |
| FIG4      | ENSG00000112367 |
| FKR1      | ENSG00000181027 |
| FKN       | ENSG00000106692 |
| FMR1      | ENSG00000102081 |
| FOLR1     | ENSG00000111015 |
| FOXC1     | ENSG00000054598 |
| FOXRED1   | ENSG00000110074 |
| FUCAl     | ENSG00000179163 |
| GAA       | ENSG00000171298 |
| GALC      | ENSG00000054983 |
| GALT      | ENSG000000213930 |
| GAN       | ENSG0000002261609 |
| GBA       | ENSG00000177628 |
| GBE1      | ENSG000001114480 |
| GCAH      | ENSG00000105607 |
| GFCAP     | ENSG00000131095 |
| GFMI      | ENSG00000168927 |
| GJA1      | ENSG00000152661 |
| GJB1      | ENSG00000169562 |
| GJC2      | ENSG00000198835 |
| GLA       | ENSG00000102393 |
| GLBL      | ENSG00000170266 |
| GLRX5     | ENSG00000182512 |
| GLUL      | ENSG00000135821 |
| GLYCTK    | ENSG00000168237 |
| GM2A      | ENSG00000196743 |
| GNAO1     | ENSG00000087258 |
| GNS       | ENSG00000135677 |
| GPHN      | ENSG00000171723 |
| HEPACAM   | ENSG00000165478 |
| HEXA      | ENSG000000213616 |
| HHHI/SLC25A15 | ENSG000000102743 |
| HIBCH     | ENSG00000198130 |
| HIHEHI    | ENSG00000149196 |
| HLC5      | ENSG000000915297 |
| HMBS      | ENSG000000256269 |
| HMGLC     | ENSG00000017305 |
| HSD17B10  | ENSG00000072506 |
| HSD17B4   | ENSG00000133835 |
| HSPD1     | ENSG00000044381 |
| HTRA1     | ENSG00000166033 |
| IBA57     | ENSG00000181873 |
| IDS       | ENSG00000010404 |
| IDUA      | ENSG000000217415 |
| IFI1H1    | ENSG00000115267 |
| ISCA1     | ENSG0000000135070 |

(continued)
| Gene name | Ensembl ID     |
|-----------|----------------|
| NDUFA10   | ENSG00000130414|
| NDUFA12   | ENSG00000184752|
| NDUFA2    | ENSG00000131495|
| NDUFA9    | ENSG00000139180|
| NDUFAF1   | ENSG00000137806|
| NDUFAF2   | ENSG00000164182|
| NDUFAF3   | ENSG00000178057|
| NDUFAF4   | ENSG00000123545|
| NDUFAF5   | ENSG00000101247|
| NDUFAF6   | ENSG00000156170|
| NDUFB3    | ENSG00000119013|
| NDUFB9    | ENSG00000147684|
| NDUFS1    | ENSG00000023228|
| NDUFS2    | ENSG00000158864|
| NDUFS3    | ENSG00000213619|
| NDUFS4    | ENSG00000164258|
| NDUFS6    | ENSG00000145494|
| NDUFS7    | ENSG00000115286|
| NDUFS8    | ENSG00000110717|
| NDUFS9    | ENSG00000167792|
| NDUFS11   | ENSG00000178127|
| NDUFS12   | ENSG00000151092|
| NDUFS16   | ENSG00000148826|
| NOTCH1    | ENSG00000148400|
| NOTCH3    | ENSG00000074181|
| NPC1      | ENSG00000141458|
| NPC2      | ENSG00000119655|
| NUBPL     | ENSG00000151413|
| OAT       | ENSG00000065154|
| OCLN      | ENSG00000197822|
| OCP1      | ENSG00000122126|
| OPA1      | ENSG00000198836|
| OPA3      | ENSG00000125741|
| OSGEP     | ENSG00000092094|
| OSTM1     | ENSG00000081087|
| OTC       | ENSG00000036473|
| PAFAH1B   | ENSG00000071686|
| PAH       | ENSG00000171759|
| PC        | ENSG00000173599|
| PCCAC     | ENSG00000175198|
| PCCB      | ENSG00000114054|
| PDHA1     | ENSG00000131828|
| PDHX      | ENSG00000110435|
| PEX1      | ENSG00000127980|
| PEX10     | ENSG00000157911|
| PEX12     | ENSG00000108733|
| PEX13     | ENSG00000162928|
| PEX14     | ENSG00000142655|
| PEX15     | ENSG00000121680|
| PEX19     | ENSG00000162735|
| PEX26     | ENSG00000021513|
| PEX5      | ENSG00000139197|
| PEX6      | ENSG00000124587|
| PGAP1     | ENSG00000197121|
| PGN       | ENSG00000197912|
| PHGDH     | ENSG00000092621|
| PHYH      | ENSG000000170573|
| PIGA      | ENSG000000165195|
| PLA2G6    | ENSG000000184381|
| PLEKHG2   | ENSG00000090924|
| PLP1      | ENSG00000123560|
| PMM2      | ENSG00000140650|
| PMP22     | ENSG00000109099|
| POLG1     | ENSG00000140521|
| POLG2     | ENSG00000256525|
| POLR1A    | ENSG00000068654|
| POLR1C    | ENSG00000171453|
| POLR3A    | ENSG00000148606|
| POLR3B    | ENSG00000135030|
| POMGNT1   | ENSG00000085998|
| POMK      | ENSG00000185900|
| POMT1     | ENSG00000130714|
| POMT2     | ENSG00000093830|
| PPRF15B   | ENSG00000158615|
| PPT1      | ENSG00000131238|
| PRF1      | ENSG00000180644|
| PRKDC     | ENSG00000253729|
| PRODH     | ENSG00000100003|
| PRUNE1    | ENSG00000143633|
| PSAP      | ENSG00000197746|
| PSAT1     | ENSG00000135069|
| PSEN1     | ENSG00000080815|
| PURA      | ENSG00000185129|
| PYCR2     | ENSG00000143811|
| QARS      | ENSG00000172053|
| RAB11B    | ENSG00000185236|
| RAS       | ENSG00000113643|
| RAS2      | ENSG00000146282|
| RMND1     | ENSG00000155906|
| RNAHEH2A   | ENSG00000104889|
| RNAHEH2B   | ENSG00000136104|
| RNAHEH2C   | ENSG00000172922|
| RNAS2T2   | ENSG00000026297|
| RNF216    | ENSG00000011275|
| RPIA      | ENSG00000153574|
| RPS6KC1   | ENSG000000136643|
| RRM2B     | ENSG00000048392|
| RXLYT1    | ENSG00000118600|
| SAMHD1    | ENSG000000101347|
| SCO2      | ENSG00000130489|
| SCP2      | ENSG00000116171|
| SDHA      | ENSG00000073578|
| SDHAF1    | ENSG00000205138|
| SDHB      | ENSG00000117118|
| SDHD      | ENSG00000204370|
| SEPSecs   | ENSG00000109618|
| SGSH      | ENSG00000181523|
| SHPK      | ENSG00000197417|
| SLC13A5   | ENSG00000141485|
| SLC16A2   | ENSG00000147100|
| SLC17A5   | ENSG00000119899|
| SLC1A4    | ENSG00000115902|
| SLC25A1   | ENSG000000100075|
A subgroup analysis of the single largest GO term of GWMD genes, “metabolic process,” showed that the most frequent GO terms in this group were organic substance metabolic process (n = 119), cellular metabolic process (n = 63), primary metabolic process (n = 20), oxidation reduction process (n = 19), and catabolic process (n = 19; Figure 2C; Supplemental Table 3).

We used a biological pathway analysis tool, Reactome,21 to identify whether GWMD genes were more represented in certain processes or shared common biological features (Table 3).
Figure 2. A, Revised genetic white matter disorders (GWMD) genes organized by Gene Ontology (GO) term biological process. B, Thirty canonical leukodystrophy genes organized by GO term biological process. C, Revised GWMD genes in the category “Metabolism” displayed by subtypes of metabolic processes.

Table 3. Reactome Pathway Listing of the 25 Most Overrepresented Biological Pathways, Grouped by Biological Mechanisms, and From Most to Fewest Number of Genes.a

| Pathway name                                 | Genes | Reactions |
|----------------------------------------------|-------|-----------|
| Metabolism                                   |       |           |
| Metabolism                                   | 177/5569 | 2.18e-9 | 2.33e-7 | 250/2213 |
| Metabolism of amino acids and derivatives     | 41/931 | 1.54e-5 | 0.001 | 41/283 |
| Diseases of metabolism                        | 23/303 | 3.04e-7 | 2.31e-5 | 33/114 |
| Metabolism of water-soluble vitamins and cofactors | 20/377 | 2.56e-4 | 0.009 | 27/140 |
| Defects in vitamin and cofactor metabolism   | 8/70 | 1.67e-4 | 0.008 | 9/22 |
| Defects in biotin metabolism                  | 6/34 | 1.11e-4 | 0.006 | 6/6 |
| Biotin transport and metabolism               | 6/48 | 6.85e-4 | 0.023 | 9/13 |
| Multiple carboxylase deficiency               | 5/32 | 7.18e-4 | 0.023 | 4/4 |
| Mitochondrial                                |       |           |
| Citric acid cycle and respiratory electron transport | 45/404 | 1.11e-16 | 2.79e-14 | 30/65 |
| Respiratory electron transport, ATP synthesis, heat production | 38/273 | 1.11e-16 | 2.79e-14 | 20/29 |
| Respiratory electron transport                | 37/215 | 1.11e-16 | 2.79e-14 | 17/19 |
| Complex I biogenesis                          | 25/144 | 3.66e-15 | 6.89e-13 | 13/13 |
| Protein                                      |       |           |
| Protein localization                          | 29/244 | 2.87e-13 | 4.30e-11 | 45/53 |
| tRNA aminoacylation                           | 15/232 | 1.99e-4 | 0.008 | 19/42 |
| Recycling of elf2:GDP                         | 5/36 | 0.001 | 0.036 | 2/2 |
| Peroxisomal                                   |       |           |
| Peroxisomal protein import                    | 17/114 | 9.31e-10 | 1.16e-7 | 23/26 |
| Class I peroxisomal protein import            | 9/40 | 3.08e-7 | 2.31e-5 | 6/6 |
| Glycosylation                                 |       |           |
| Diseases of glycosylation                     | 22/234 | 1.48e-8 | 1.39e-6 | 24/77 |
| Diseases associated with glycosylation precursor biosynthesis | 7/65 | 5.99e-4 | 0.021 | 8/16 |
| Diseases associated with N-glycosylation of proteins | 7/49 | 1.11e-4 | 0.006 | 8/23 |
| Defective POMT1                               | 3/5 | 1.90e-4 | 0.008 | 1/1 |
| Defective POMT2                               | 3/5 | 1.90e-4 | 0.008 | 1/1 |
| Other                                         |       |           |
| Branched chain amino acid catabolism          | 10/106 | 1.26e-4 | 0.007 | 11/28 |
| Mucopolysaccharidases                         | 6/37 | 1.75e-4 | 0.008 | 12/22 |
| Loss of MECP2 binding to DNA                 | 2/2 | 8.98e-4 | 0.028 | 1/1 |

Abbreviation: FDR, false discovery rate.

*aMany genes are counted in more than one category (eg, metabolism, diseases of metabolism).
An analysis of the 25 most significantly represented biological pathways revealed that the majority of GWMD genes were involved in just 2 general categories: metabolism (metabolism, diseases of metabolism, metabolism of amino acids, biotin metabolism, defects in vitamin and cofactor metabolism, metabolism of water soluble vitamins and cofactors, biotin transport) and respiratory electron transport/mitochondrial function (respiratory electron transport; respiratory electron transport, ATP synthesis, and heat production; citric acid cycle; complex I biogenesis) (Figure 3).

We also manually evaluated the biological roles of GWMD genes, to confirm the GO and Reactome classifications, as well as to evaluate in greater details gene functions. Genes with roles in the mitochondrion or mitochondrial function (COX7, HSPD1, RMND1, etc) were the single largest group. Interestingly, although as expected genes with lysosomal or peroxisomal roles were frequent, GWMD genes that are transcription factors were approximately as frequent (MEF2C, SOX10, TAF2, etc).

**Discussion**

We have identified a significantly greater number of genes than previously recognized, 399, that are associated with myelin signal changes on T2 MRI. This larger group of GWMD (leukodystrophy and leukoencephalopathy) genes was similar in GO group composition to previous more restrictive definitions of leukodystrophy genes.

Of a total of 27 possible biological pathways represented in the analysis tool Reactome, GWMD genes were present in 23 of those groups, confirming the diverse potential etiologies of GWMDs. Genes involved in metabolic pathways were the most represented group of genes.

While nearly 400 genes is a significantly larger number of genes associated with GWMDs than previously considered, it is only a small proportion (1.9%) of the estimated 21 000 protein-coding genes in the entire human genome. From this perspective, given the complexities of myelin development and maintenance, and the diverse cell types that can affect myelin involved including oligodendrocytes, astrocytes, neurons, and microglia, 399 genes seem proportionate.

The definition of leukodystrophies has been a contentious and at times divisive topic. An initial organized attempt was made in 2015, but already in a short period of time new data suggested potential revisions to this list of approximately 30 genes.

Our approach consisted solely of inclusion based on the presence of white matter T2 signal hyperintensity on MRI and presumed/proven genetic etiology. This methodology poses certain limitations, in that there is no consistent pathophysiology. However, this limitation is also a strength in avoiding certain biases. Since T2 signal hyperintensity of the myelin is essentially a defining term of glial/myelin sheath abnormality, this meets the Vanderver et al inclusion criteria. Further, we avoided exclusion criteria that could be construed as arbitrary. For example, when considering inborn errors of metabolism, lysosomal sialic acid

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Figure 3. Reactome pathway analysis of genetic white matter disorders (GWMD) genes. Analysis is arranged in a hierarchy, with the center of each circular “burst” as the root of one top-level pathway. Each step away from center represents the next level lower in the pathway hierarchy. Yellow-coded pathways are significantly overrepresented; light gray signifies pathways not significantly overrepresented. A, Reactome pathway analysis of entire revised GWMD gene set. B, Reactome pathway analysis of 30 canonical leukodystrophy genes. C, Reactome pathway analysis of contrast-enhancing genes. D, Reactome pathway analysis of hypomyelinating gene set.
storage disorder (Salla disease) met inclusion but the lysosomal disorder Niemann-Pick C did not.7

This finding of a large number of genes that can cause a white matter disorder (leukodystrophy or leukencephalopathy) highlights that early use of an NGS approach such as whole exome sequencing or whole genome sequencing should be considered as a first-line diagnostic approach. With so many different genes that can cause similar T2 signal changes, NGS can provide lower costs and faster time to diagnosis.23 For the clinician, this information about the many different genes that can cause GWMD further emphasize the need for early use of NGS in diagnosis.

An important and unresolved question is why this diversity of different genes all cause white matter pathology. In the undertaking of this project, we hypothesized that shared biological mechanisms and pathophysiology would be revealed. We did observe common themes, including overrepresentation of genes involved in metabolism and in mitochondrial function. This suggests, and is concordant with commonly accepted understanding, that the white matter is particularly sensitive to disturbances in metabolism and in energy homeostasis. It is possible that therapies directed toward these downstream targets (metabolic and energy homeostasis) could provide broad benefits for many different GWMD. Another interesting issue is the phenotypic variability, including age of onset and disease severity. This phenotypic diversity is seen even within the same disease, such as X-linked adrenoleukodystrophy or metachromatic leukodyostrophy. Thus, while it is not currently possible to generalize about phenotypic presentation or age of onset, perhaps there are patterns of severity that could be experimentally explored. For example, whether diseases with more profound disturbances of energy homeostasis cause an earlier and more severe presentation.

Conclusions

We found 399 genes that are associated with white matter changes on T2 MR image sequences. This is approximately 10-fold higher than has been standardly considered as the number of genes responsible for leukodystrophies. There are not consistent biological differences between this revised list and previous definitions of leukodystrophy genes. This expanded understanding of the genetics of GWMDs including leukodystrophies and leukencephalopathies can be useful in analysis and interpretation of NGS results for diagnosis and in understanding the pathophysiology of GWMDs.

Authors’ Note

VMU, MS, and HS contributed equally to the manuscript. All data reported in this study are included in this publication.

Author Contributions

VMU, MS, and JLB contributed to conception and design. JLB drafted manuscript. All authors contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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: M.S. is an employee of NXP Semiconductor. J.L.B. has served as a consultant to Bluebird Bio, Calico Life Sciences, Denali Inc, Enzyme, and Neurogene; is on the board of directors of wFluidx Inc; and owns stock in Orchard Therapeutics.

Ethical Approval

The University of Utah IRB granted this work an exemption as non-human subjects research.

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Supplemental Material

Supplemental material for this article is available online.

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