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REVIEW

The Role of Microglia in Inherited White-Matter Disorders and Connections to Frontotemporal Dementia

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Abstract: Microglia play a critical but poorly understood role in promoting white-matter homeostasis. In this review, we leverage advances in human genetics and mouse models of leukodystrophies to delineate our current knowledge and identify outstanding questions regarding the impact of microglia on central nervous system white matter. We first focus on the role of pathogenic mutations in genes, such as *TREM2, TYROBP*, and *CSF1R,* that cause leukodystrophies in which the primary deficit is thought to originate in microglia. We next discuss recent advances in disorders such as adrenoleukodystrophy and Krabbe disease, in which microglia play an increasingly recognized role. We conclude by reviewing the roles of *GRN* and related genes, such as *TMEM106B, PSAP*, and *SORT1,* that affect microglial biology and associate with several types of disease, including multiple leukodystrophies as well as forms of frontotemporal dementia (FTD) presenting with white-matter abnormalities. Taken together, mouse and human data support the notion that loss of microglia-facilitated white-matter homeostasis plays an important role in the development of leukodystrophies and suggest novel mechanisms contributing to FTD.

Keywords: leukodystrophies, leukoencephalopathies, frontotemporal dementia, white matter, microglia, progranulin

Introduction

Leukodystrophies include a vast group of rare, multifarious genetic disorders that selectively and primarily affect the central nervous system (CNS) white matter. These disorders encompass defects in the generation, maintenance, and repair of white matter, and the primary molecular deficit may arise not only in myelin-producing oligodendrocytes but also in astrocytes, microglia, or other cell types.[1–3] Several informative reviews published in the last several years provide broad overviews of inherited diseases of white matter, including those focused on childhood[4] and adult-onset[5,6] disorders. Here we will focus primarily on leukodystrophies that are apparently caused by primary microglial defects, disorders that are sometimes termed microgliopathies.[7]

Microglia are macrophages of the brain parenchyma that are now understood to play essential roles in brain development, homeostasis, inflammation, and neurodegeneration.[8,9] The particular importance of microglia in promoting the health and resilience of CNS white matter has emerged in the 21st century due in large part to the identification of pathogenic mutations in microglia-expressed genes in Mendelian white-matter disorders.

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In the first section, we leverage work in human and mouse genetics to describe the primary microglia-associated leukodystrophies, which are caused by pathogenic mutations in genes such as *TREM2* (encoding the triggering receptor expressed on myeloid cells 2), *TYROBP* (TYRO protein tyrosine kinase-binding protein), *CSF1R* (colony-stimulating factor 1 receptor), and *USP18* (ubiquitin-specific protease 18). Building on these findings, we transition our focus toward diseases in which microglia play an increasingly recognized role and explore recent advances in our understanding of white-matter microglia. Our overarching goal in exploring these disorders and their genetic causes is to synthesize a more robust understanding of the mechanisms by which microglia maintain CNS white-matter homeostasis, not only after acute white-matter insult but also over the entire lifespan and in disease. Finally, we highlight a new frontier in the study of leukodystrophies: a small group of genes associated with the expression and/or function of the secreted glycoprotein, progranulin. Members of this group of genes influence lysosomal function,[10,11] shape microglial biology in important ways,[12–14] and are causally involved in several distinct forms of leukodystrophy[15,16] as well as early-onset neurodegenerative disease resulting in a clinical syndrome of frontotemporal dementia (FTD).[17,18] Intriguingly, the FTD cases associated with this group of genes (including *GRN* [encoding progranulin], *TMEM106B* [transmembrane protein 106B] and *SORT1* [sortilin]) show evidence of white-matter changes that are otherwise atypical for FTD.[19–22]

Primary Microglial Leukodystrophies

Nasu-Hakola Disease: Role of *TYROBP* and *TREM2*

Nasu-Hakola disease, also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), was first associated with pathogenic mutations in *TYROBP* (encoding a protein often called DAP12 [DNAX-activating protein of 12 kDa]) approximately 20 years ago.[23] Shortly after this discovery, additional Nasu-Hakola patients harboring pathogenic mutations in *TREM2* were identified.[24] Given that TREM2 is a microglial receptor that interacts with and signals via DAP12,[25] the identification of loss-of-function mutations in the genes encoding both of these proteins – which cause the same recessively inherited disorder – provided some of the first strong evidence that aberrant microglia function could cause an adult-onset leukodystrophy.

Nasu-Hakola disease classically involves phenotypes beyond loss of myelin and cerebral axons, including formation of bone cysts and basal ganglia calcification;[26,27] however, several cases of early-onset FTD-like syndromes involving white-matter loss but lacking overt bone phenotypes have also been associated with loss-of-function mutations in *TREM2*.[28–30] Consideration of these cases suggests that while loss of TREM2 function in osteoclasts can in some cases be compensated for, TREM2 function in microglia appears to be essential for the maintenance of white matter throughout the lifespan. In addition to these early-onset FTD-like syndromes associated with complete or near-complete loss of TREM2 function, rare heterozygous variants in *TREM2* are also thought to increase risk for FTD[31,32] (in addition to their well-established role in increasing risk for Alzheimer disease[33,34]), although it remains unclear if partial loss of TREM2 function increases risk for FTD via loss of white-matter integrity, reduced microglial clearance of pathological proteins more typically associated with FTD (eg, tau and TDP-43), or a combination of these or other mechanisms.

TREM2 binds a variety of lipidic ligands including anionic and zwitterionic phospholipids, bacterial lipopolysaccharide, and myelin-enriched lipids, such as sulfatide and sphingomyelin (reviewed in[25,35–37]). In addition, TREM2 can interact with several protein ligands including apolipoproteins (eg, APOE) and amyloid-β.[25] Given TREM2's ability to sense myelin-derived lipids, and the known role of *TREM2, TYROBP*, and microglia in leukodystrophies, it is reasonable to hypothesize that proper microglial maintenance of white-matter homeostasis involves direct sensing of myelin-derived components and subsequent signal transduction via a functional TREM2-DAP12 complex. Indeed, several papers employing cuprizone-induced demyelination in mice lacking Trem2 support this possibility.[38,39] More recent work suggests that loss of Trem2 specifically leads to pathological cholesteryl ester accumulation in microglia downstream of myelin debris phagocytosis in a chronic demyelination model.[40] Encouragingly, activation of Trem2 in vivo with an agonistic antibody enhances myelin debris clearance after cuprizone treatment and promotes the repopulation of oligodendrocytes, subsequent remyelination, and partial protection against axonal damage.[41] Collectively, mouse models of Trem2 deficiency suggest a role for microglial Trem2/Dap12 in maintaining white-matter health by (i) sensing myelin-derived lipids that result from myelin damage; (ii) generating signaling cascades

that promote phagocytosis of debris; (iii) enabling homeostatic metabolism and clearance of myelin-derived cholesterol; and (iv) promoting recruitment of the oligodendrocyte precursor cells (OPCs) that are required for remyelination and, ultimately, preservation of axonal integrity.

ALSP: Role of *CSF1R* and *AARS2*

Formerly considered to be two distinct clinical entities, hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) and pigmented orthochromatic leukodystrophy (POLD) have been unified into a single clinicopathologic entity – adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) – with the identification of *CSF1R* mutations in both disorders.[42–45] ALSP is a progressive and clinically heterogeneous disorder with antemortem diagnoses from early family studies including FTD, Alzheimer disease, and even multiple sclerosis.[43] Histologically, the disorder is characterized by degeneration of white matter and axons as well as the presence of pigment-laden macrophages.[45] Given that CSF1R is expressed on microglia within the brain and CSF1R signaling is essential for the development of microglia,[46,47] ALSP due to *CSF1R* mutations can be considered to be a primary microglial leukodystrophy.[1,48] ALSP caused by *CSF1R* mutations is inherited in an autosomal-dominant manner, with many of the described mutations abrogating autophosphorylation within the intracellular tyrosine kinase domain.[43,44] The presence of heterozygous loss-of-function mutations in ALSP suggests that haploinsufficiency of CSF1R signaling is sufficient to cause severe adult-onset white-matter degeneration downstream of microglial dysfunction.[48] Interestingly, recent work from our institution highlights hematopoietic stem cell transplantation (HSCT) as a potentially promising clinical therapy for ALSP, with both patients in the study demonstrating partial clinical stabilization and reduced white-matter abnormalities on brain MRI.[49] The findings from this case study are consistent with the possibility that transplant-derived myeloid cells are capable populating the microglial niche and restoring CSF1R signaling.

The recent identification of homozygous *CSF1R* mutations in childhood-onset leukodystrophy involving agenesis of the corpus callosum[50] not only underscores the importance of microglial CSF1R signaling in white-matter maintenance but further suggests a role for microglia in supporting the development of CNS white matter. Work from mouse models suggests that interleukin 34 (IL-34), rather than CSF-1, is the critical CSF1R ligand enabling the downstream signaling that is necessary for microglial development and/or maintenance.[47,51] Recent work in zebrafish has suggested that brain-derived IL-34 drives the recruitment of embryonic macrophages (ie, microglia precursors) into the CNS,[52] although prior work in mice has suggested that IL-34 may be particularly important for maintenance (rather than development) of microglia in the mammalian brain.[51] Considering our current knowledge of IL-34–CSF1R signaling, the future discovery of *IL34* mutations in otherwise unexplained cases of leukodystrophy would not be unexpected.

After the discovery of *CSF1R* mutations as a cause of ALSP, additional cases remained that lacked such mutations. Some of these individuals were subsequently found to harbor compound heterozygous or homozygous loss-of-function mutations in *AARS2*, encoding mitochondrial alanyl-tRNA synthetase 2.[53–55] It is noteworthy that mutations in *AARS2*, encoding a protein with a function unrelated to that of CSF1R – whose expression is ubiquitous rather than restricted to the myeloid lineage – can result in an adult-onset leukodystrophy resembling ALSP (albeit with additional phenotypes, such as ovarian failure in women). Additional research is needed to determine how loss of a seemingly disparate biochemical function can promote such a clinically similar phenotype.

Pseudo-TORCH Syndrome and the Role of USP18 in Microglia

Pseudo-TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex virus) syndrome due to loss-of-function mutations in *USP18* represents an interferonopathy and microgliopathy resulting in white-matter damage in mice and humans.[56–58] Elucidation of the role of USP18 – a multifunctional protein that possesses both isopeptidase activity and inhibitory activity toward type I interferon (IFN) signaling[59] – in microglia suggests that loss of a crucial inflammation-dampening mechanism is sufficient to produce CNS pathology. In particular, the derepression of signaling resulting in the expression of IFN-stimulated genes in microglia appears likely to be a culprit in the microglia-mediated destruction of white matter.[60]

Integrating the literature on Nasu-Hakola disease and ALSP with *USP18*-mediated pseudo-TORCH syndrome suggests that microglia can cause destructive white-matter disease in at least two apparently opposing manners: (i) loss of beneficial signaling required to promote

microglial survival, proliferation, and metabolism prevents microglia from appropriately responding to and clearing incipient white-matter damage (eg, via loss of TREM2-DAP12 or CSF1R-DAP12 signaling); and (ii) loss of negative regulation of the type I IFN pathway unleashes toxic inflammatory processes leading to white-matter pathology (eg, via loss of USP18 negative regulation). Additional mechanisms are likely to be uncovered in the coming years. Despite the fact that *Usp18* expression is enriched in white-matter microglia,[56] it is not fully clear why USP18-associated disease appears to selectively affect microglia in the white matter; future studies will be needed to address this issue.

Microglia-Modulated Leukodystrophies and White-Matter Microglia

Microglia as Previously Unappreciated Modulators of Leukodystrophies

Microglia as Drivers of Neuronal Death and Disease Progression in Adrenoleukodystrophy

Adrenoleukodystrophy occurs due to peroxisomal dysfunction that causes very long chain fatty acid (VLCFA) accumulation in all tissues due to an X-linked mutation in *ABCD1* (encoding ATP-binding cassette D1, which transports VLCFA into peroxisomes).[61] The clinical phenotype is highly variable, but usually includes early-onset adrenal insufficiency (median time to glucocorticoid replacement therapy ~16 years) and a variable neurological phenotype with cerebral and/or spinal cord demyelination (median time to cerebral disease ~35 years).[62] The neurological phenotype increases in prevalence as a patient ages, with ~80% of patients surviving past age 64 having cerebral disease. Historical work has focused largely on VLCFA toxicity in oligodendroglia given their high lipid content,[61] but the central role of microglia in cerebral and spinal demyelination is becoming increasingly apparent. For example, recent work in mouse models of adrenoleukodystrophy has found that microglial activation preceded synaptic loss and that *Abcd1*-deficient microglia demonstrated a pro-phagocytotic phenotype with upregulated Trem2 expression.[63] Analysis of brain tissue samples from adrenoleukodystrophy patients by Bergner et al support this finding – prelesional areas were remarkable for only minimal changes to oligodendroglial and neuronal morphology but with microglia showing signs of activation, including decreased TMEM119 expression and conversion to an amoeboid phenotype.[64] This and prior studies also demonstrate microglial depletion in prelesional areas compared to healthy white matter and demyelinated regions, suggesting that activated microglia may undergo apoptosis just prior to demyelination.[64,65] Of note, a similar pattern of microglial depletion prior to demyelination has also been observed in metachromatic leukodystrophy, a disorder caused by mutations in *ARSA* – encoding the lysosomal enzyme arylsulfatase A that breaks down sulfatides – and, less frequently, in *PSAP* – which encodes prosaposin and will be discussed in detail below in the context of progranulin function.[16,64]

Treatment of adrenoleukodystrophy is distinctive amongst leukodystrophies and further highlights the importance of immune cells in the pathophysiology of neurodegeneration secondary to *ABCD1* mutations. If given early, bone marrow transplantation has been shown to slow or halt the progression of adrenoleukodystrophy.[66] More recently, the therapy has been refined further and autologous transplants of CD34+ cells with a functioning copy of *ABCD1* now show promise in clinical trials[67] with similar results to a conventional bone marrow transplant but notably without signs of graft-versus-host disease or other transplant-related complications. This development is of clinical and scientific significance because it suggests that the disease-modifying aspects of CD34+ transplants may be due to the impact of properly functioning macrophages (which can migrate into the brain and potentially fill the microglial niche) rather than the immunosuppressive medications required after conventional HSCT.

Microglia in Krabbe Disease: Drivers of Demyelinating Disease or Innocent Bystanders?

Krabbe disease, also known as globoid cell leukodystrophy, occurs in patients with deficiency of the lysosomal enzyme galactocerebrosidase (encoded by *GALC*).[68,69] Patients with Krabbe disease accumulate both galactosylceramide and galactosylsphingosine (also known as psychosine), leading to widespread demyelination with reactive gliosis remarkable for both multinucleated microglia (globoid cells) and astrocytosis.[70,71] Interestingly, in vitro work has shown that psychosine alone is sufficient to produce a globoid cell-like phenotype,[72] suggesting that globoid-cell formation may occur independently of oligodendroglial death rather than as a reaction to it. Adding to the intrigue of this finding is evidence from new mouse models of Krabbe disease that demonstrate early gliosis, globoid cell formation, and elevated psychosine levels

prior to cell death and in the absence of substantial demyelination.[73] While psychosine is a known oligodendroglial toxin,[74] the possibility that aberrant microglial function could contribute to white-matter disease is supported by data from fetal human tissue with elevated psychosine, confirming the presence globoid cells without concurrent demyelinating disease.[75]

The potential import of this finding is heightened by the fact that immunomodulation in the form of HSCT is the most effective disease-modifying therapy for Krabbe disease.[76,77] As in adrenoleukodystrophy, HSCT is more effective when given prior to the onset of clinical symptoms and sometimes associated with reduced white-matter disease on T2-weighted imaging.[77,78] Although the precise therapeutic mechanisms responsible for the relative success of HSCT in Krabbe disease remain unknown, these findings on balance suggest that the microglial contributions to Krabbe disease pathophysiology – including demyelination in particular – may be underappreciated and that future research will be required to determine the specific mechanisms by which microglia modulate and possibly even drive aspects of demyelinating pathology.

Advances in Our Understanding of White-Matter Microglia

How do microglia promote white-matter homeostasis in health and disease? A variety of novel mouse models have refined our knowledge of microglia residing in the white matter and suggest additional relevant mechanisms. For example, microglial transglutaminase-2 activity supports the survival of OPCs and promotes both developmental myelination and remyelination.[79] This finding bolsters the notion that microglial support of white-matter physiology is not merely a function of sensing and clearing nascent white-matter damage, but rather involves active trophic support of oligodendroglial cells. Studies of remyelination using the optic nerve crush model indicate that microglial activation soon after injury is crucial for robust OPC proliferation but ultimately inhibits the differentiation of these precursor cells into mature, myelination-competent oligodendrocytes.[80] Accordingly, depletion of microglia using a small-molecule CSF1R inhibitor several weeks after injury (but not earlier) enabled differentiation of recently generated OPCs, and in conjunction with inhibition of the oligodendrocyte G protein-coupled receptor (GPR) 17, enabled remyelination of the injured optic nerve.[80]

In contrast to the supportive role that microglia can play in myelination, several recent papers indicate that disrupted transforming growth factor (TGF)-β signaling in microglia – as well as peripheral monocytes capable of colonizing the CNS as tissue-resident macrophages under defined conditions – can result in potent white-matter destruction.[81,82] Among other effects, loss of microglial TGF-β signaling results in impaired OPC differentiation into mature, myelin-producing oligodendrocytes.[83] On balance, this body of literature highlights that, while microglia can – in specific contexts – provide essential support to oligodendroglial cells, they also possess a latent, tightly regulated potential to engage in highly pathogenic behavior in the white matter.

In addition to the above hypothesis-driven studies, large-scale, single-cell RNA sequencing studies have revealed a transient subpopulation of microglia localizing to early postnatal white matter[84] and a population of microglia associated with aging white matter.[85] Given that the early postnatal microglial subpopulation is observed in the developing corpus callosum and that children with homozygous, loss-of-function *CSF1R* mutations show agenesis of the corpus callosum (described above[50]), it is reasonable to speculate that specialized, developing white-matter microglia may be conserved in humans and involved in the proper development of CNS white matter.

Progranulin-Associated Genes: Role in Disorders of White Matter

Progranulin

Haploinsufficiency of the secreted glycoprotein progranulin, encoded by *GRN*, was first linked to familial frontotemporal lobar degeneration (FTLD) characterized by pathologic TAR DNA-binding protein (TDP)-43 inclusions in 2006.[17,18] Other common causes of familial FTLD include pathogenic hexanucleotide repeat expansion intronic to *C9orf72* (chromosome 9 open reading frame 72) and pathogenic mutations in *MAPT* (microtubule-associated protein tau).[86] Of note, FTLD cases attributable to *GRN, C9orf72*, and *MAPT* demonstrate gene-specific white-matter changes measured using diffusion tensor imaging (DTI).[87,88] However, pathogenic *GRN* mutations are further differentiated among these common causes of familial FTLD in that a subset of cases (13–20%) demonstrate substantial white-matter hyperintensities (WMH) beyond the DTI and gray-matter changes seen across the spectrum of neurodegenerative phenotypes with TDP-43 and tau neuropathology (Table 1).[19,20,89] This finding's relevance to leukodystrophies is further heightened by

Table 1 Progranulin (*GRN*)-Related Genes Associated Directly or Indirectly with Frontotemporal Dementia (FTD) and Inherited White-Matter Disorders

Gene Symbol	Expressed in Microglia?	Enriched in Microglia?	Affects GRN Trafficking or Circulating Levels?	Genetic Association with FTD?	Genetic Association with White-Matter Disease?	Selected References
GRN	Yes	Yes	N/A	Causative	Subset of FTLD-*GRN* shows WMH	[17–20,89–91,93]
TMEM106B	Yes	No	Circulating levels	Risk modifier	Hypomyelinating leukodystrophy	[15,20,94–97,102–105]
PSAP	Yes	Yes	Trafficking and circulating levels	Not yet	Metachromatic leukodystrophy; other sphingolipidoses	[16,111,115,118]
SORT1	Yes	No	Trafficking and circulating levels	Risk factor	Subset of FTD cases harboring rare *SORT1* variants present with WMH	[22,119]

Notes: The *GRN*-associated genes *TMEM106B, PSAP,* and *SORT1* are associated with circulating progranulin levels and in some cases also influence progranulin sorting. Most of the above genes are genetically associated with FTD as well as various forms of leukodystrophy or white-matter hyperintensities in the context of frontotemporal lobar degeneration pathology. These findings, when considered collectively, suggest that variation in the *PSAP* locus may ultimately be identified as a risk factor for FTD. Moreover, the findings suggest that progranulin-associated proteins may impart risk for FTD by modulating microglial function and white-matter resilience over the lifespan.
Abbreviations: FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; *GRN*, progranulin; *PSAP,* prosaposin; *SORT1*, sortilin; *TMEM106B*, transmembrane protein 106B; WMH, white-matter hyperintensities.

the absence of other potential explanations for the substantial WMH observed in FTLD-*GRN* patients, such as vascular disease or major vascular risk factors, mitochondrial or metabolic disease, or other neuroinflammatory conditions.[19,90] A recent case report provided additional insight into this discovery, demonstrating that the WMH seen on MRI are associated with marked microgliosis but only mild axonal loss and minimal vascular disease.[91] Taken together, these observations suggest that the white-matter findings reported for FTLD-*GRN* patients are likely specific to the microglial dysfunction caused by *GRN* mutations rather than other, more established, causes of WMH.

At the subcellular level, progranulin appears to be particularly important for maintaining lysosomal homeostasis.[10] Progranulin – which is synthesized as a precursor protein that can be proteolyzed into peptides termed granulins – is sorted to the lysosome by virtue of its interaction with sortilin and another secreted glycoprotein, prosaposin (see below), although it remains unclear precisely which aspects of lysosomal function progranulin regulates once delivered to the lysosome.[10] One intriguing model suggests that partial or complete loss of progranulin results in reduced delivery of prosaposin to the neuronal lysosome, which in turn would lead to impaired glycosphingolipid metabolism.[92]

At the cellular level, loss of progranulin affects microglial biology in numerous ways. For example, loss of *Grn* in mice results in pathologic activation of microglia during aging in a process that involves inappropriate complement production.[12,14] In addition, microglia-specific deletion of *Grn* results in specific behavioral alterations downstream of aberrant microglial activation of nuclear factor (NF)-κB and tumor necrosis factor (TNF)-α.[13] Interestingly, despite the fact that loss-of-function mutations in both *GRN* and *TREM2* are associated with neurodegeneration and white-matter pathology – and that both genes regulate microglial physiology – a direct comparison of the transcriptomes of microglia lacking either *Grn* or *Trem2* revealed highly divergent microglial transcriptional profiles.[93] In particular, loss of *Trem2* results in increased expression of so-called homeostatic microglial genes and decreased expression of disease-associated genes, whereas the opposite profile is observed in *Grn*-null microglia.[93]

A careful consideration of the role of *GRN* and *TREM2* in shaping microglial biology therefore further supports the notion that neurodegeneration and white-matter damage downstream of pathogenic mutations in microglia-expressed genes are unlikely to result from a single, monolithic shift in microglial physiology. Rather, the data here once again suggest a more likely scenario in which both the inability of microglia to respond appropriately to incipient cellular damage as well as chronic hyperactivation of microglia can similarly result in downstream white-matter damage and neuropathology.

TMEM106B

TMEM106B, encoding a transmembrane protein that localizes primarily to lysosomes, represents an important genetic modifier of FTLD risk due to pathogenic *GRN* mutations,[94–96] and the protective allele of *TMEM106B* is associated with increased plasma levels of progranulin.[94,95] Carriers of pathogenic *GRN* mutations frequently show evidence of white-matter loss before symptom onset,[97] and the risk allele of *TMEM106B* is associated with exacerbated disease-associated functional connectivity changes in presymptomatic *GRN* carriers compared to healthy controls.[21] These findings suggest that the modulation of FTLD risk by *TMEM106B* may be mediated not only via effects on circulating progranulin levels but also by modulating the severity of the white-matter phenotype observed in these individuals. Further, given what we know about the role of progranulin, these seemingly disparate effects may in fact be directly related to one another (Table 1).

A series of recently published papers have independently converged on the finding that loss of *Tmem106b* exacerbates a variety of neurodegeneration-associated phenotypes in mice also lacking *Grn*.[98–101] Moreover, mice lacking both *Tmem106b* and *Grn* displayed exacerbated lysosomal dysfunction as well as signs of myelin damage. Indeed, loss of *Tmem106b* on a wild-type *Grn* background is sufficient to produce oligodendroglial and myelination defects, possibly downstream of lysosomal dysfunction.[102,103] The white-matter abnormalities described in *Tmem106b*-deficient mice are not surprising given that pathogenic *TMEM106B* mutations have been identified as a cause of hypomyelinating leukodystrophy.[104] In particular, a recurrent, dominant, and in some cases de novo mutation in *TMEM106B* has been found to cause a relatively mild form of hypomyelinating leukodystrophy.[15,105]

Given (i) the clear role of *GRN* in maintaining lysosomal and microglial homeostasis; (ii) the established genetic interaction between *GRN* and *TMEM106B*; (iii) evidence of white-matter abnormalities in individuals with FTLD due to pathogenic *GRN* mutations; and (iv) the importance of *TMEM106B* in lysosome function and myelination, it is apparent that the *GRN-TMEM106B* axis regulates white-matter integrity at least in part by promoting lysosomal and microglial homeostasis. In light of the above considerations, it is reasonable to speculate that heightened white-matter resilience in individuals harboring the protective allele of *TMEM106B* may represent a plausible mechanism for the modulation of FTLD risk due to pathogenic *GRN* mutations. Interestingly, given that reductions in white-matter integrity have also been observed in *C9orf72* pathogenic repeat expansion carriers,[90,106] that C9orf72 protein also affects lysosomal function,[107] and that *TMEM106B* also modulates FTLD risk due to *C9orf72* expansion,[108,109] it is possible that white-matter resilience plays a role in the modulation of FTLD risk even beyond that contributed by *GRN*.

Early evidence from the Genetic FTD Initiative (GENFI) study suggests that, among individuals harboring pathogenic *GRN* mutations, those carrying the risk-conferring variant in *TMEM106B* accrue white-matter changes more rapidly.[20] Beyond these changes, grey-matter volume analyses in autosomal dominant FTD (a combined cohort that included *GRN, C9orf72*, and *MAPT* mutation carriers from GENFI) found that *TMEM106B* genotype modulated the association between education and grey-matter volumes.[110] Whether these grey-matter changes were preceded by or occurred in parallel with white-matter disturbances was not investigated but remains an exciting avenue for future research. Overall, these findings provide early evidence suggesting that multiple pathogenic hits to lysosomal and microglial homeostasis may confer susceptibility to and/or accelerate white-matter disease.[20]

Prosaposin

PSAP, encoding prosaposin, is genetically linked to several hereditary sphingolipidoses including metachromatic leukodystrophy,[16] atypical forms of Krabbe disease[111] and Gaucher disease,[112] and combined prosaposin deficiency.[113] Somewhat analogously to progranulin, prosaposin is synthesized as a precursor protein that, upon proteolysis, is converted into smaller proteins termed sphingolipid activator proteins or saposins.[114] Pathogenic mutations in *PSAP*, generally found as homozygous or compound heterozygous variants, result in the loss of specific saposins and in some cases the entire precursor protein. As mentioned above, prosaposin is involved in the sorting of progranulin to the lysosome,[115] and the loss of progranulin in turn impairs lysosomal delivery of prosaposin.[92] The impaired sorting and processing of prosaposin in *GRN*-mutant cells appears to result in reduced glucocerebrosidase activity,[116,117] providing an interesting link to Gaucher disease and another potential mechanism that may contribute to disease risk in progranulin-haploinsufficient cells. Variation in the *PSAP* locus is

also associated with circulating progranulin levels, which indicates an important genetic interaction in addition to the known biochemical interaction.[118] Taken together, these functional connections between prosaposin and progranulin coupled with the clear genetic link between *PSAP* and leukodystrophy further reinforce the notion that progranulin-associated proteins are crucial for white-matter integrity (Table 1). Moreover, given what is known about *GRN* and *TMEM106B*, it would not be surprising if variation in the *PSAP* locus is ultimately found to be associated with FTD risk as well.

Sortilin

In addition to prosaposin, the transmembrane protein sortilin is also involved in the delivery of progranulin to the lysosome.[119] Quite interestingly, rare variation in *SORT1*, encoding sortilin, is now also implicated in risk for FTD.[22] Moreover, a subset of the patients harboring rare, nonsynonymous variants in *SORT1* show substantial WMH by neuroimaging,[22] similar to what is frequently observed in FTLD due to pathogenic *GRN* mutations. Collectively, a consideration of the genetic and functional interactions between *GRN, TMEM106B, PSAP*, and *SORT1*; the known role of progranulin in promoting microglial homeostasis; and the association of this group of genes with various inherited white-matter disorders as well as forms of FTD often involving otherwise atypical white-matter findings suggests that these progranulin-associated genes shape microglial biology and bolster white-matter health during aging. By the same token, these genes illuminate underappreciated connections between white-matter resilience and risk for FTD (Table 1).

Discussion and Future Directions

In this review, we aimed to synthesize knowledge about and uncover connections between the primary microglial leukodystrophies – including Nasu-Hakola disease, ALSP, and pseudo-TORCH syndrome due to pathogenic *USP18* mutations – and inherited white-matter disorders such as adrenoleukodystrophy and Krabbe disease, in which microglia play an increasingly recognized role. In addition, we considered the literature surrounding progranulin and its functionally associated genes to draw connections between their roles in distinct leukodystrophies as well as forms of FTD involving otherwise atypical white-matter findings. The impact of progranulin on microglial and lysosomal physiology suggests that these cells and organelles are crucial for the facilitation of white-matter homeostasis. The loss of progranulin function, and that of progranulin-related proteins, highlights their role not only in traditionally recognized white-matter disorders but also in a seemingly unrelated disease – FTD – that nevertheless sometimes involves white-matter pathology in the absence of vascular risk factors.

Providing a rational basis for linking particular microglial phenotypes associated with pathogenic mutations to specific white-matter diseases and their typical ages of onset remains challenging. Nevertheless, we have summarized the current state of knowledge regarding the disorders discussed herein and the primary microglial phenotypes with which they are thought to be associated (Figure 1). Pseudo-TORCH syndrome due to *USP18* mutations, representing a type I interferonopathy, leads to very early pathology, with signs of disease at or before birth.[57] On the other hand, congenital absence of microglia observed in an individual harboring a homozygous splice-site mutation in *CSF1R* has also been associated with prenatal symptoms; an additional patient with a homozygous missense mutation in *CSF1R* showed symptom onset at age 12.[50] Histological studies of adrenoleukodystrophy, which has a wide age range of symptom onset, suggest that microglial activation, acquisition of an amoeboid phenotype, and loss of microglia may all be relevant cellular phenotypes.[63–65] Moving to the adult-onset, inherited white-matter disorders, evidence from mouse models suggests that Nasu-Hakola disease (due to loss of *TREM2* or *TYROBP*) may be associated with heightened microglial susceptibility to apoptosis[120] and impaired microglial lipid metabolism.[40] Similarly, ALSP due to partial loss of *CSF1R* may be associated with a reduction in microglia density,[121] a shift toward an inflammatory microglial state,[122] or both. Finally, FTLD due to *GRN* haploinsufficiency, which often presents with white-matter pathology, may be associated with excessive complement production by microglia.[12,14]

Future studies of the primary microglial leukodystrophies should focus on determining precisely how alterations in seemingly disparate molecular pathways within microglia, such as those caused by pathogenic mutations in *TREM2* and *USP18*, ultimately converge on the destruction of white matter. Further work in adrenoleukodystrophy and Krabbe disease will be needed to determine whether the therapeutic benefit observed for HSCT is derived from the engraftment of myeloid cells within an otherwise defective microglial niche, as is currently suspected. Evidence from mouse models suggests that under

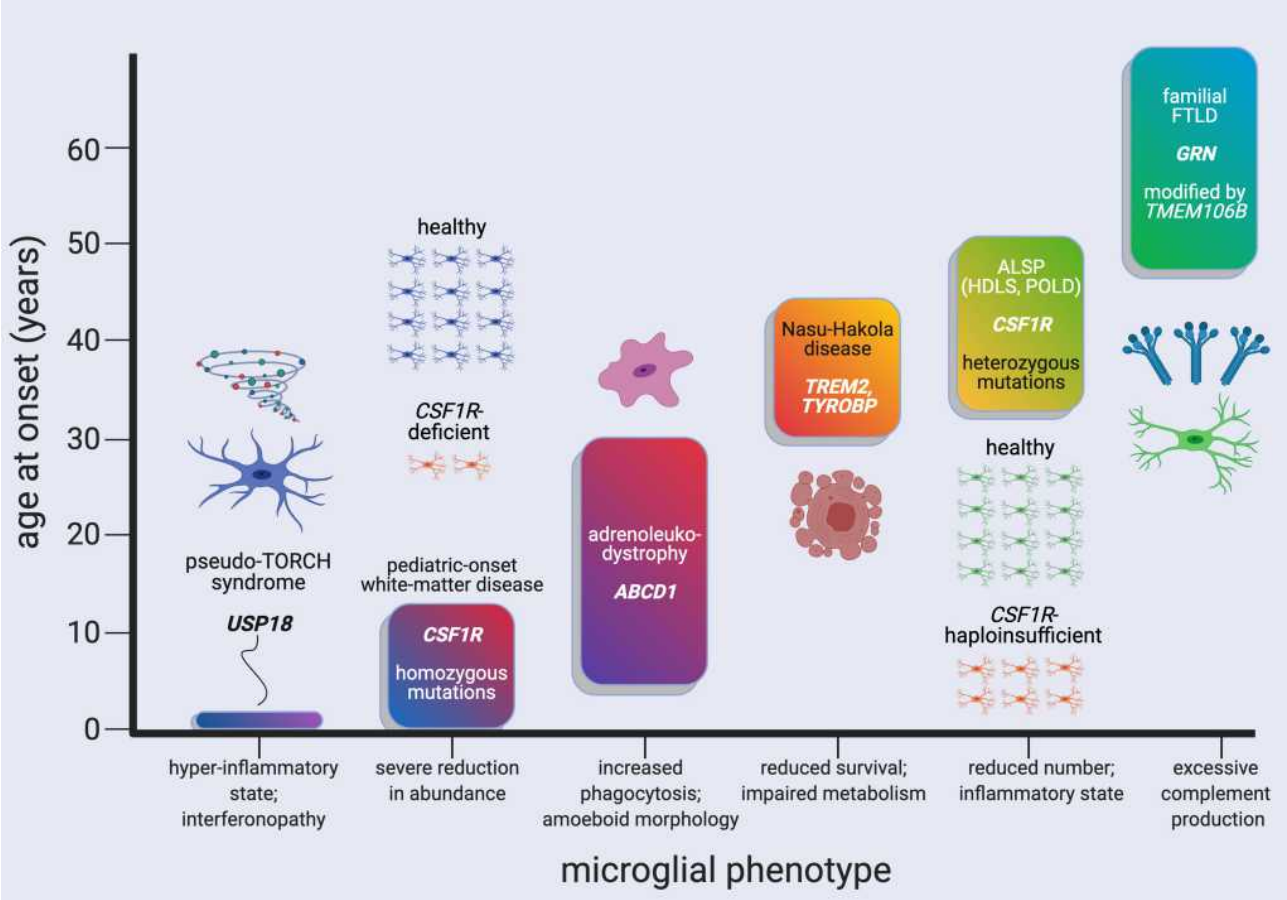


Figure 1 Distinct pathogenic mutations and microglial phenotypes are associated with white-matter disorders with highly variable ages of neurological symptom onset. White-matter diseases and the major microglial phenotypes they may be associated with are ordered according to their typical, approximate age range of onset. The characteristic microglial phenotypes listed are from histopathological studies and/or relevant mouse models of disease; see main text for references. Ages of neurological symptom onset can range from prenatal for type I interferonopathy associated with *USP18* deficiency and congenital absence (or near-absence) of microglia due to homozygous mutations in *CSF1R*, up to the 50s–70s for some cases of frontotemporal lobar degeneration with white-matter hyperintensities associated with pathogenic *GRN* mutations. Created with BioRender.com.

Abbreviations: *ABCD1*, ATP-binding cassette D1; ALSP, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; *CSF1R*, colony-stimulating factor 1 receptor; FTLD, frontotemporal lobar degeneration; *GRN*, progranulin; HDLS, hereditary diffuse leukoencephalopathy with axonal spheroids; POLD, pigmented orthochromatic leukodystrophy; *TMEM106B*, transmembrane protein 106B; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex virus; *TREM2*, triggering receptor expressed on myeloid cells 2; *TYROBP*, TYRO protein tyrosine kinase-binding protein; *USP18*, ubiquitin-specific protease 18.

certain circumstances (such as acute ablation of microglia) peripheral myeloid cells are capable of efficiently migrating into the brain, where they acquire a similar – but not identical – phenotype to that of genuine microglia.[123] Thus, it remains to be seen whether the benefits of HSCT in adrenoleukodystrophy and Krabbe disease are due to the restoration of *ABCD1* and *GALC* function, respectively, within brain-engrafted "microglia-like" cells derived from the transplant. Mouse models should enable this issue to be addressed in the future.

Finally, what are we to make of the WMH observed in a subset of patients with FTLD due to *GRN* mutations or FTD associated with rare variation in *SORT1*? Should this subset of patients be considered to have an adult-onset leukodystrophy? The extent of white-matter involvement in some cases seems to support this interpretation, although in these cases the white-matter pathology co-occurs with a prominent gray-matter structural phenotype and, presumably, TDP-43 neuropathology. Relatedly, it may be useful to consider the possibility that subtypes of FTLD-*GRN* exist, including those with and without extensive white-matter damage. Perhaps the involvement of white-matter pathology requires a "second hit," such as inheritance of the risk-conferring allele of *TMEM106B* or concomitant reduction in the function of prosaposin or sortilin. Future discoveries in the genetics of FTD will determine whether there are additional, as-yet undiscovered connections between leukodystrophy and FTD, but the identification of variants in *USP18* or *PSAP*, for example, that

confer risk for FTD, would provide support for this intriguing possibility.

Disclosure

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