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Emerging cellular themes in leukodystrophies

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Leukodystrophies are a broad spectrum of neurological disorders that are characterized primarily by deficiencies in myelin formation. Clinical manifestations of leukodystrophies usually appear during childhood and common symptoms include lack of motor coordination, difficulty with or loss of ambulation, issues with vision and/or hearing, cognitive decline, regression in speech skills, and even seizures. Many cases of leukodystrophy can be attributed to genetic mutations, but they have diverse inheritance patterns (e.g., autosomal recessive, autosomal dominant, or X-linked) and some arise from *de novo* mutations. In this review, we provide an updated overview of 35 types of leukodystrophies and focus on cellular mechanisms that may underlie these disorders. We find common themes in specialized functions in oligodendrocytes, which are specialized producers of membranes and myelin lipids. These mechanisms include myelin protein defects, lipid processing and peroxisome dysfunction, transcriptional and translational dysregulation, disruptions in cytoskeletal organization, and cell junction defects. In addition, non-cell-autonomous factors in astrocytes and microglia, such as autoimmune reactivity, and intercellular communication, may also play a role in leukodystrophy onset. We hope that highlighting these themes in cellular dysfunction in leukodystrophies may yield conceptual insights on future therapeutic approaches.

KEYWORDS

leukodystrophy, oligodendrocyte, myelin, white matter (WM), astrocyte, microglia, glia

Introduction

White matter development initiates *in utero* in the fetus, continues into late adolescence and adulthood, and culminates to constitute ~40% of adult human brains. White matter contains both neuronal axons and myelin sheaths that wrap concentrically in many layers around axons like paper towels. White matter is so named, because myelin is lipid rich and has a white, fatty appearance. Myelin functions to insulate axons, to facilitate saltatory conduction, and to increase axon potential velocity. During human development, myelin production begins slowly during the third trimester of pregnancy, and rapidly accelerates postnatally and during early childhood (Barkovich et al., 1988; Jakovcevski et al., 2009; Tomassy, Dershowitz, and Arlotta 2016). By 2 years of age, the majority of myelination is complete, as visualized by MRI scans (magnetic resonance imaging) and postmortem silver staining (Flechsig 1920;

BOX 1 Non-genetic Factors

Non-genetic factors, particularly neonatal white matter injury, can adversely affect neurodevelopment in long-lasting ways. Abnormal MRI findings in premature infants are very strong predictors of unfavorable neurodevelopmental outcomes, including cognitive delays, motor delays, and cerebral palsy (Woodward et al., 2006). Congenital heart disease is the most common major birth defect, and can place infants at risk of hypoxia (Marelli et al., 2007). Hypoxic insult causes oligodendrocyte death and delayed oligodendrocyte differentiation, thus leading to abnormalities in developmental myelination (Back et al., 2001; Jablonska et al., 2012). Interestingly, hypoxic newborn brains may share some common molecular markers with adult multiple sclerosis (MS) brains. Indeed, the remyelination regulator *Axin2* is present in white matter lesions that are found in both human newborn brains with hypoxic damage and active MS lesions in adults (Fancy et al., 2011).

Pathogens and the immune responses that they instigate can also have effects on white matter development. Perinatal inflammatory insult subsequent to maternal infection is associated with cerebral palsy as well as low scores on a number of development indexes (Stoll et al., 2004). For example, *E. coli* infection reduces the expression of oligodendrocyte-differentiation promoting transcripts and leads to myelin loss during a critical period of peak myelination (Favrais et al., 2011; Lieblein-Boff et al., 2013). Thus, the etiology of leukodystrophies are diverse and genetic causes are not the only consideration in white matter development and disease.

Wolf et al., 1993). Although white matter volume continues to increase into adulthood, its rate of formation is significantly slower (Fields 2010; Groeschel et al., 2010).

Developmental white matter diseases generally fall under the category of leukodystrophies. The term leukodystrophy can be broken down into its Greek origins: "leuko" for white, "dys" for bad or abnormal, and "trophy" for growth. Together, these root words define leukodystrophies as a broad spectrum of neurological disorders that are characterized primarily by deficiencies in myelin formation that are usually not secondary to neuronal defects. Incidence estimates range from one in 8,000 to lower estimates of one in 50,000 or one in 80,000 (Vanderver et al., 2012). Symptom onset typically occurs during childhood, when neural pathways and associated white matter tracts involved in speech, motor coordination, and memory are refined. Thus, common symptoms of leukodystrophies include regression or loss of developmental abilities, such as speech and walking, poor motor control, and cognitive defects. Though the majority of leukodystrophies present during childhood, some are adult-onset. This disparity in age of onset likely reflects diverse etiologies and disease mechanisms and, therefore, is an ongoing topic of research.

Though some cases of leukodystrophy have unclear etiology (see Box 1), many types have a genetic cause with diverse patterns of inheritance, including autosomal recessive, autosomal dominant, or X-linked recessive. These modes of inheritance dictate the appropriate types of therapeutic approaches that have been attempted in translational studies. Recessive leukodystrophies are often addressed through replacement therapies that aim to restore loss of function. These approaches include nutrient supplementation, enzymatic replacement via viruses, and transplantation of stem cells. For example, iPSCs (induced pluripotent stem cells) derived from human skin cells can be induced to become specialized cells, such as oligodendrocytes (Chanoumidou et al., 2020). Autosomal dominant leukodystrophies are often addressed through therapies that aim to suppress the mutant gene, mRNA, or protein. Traditional small molecule drug screens have been performed, typically on cellular models of leukodystrophy. In addition, a new class of drug called ASOs (antisense oligonucleotides) can bind to RNA targeting sequences to achieve gene silencing. ASOs for the treatment of SMA (spinal muscular atrophy) are FDA-approved and several ongoing ASO clinical trials target ALS (amyotrophic lateral sclerosis) and other genetic neurological diseases (Amado and Davidson 2021). Thus, multiple therapeutic approaches are available to address the diverse types of leukodystrophies.

In this review, we provide an updated overview of 35 hypomyelinating leukodystrophies and home in on cellular mechanisms for disease. We find many common mechanisms affecting oligodendrocytes, the brain cells responsible for making myelin sheaths. These mechanisms often affect specialized oligodendrocyte functions, such as defects in myelin protein production, lipid processing, and peroxisome health. Additional oligodendrocyte-centric mechanisms include metabolic dysfunction, transcriptional and translational alterations, cytoskeletal dysregulation, and defects in cell junctions. Other glial cells, including astrocytes and microglia, may also be involved in certain leukodystrophies (Figure 1; Table 1). By identifying these emerging themes in cellular dysfunction, we hope to highlight conceptual insights that can contribute to the development of future therapeutic strategies for leukodystrophies.

Lysosomal lipid metabolism and catabolism defects

Oligodendrocytes are extraordinary producers of membranes and each oligodendrocyte is capable of forming multiple myelin sheaths. For example, oligodendrocytes from the cortex region of the brain can make as many as 50 myelin sheaths (Hughes et al., 2013). Each oligodendrocyte can make an estimated 2 mm^2 of membrane surface area, which is 200 times higher than a typical epithelial cell (Poitelon, Kopec, and Belin 2020). Thus, oligodendrocytes are one of the most lipid-rich cell types in the body and, therefore, perhaps more vulnerable to mutations affecting lipid production.

Many mutations associated with leukodystrophies affect pathways involved in the production or breakdown of myelin

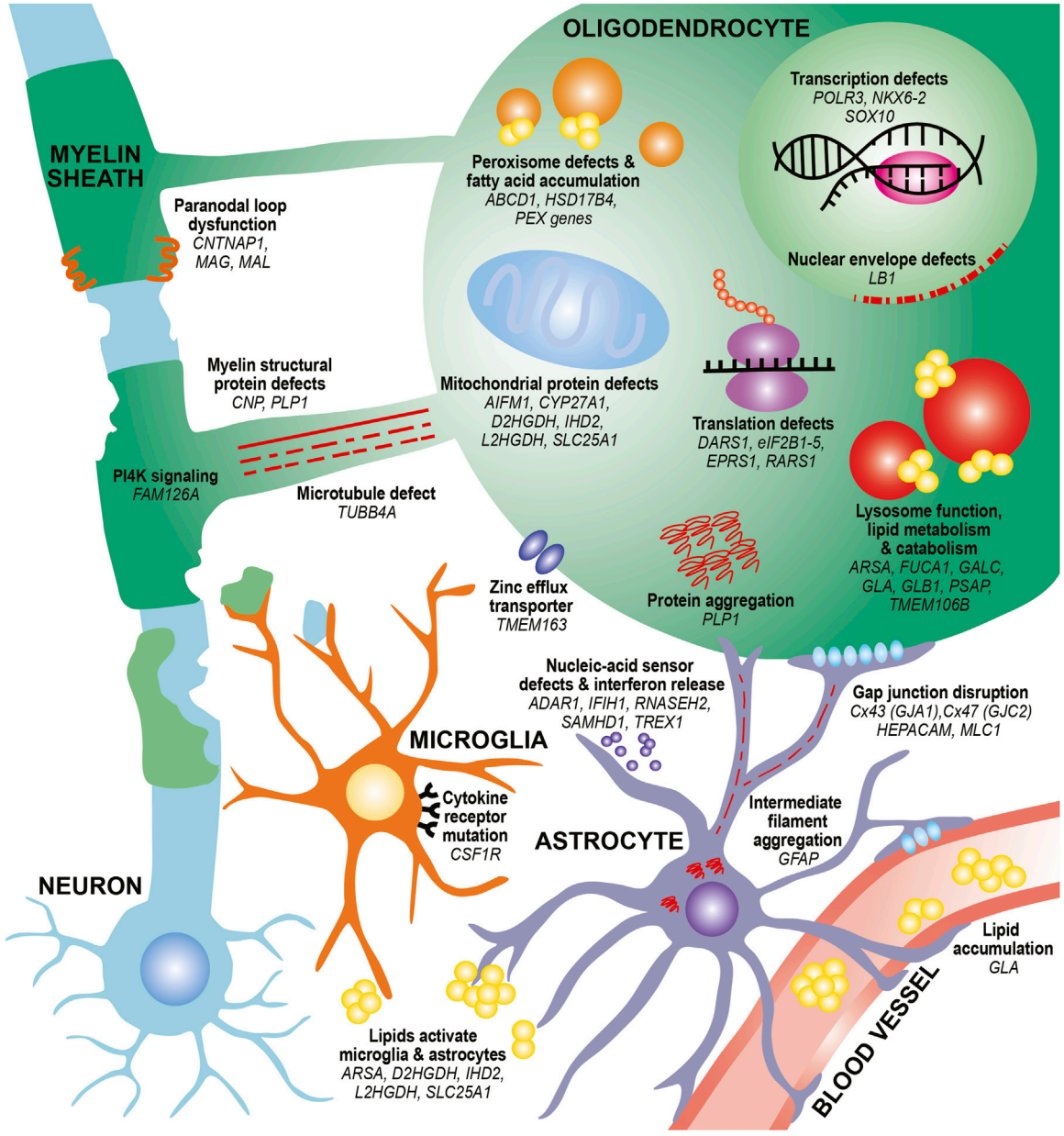

FIGURE 1
Diverse mechanisms and cell types contribute to hypomyelination in leukodystrophies. In oligodendrocytes, mutations in myelin structural proteins (*CNP*, *PLP1*) can lead to thinner myelin sheaths and paranodal loop malformation (*CNTNAP1*, *MAG*, *MAL*). PLP mutations can also lead to aberrant protein aggregation. Other mutations can affect the function of organelles that participate in lipid metabolism and catabolism, such as peroxisomes (*ABCD1*, *HSD17B4*, *PEX* family genes) and lysosomes (*ARSA*, *FUCA1*, *GALC*, *GLA*, *GLB1*, *PSAP*). These defects can also lead to toxic lipid accumulation that builds up in the bloodstream (*GLA*) or activate astrocytes and microglia (*ARSA*). Finally, mutations affecting transcription factors (*NKX6-2*, *SOX10*), transcriptional machinery (*POLR3* genes) and translation machinery (*DARS1*, *eIF2B* genes, *EPRS1*, *RARS1*) cause impair differentiation of oligodendrocytes and reduce production of myelin proteins. Defects in microtubules that project toward and within the myelin sheath (*TUBB4A*) as well as in PI4K signaling pathways that contribute to wrapping (*FAM126A*) can affect myelin sheath growth. Mutations in mitochondrial genes can lead to lipid processing defects (*CYP27A1*), aberrant activation of apoptotic pathways (*AIFM1*), and metabolic issues (*D2HGDH*, *IHD2*, *L2HGDH*, *SLC25A1*). Other pathways, such as nuclear envelope integrity (*LB1*) and zinc efflux (*TMEM163*) can also affect oligodendrocyte health. In astrocytes, intermediate filament protein mutations (*GFAP*) can lead to its aggregation and formation of Rosenthal fibers. Mutations affecting gap junctions can disrupt cell junctions between astrocytes and oligodendrocytes (*GJA1*, *GJC2*) and between astrocytes and vasculature (*HEPACAM*/*GLIALCAM*, *MLC1*). Mutations affecting nucleic-acid sensors (*ADAR1*, *IFIH1*, *RNASEH2* genes, *SAMHD1*, *TREX1*) can activate an immune response and release of interferons from astrocytes. In microglia, mutations in cytokine receptors (*CSF1R*) can affect microglial proliferation, differentiation, and activation. Finally, mutations affecting lipid processing (*ARSA*, *D2HGDH*, *IHD2*, *L2HGDH*, *SLC25A1*) can lead to aberrant lipid accumulation, which can activate microglia and astrocytes.

TABLE 1 Leukodystrophy-causing mutations and their cellular mechanisms.

Disease type	Name	Gene(s)	Cell type	Cellular mechanism	Inheritance
Lysosomal Lipid Metabolism and Catabolism Defects	Fabry Disease (FD)	*GLA*	Unknown	Lysosomal enzyme α-galactosidase A (GLA) metabolizes globotriaosylceramide. Mutant α-galactosidase cannot break down glycolipids leading to accumulation in tissues.	X-linked Recessive, but female carriers can be affected
	Fucosidosis	*FUCA1*	Oligodendrocytes	Lysosomal α-L-fucosidase 1 (FUCA1) degrades fucose-containing glycoproteins and glycolipids. Mutant α-L-fucosidase cannot break down glycolipids and glycoproteins, leading to accumulation in tissues, reduction of oligodendrocyte differentiation, and increased apoptosis.	Autosomal Recessive
	GM1 Gangliosidosis	*GLB1*	Oligodendrocytes	Lysosomal enzyme β-galactosidase (GLB1) degrades glycosphingolipids into sphingosine, which is used in myelin synthesis. Mutant β-galactosidase cannot break down GM1 ganglioside, which accumulates in tissues and the brain.	Autosomal Recessive
	Krabbe Disease; Globoid-Cell Leukodystrophy (GCL)	*GALC*	Oligodendrocytes Macrophages	Lysosomal enzyme galactosylceramidase (GALC) catabolizes galactosylceramide and galactosylsphingosine (psychosine) during normal myelin turnover. Mutant GALC cannot catabolize sphingolipids, leading to accumulation and oligodendrocyte cell death. Lipid accumulation attracts macrophages, which form multinucleated globoid cells.	Autosomal Recessive
	Metachromatic Leukodystrophy (MLD)	*ARSA, PSAP*	Oligodendrocytes, Microglia, Macrophages	Lysosomal arylsulfatase A (ARSA) metabolizes sulfatides, which are abundant in myelin. Mutant ARSA cannot metabolize sulfatides, which accumulate and activate microglia and macrophages, leading to apoptosis and demyelination.	Autosomal Recessive
Peroxisome Defects and Fatty Acid Accumulation	D-Bifunctional Protein (DBP) Deficiency	*HSD17B4*	Neurons; Oligodendrocytes	DBP catalyzes β-oxidation of fatty acids. DBP deficiency in animal models leads to lipid accumulation, brain atrophy, and hypomyelination.	Autosomal Recessive
	X-linked Adreno-leukodystrophy (X-ALD)	*ABCD1*	Neurons, Astrocytes, Oligodendrocytes	*ABCD1* encodes adrenoleukodystrophy protein (ALDP), a peroxisomal transmembrane protein responsible for transporting very long-chain fatty acids (VLCFA) into peroxisomes. Mutations in *ABCD1* disrupt VLCFA metabolism. Accumulation of VLCFA is toxic to neurons, oligodendrocytes, and astrocytes.	X-linked recessive
	Zellweger Syndrome Spectrum Disorders (ZSDs)	*PEX1, PEX2, PEX3, PEX5, PEX6, PEX10, PEX11, PEX12, PEX13, PEX14, PEX16, PEX19, PEX26*	Oligodendrocytes	*PEX* genes assemble and allow transport into and out of peroxisomes. Mutations in *PEX* genes cause misassembly of peroxisomes, which dysregulates lipid synthesis and metabolism.	Autosomal Recessive
Mitochondrial Protein Defects and Other Metabolic Deficiencies	Cerebrotendinous Xanthomatosis (CTX)	*CYP27A1*	Microglia, Oligodendrocytes	Sterol-27 hydroxylase breaks down cholesterol into a bile acid. Sterol-27 hydroxylase deficiency leads to cholesterol-derivative accumulation.	Autosomal Recessive
	Hypomyelination with Spondylometa physeal Dysplasia (H-SMD)	*AIFM1*	Unknown	Mitochondrial apoptosis-inducing factor 1 (AIFM1) stabilizes complexes I and III through its redox activity. Mutant AIFM1 may not perform its electron-transport chain functions.	X-linked recessive

(Continued on following page)

TABLE 1 (*Continued*) Leukodystrophy-causing mutations and their cellular mechanisms.

Disease type	Name	Gene(s)	Cell type	Cellular mechanism	Inheritance
	2-Hydroxyglutaric Aciduria (2HGA)	*D2HGDH, IHD2, L2HGDH, SLC25A1*	Neurons, Astrocytes Oligodendrocytes, Microglia	Mitochondrial enzymes break down D-2-hydroxyglutarate and L-2-hydroxyglutarate. Various mitochondrial enzymes cannot metabolize 2-hydroxyglutarate, leading to oxidative stress, metabolic dysregulation, glial cell death, and myelin degradation.	Autosomal Recessive; Autosomal Dominant (Type II D-2-HGA)
	Canavan Disease	*ASPA*	Oligodendrocytes	Aspartoacylase (ASPA) catabolizes N-acetyl-L-aspartic acid (NAA) into acetate and aspartate. ASPA deficiency leads to accumulation of NAA and deficiency of acetate and aspartate in oligodendrocytes, thus reducing myelin production.	Autosomal Recessive
Cytoskeletal Proteins	Alexander Disease (AxD)	*GFAP*	Astrocytes	Glial fibrillary acidic protein (GFAP) is an astrocyte-specific intermediate filament protein. GFAP overexpression leads to aggregation (Rosenthal fibers) and cell toxicity.	Autosomal Dominant; *De novo*
	Autosomal Dominant Leukodystrophy with Autonomic Disease (ADLD)	*LMNB1*	Oligodendrocytes	Lamin B1 is an intermediate filament that builds the nuclear lamina. Gene duplication of *LMNB1* causes overexpression, affecting expression of lipid synthesis genes.	Autosomal Dominant
	Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC)	*TUBB4A*	Oligodendrocytes, Neurons	*TUBB4A* encodes the microtubule protein β-tubulin. Mutations at the α-β dimer interface affect tubulin dynamics and motor protein binding, which can cause reduced myelination and cell death.	Autosomal Dominant
Transcription Defects	4H Leukodystrophy; POLR3-related Leukodystrophy	*POLR3A, POLR3B, POLR3C, POLR3K*	Oligodendrocytes	RNA polymerase III (POLR3) transcribes DNA into RNA. Mutations affect assembly of the RNA polymerase III complex and its DNA binding properties, thus reducing transcription of rRNA and tRNA.	Autosomal Recessive
	NKX6-2-related Spastic Ataxia with Hypomyelination (SPAX8)	*NKX6-2*	Oligodendrocytes	NKX6-2 is a transcription factor involved in oligodendrocyte differentiation and myelination.	*De novo*
	Waardenburg–Hirschsprung disease (WS4)	*SOX10*	Oligodendrocytes, Schwann cells	SOX10 is a transcription factor involved in oligodendrocyte differentiation and myelination.	*De novo*
Translational Machinery	tRNA Synthetase-related Leukodystrophies	*DARS1, EPRS1, RARS1*	Oligodendrocytes, Neurons	Mutations affecting proteins in the tRNA synthetase complex may disrupt protein translation	Autosomal Recessive
	Vanishing White Matter (VWM) Disease; Childhood Ataxia and Cerebral Hypomyelination (CACH)	*EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5*	Oligodendrocytes	Eukaryotic translation initiation factor 2B (EIF2B) initiates mRNA translation and is a GTPase. Mutations impair translational control, thus reducing OPC differentiation and myelin production.	Autosomal Recessive
Cell Junction Defects	Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC); van der Knaap Disease	*MLC1, HEPACAM (GLIALCAM)*	Astrocytes, Oligodendrocytes	MLC1 and HEPACAM (GLIALCAM) contribute to astrocytic osmoregulation. Mutations can lead to gliovascular coupling defects, causing fluid buildup and macrocephaly.	Autosomal Recessive
	Oculodentodigital Dysplasia (ODDD)	*GJA1 (Cx43)*	Astrocytes, Oligodendrocytes	Gap junction α1/Connexin 43 create astrocyte gap junctions. Mutations disrupt gap junction formation and function between astrocytes and oligodendrocytes.	Autosomal Dominant; Autosomal Recessive; *De novo*

(Continued on following page)

TABLE 1 (*Continued*) Leukodystrophy-causing mutations and their cellular mechanisms.

Disease type	Name	Gene(s)	Cell type	Cellular mechanism	Inheritance
	Pelizaeus-Merzbacher-like Disease (PMLD)	*GJC2 (Cx47)*	Astrocytes; Oligodendrocytes	Mutations in connexin 47 disrupt gap junction function and electrical coupling.	Autosomal Recessive
Myelin Structural Protein Defects	*CNP*-related hypomyelinating leukodystrophy	*CNP*	Oligodendrocytes	Mutant 2′,3′-cyclic nucleotide-3′-phosphodiesterase (CNP) protein is expressed at very low levels.	Autosomal Recessive
	CNTNAP1-related Arthrogryposis and Leukodystrophy	*CNTNAP1*	Neurons, Oligodendrocytes	*CNTNAP1* encodes the paranodal axonal cell-adhesion protein contactin-associated protein 1 (Caspr1). Patient sural nerve EMs lack paranodal junctions.	Autosomal Recessive
	MAG-related PMLD	*MAG*	Oligodendrocytes	Mutant myelin-associated glycoprotein (MAG) is retained in the ER, resulting in misshapen paranodes and thin myelin sheaths.	Autosomal Dominant
	MAL-related Leukodystrophy	*MAL*	Oligodendrocytes	Myelin and lymphocyte (MAL) protein is important for the structure of paranodal loops. Mutant MAL accumulates in the ER, indicative of protein misfolding.	*De novo*
	Pelizaeus–Merzbacher Disease (PMD)	*PLP1*	Oligodendrocytes	PLP is the most abundant protein in myelin and important for compaction. Mutant PLP protein can misfold and aggregate. Disruption of iron metabolism may occur.	X-linked Recessive
Other Transmembrane Protein Defects	Hypomyelination with Congenital Cataracts (HCC)	*FAM126A*	Oligodendrocytes	*FAM126A* encodes hyccin, a transmembrane protein expressed in the brain. Hyccin is a component of the PI4K complex that is important for phosphoinositide signaling, which regulates myelin wrapping.	Autosomal Recessive
	SLC35B2-related Chondrodysplasia with Hypomyelinating Leukodystrophy	*SLC35B2 (PAPST1)*	Unknown	SLC35B2 is a PAPS transporter that is important for making sulfated proteoglycans. Mutant SLC35B2 loses its localization to Golgi.	Autosomal Recessive
	Transient Infantile Hypomyelinating Leukodystrophy-19 (HLD19)	*TMEM63A*	Oligodendrocytes	TMEM63A is a mechanosensitive ion channel. Mutant TMEM63A does not produce stretch-activated currents in response to mechanical stimulation.	Autosomal Dominant
	TMEM106B-related Hypomyelinating Leukodystrophy	*TMEM106B*	Oligodendrocytes, Neurons	TMEM106B is involved in lysosomal trafficking and acidification. Mutant TMEM106B disrupts these lysosomal functions and may reduce PLP trafficking.	*De novo*
	TMEM163-related Hypomyelinating Leukodystrophy	*TMEM163*	Oligodendrocytes	TMEM163 is a zinc efflux transporter. In cultured cells, mutant TMEM163 is hyperactive in zinc efflux.	*De novo*
Immune System Activation	Aicardi-Goutieres Syndrome (AGS)	*TREX1, RNASEH2A/B/C, SAMHD1, ADAR1, IFIH1*	Astrocytes, Oligodendrocytes	These genes encode the intracellular nucleic acid sensor machinery that induces astrocyte release of interferons and subsequent cell death when foreign or defective genetic material is detected.	Autosomal Recessive
	Hereditary Diffuse Leukoencephalo pathy with Spheroids (HDLS)	*CSF1R*	Microglia; Oligodendrocytes; Neurons	Mutant CSF1 receptor is defective in activating following CSF1 ligand binding, leading to defects in microglia function and demyelination.	Autosomal Dominant

lipids. The three major classes of lipids found in the myelin sheath include cholesterol, phospholipids (e.g., plasmalogen, phosphatidylcholine), glycolipids (e.g., galactosylceramide and its sulfated form, sulfatide), and sphingomyelin. Early studies found CNS myelin to contain molar percentages of 40–46% cholesterol, 26% phospholipid, 19–20% glycolipid, and 4–6% sphingomyelin (O'Brien 1965; Norton and Poduslo 1973). Leukodystrophy mutations affect lysosomal enzymes that participate in both lipid metabolism and catabolism. Defects in lipid metabolism can lead to aberrant lipid accumulation and dysfunctional myelin growth. Myelin is dynamic and, in addition to developmental myelin growth, myelin turnover replaces old membranes. This involves the modification of myelin and lipid breakdown as well as the formation of organelles called myelinoid bodies within the myelin sheath (Meschkat et al., 2022). Though it is still unclear whether lysosomal function is necessary for myelin clearance, myelin turnover may explain why mutations in lysosomal enzymes affecting lipid catabolism can lead to disease. Thus, understanding the nuanced relationship between lysosomal lipid metabolism and catabolism could be crucial to understanding the following leukodystrophies.

Fabry disease (FD)

Fabry disease is a lysosomal storage disorder characterized by deposits of glycosphingolipids in blood vessels and smooth muscle tissue (Sweeley and Klionsky 1963; Aerts et al., 2008). Patients present with clusters of dark red spots on the skin (angiokeratomas), cloudy corneas, episodes of pain localized to hands and feet (acroparesthesias), gastrointestinal symptoms, and hearing loss. Symptoms eventually progress to affect the heart and kidneys, with patient death usually attributed to renal failure (Schiffmann et al., 2009). The most severe cases of FD begin between 3 and 10 years of age (Hopkin et al., 2008), but large-scale metabolic screening of newborns revealed that undiagnosed later-onset FD is about 11 times more common (Spada et al., 2006).

FD is caused by mutations in the *GLA* gene encoding α-galactosidase A. This enzyme is involved in the catabolism of multiple glycoproteins, glycolipids, and polysaccharides (Brady et al., 1967). The majority of the nearly 600 mutations associated with FD are thought to cause a complete loss of function (Gal 2010). *GLA* is located on the X chromosome, and thus FD-causing mutations are inherited in an X-linked pattern. Interestingly, women heterozygous for FD mutations are not unaffected but in fact also experience significant disease burden, including renal and cardiovascular involvement (Wang et al., 2007; Waldek et al., 2009). Indeed, women carriers experience lifespan reduction of ~10–15 years while men with FD experience lifespan reduction of ~20 years (MacDermot et al., 2001; 2001).

Hypomyelination is one facet of progressive FD. Both affected men and women over the age of 35 display white-matter lesions (WML) in the central nervous system (CNS) (Fellgiebel et al., 2005), but the mechanism for this is unclear. Changes in cerebral blood flow and vascular changes due to glycolipid deposits have been suggested to contribute to glial cell death and demyelination. However it is unclear if cerebral blood flow increases or decreases in FD. One MRI study found that FD patients have increased cerebral blood flow and reduced glucose metabolism (Moore et al., 2003; Vagli et al., 2020). However, both a *Gla* knockout mouse model of FD and human imaging studies found reduced cerebral blood flow (Itoh et al., 2001; Hilz et al., 2004). Thus, the mechanism for hypomyelination in FD remains a mystery.

There are two standard treatment courses for FD: enzyme replacement therapy and oral chaperone therapy. First, enzyme replacement consists of infusions of recombinant human GLA enzyme (Eng et al., 2001), which reduces sphingolipid levels in the urine, plasma, and tissues (Rombach et al., 2013) and has been shown to stabilize WML progression. However, it is time-consuming and does not cure FD (Fellgiebel et al., 2005). Second, oral chaperone therapy introduces a small molecule ligand that aims to stabilize mutant GLA and restore its enzymatic activity. In cultured patient fibroblasts, this ligand increased baseline GLA levels and reduced accumulated sphingolipids (Yam, Zuber, and Roth 2005; Benjamin et al., 2009). Oral chaperone therapy presents some benefits over enzyme replacement, because patients display improvements in cardiac and digestive symptoms and do not develop antibodies to the ligand (Wilcox et al., 2012; Lenders et al., 2016). However, OCT is only effective in patients with certain mutations, thus limiting its use (Germain et al., 2016; Hughes et al., 2017).

Very recently, five men with FD received stem cell therapy through transfusions of hematopoietic stem cells (HSCs) transduced with human *GLA* cDNA. All patients who received this treatment reached healthy reference levels of circulating GLA enzyme and remained above baseline levels indefinitely (Khan et al., 2021). Thus, stem cell therapy is a promising therapeutic for FD patients, but additional clinical studies are required before this option can become widely available to patients.

Fucosidosis

Fucosidosis is a progressive lysosomal storage disorder with autosomal recessive inheritance pattern. Patients with fucosidosis present with aberrant facial features (enlarged head, lips, and tongue, small or malformed teeth, and flattened nose), impaired physical growth and intellectual ability, recurrent respiratory infections, progressive skeletal dysplasia, and neurodegeneration (Stepien, Ciara, and Jezela-Stanek 2020). The mean age of onset is ~1 year old (Willems et al., 1991). Fucosidosis presents with myelin loss in the cerebellum and cerebrum that is visible by MRI (Steenweg

et al., 2010; Jain et al., 2012). Some patients display rapidly progressing neurodegeneration resulting in death before the age of 10 (Loeb et al., 1969) while others have a life expectancy into young adulthood (Kousseff et al., 1976).

Fucosidosis is linked to mutations in *FUCA1* (α-L-fucosidase 1), that lead to enzymatic deficiency (Willems et al., 1988; 1991). This results in the inability to metabolize certain sugar compounds (e.g., fucose-containing glycolipids and fucose-containing glycoproteins), which then accumulate (Van Hoof and Hers 1968). A canine model of fucosidosis displayed reduced expression of key oligodendrocyte differentiation genes, including *CNP, PLP* (proteolipid protein), *MAG, MAL, MRF, OPALIN*) as well as oligodendrocyte death that was confirmed with apoptosis markers. Because these defects were observed during developmental stages, they support a mechanism of hypomyelination rather than demyelination (Fletcher et al., 2011; 2014). In addition, a *Fuca1* knockout mouse exhibited lysosomal dysregulation, lipid accumulation, neuroinflammation, and behavioral deficits (e.g., impaired coordination and spatial learning) that parallel the motor and intellectual deficits observed in fucosidosis patients (Stroobants et al., 2018). Thus, both canine and murine disease models indicate that many downstream effects of FUCA1 deficiency contribute to myelin defects in fucosidosis.

Most potential fucosidosis treatment strategies aim to ameliorate symptoms. Canine studies have shown success with enzyme replacement, which reduces vacuolation, neuron death, and neuroinflammation. However, these therapies only reduce symptoms and do not stop neurological progression (Kondagari et al., 2011; 2015). Bone marrow transplantation has shown success in both canine models and one human patient, but the risks and side effects of this procedure may outweigh the benefits (Taylor, Farrow, and Stewart 1992; Vellodi et al., 1995; Miano et al., 2001). Thus, additional preclinical studies are needed in order for any of these approaches to move forward as viable therapies for fucosidosis.

GM1 gangliosidosis

GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder ranging from infantile-onset to chronic presentation. Patients experience intrauterine growth restriction, abnormal fluid accumulation in serous cavities, and placental vacuolization (Regier et al., 1993) coupled with the rapid progression of CNS dysfunction including blindness, deafness, seizures, and feeding difficulties. Pathologically, multiple brain regions including caudate, putamen, corpus callosum, basal ganglia, and cerebellar white matter are atrophied (Nestrasil et al., 2018). MRI scans and postmortem brain analyses revealed hypomyelination and atrophy of the caudate, putamen, corpus callosum, and basal ganglia (King et al., 2020; Uchino et al., 2020).

GM1 gangliosidosis is a result of homozygous or compound heterozygous (biallelic) mutations in the *GLB1* gene (Morrone et al., 2000; Bidchol et al., 2015). *GLB1* encodes for the ubiquitous lysosomal enzyme β-galactosidase (β-GAL), which is responsible for the degradation of GM1 ganglioside, a type of glycosphingolipid composed of a ceramide lipid tail linked to a glycan headgroup containing a sialic acid residue (Regier et al., 1993; Sipione et al., 2020). The breakdown of GM1 gangliosides creates the downstream catabolite sphingosine, which is used in sphingomyelin synthesis and ultimately myelin formation. Mutations in *GLB1* cause reduced or null β-GAL enzymatic activity, which leads to toxic and progressive accumulation of GM1 gangliosides and other glycoproteins (Kajihara et al., 2020).

Several studies have revealed cellular pathways involved in GM1 gangliosidosis pathogenesis, such as an activated unfolded protein response (Tessitore et al., 2004), calcium signaling in the endoplasmic reticulum (ER) (Sano et al., 2009), autophagy (Takamura et al., 2008), and inflammasome activation (Son et al., 2015). Additional studies could elucidate molecular and cellular mechanisms of hypomyelination in GM1 gangliosidosis.

Recent studies have focused on two potential therapeutic approaches. First, multiple studies have used viruses, such as AAV9 (adeno-associated virus), a virus with broad CNS tropism, to deliver a functional copy of the *GLB1* gene. In one study, *Glb1* knockout mice received intravenous injections of AAV9 containing the *GLB1* gene, which increased β-GAL activity in various regions of the brain and in peripheral tissues. Interesting sex-specific effects were observed, including more viral copies in females and a significant difference in median survival from ~100 to ~577 days (in females) and ~398 days (in males) (Weismann et al., 2015). In a more recent study, researchers used human iPSCs to create *GLB1* knockout cerebral organoids that recapitulated GM1 gangliosidosis by exhibiting progressive accumulation of gangliosides at 10 and 20 weeks in culture. Delivering AAV9 containing the *GLB1* gene significantly increased β-GAL activity and reduced GM1 accumulation in these organoids (Latour et al., 2019). Thus, enzyme replacement via stem cell therapy is a viable strategy for the treatment of GM1 gangliosidosis.

Researchers have also taken a drug screening approach. iPSCs from GM1 gangliosidosis patients were differentiated into neural stem cells, which model disease biochemistry by exhibiting accumulated GM1 gangliosides. High-content screening identified 25 small molecule compounds that reduced the accumulation of GM1 gangliosides. Of these, amodiaquine (a heme polymerase inhibitor) and thiethylperazine (an adrenergic antagonist) were the most effective. When administered *in vivo* to β-GAL null mice, these two compounds decreased GM1 ganglioside accumulation in the brain (Kajihara et al., 2020). Thus, researchers are exploring both stem cell-based enzymatic

replacement and drug therapies as therapeutic strategies to treat GM1 gangliosidosis.

Krabbe disease

Krabbe disease, also known as globoid-cell leukodystrophy (GCL), is a rapidly progressive autosomal recessive neurodegenerative disorder. Patients have rapid demyelination resulting in near total loss of myelin, severe astrogliosis, and the presence of multinucleated globoid cells in the white matter (Suzuki and Suzuki 1970). Hypomyelination in the CNS leads to muscle spasticity, paralysis, irritability, loss of vision and hearing, seizures, peripheral neuropathy, and premature death (Hagberg, Sourander, and Svennerholm 1963; Morse and Rosman 2006; Sakai 2009; Brodsky and Hunter 2011; Beltran-Quintero et al., 2019). The median survival is 1.5 and 9.5 years for early- and late-infantile Krabbe disease, respectively, whereas juvenile- and adult-onset subtypes have projected survival beyond 30 years of age (Komatsuzaki et al., 2019).

Krabbe disease patients have mutations in the *GALC* (galactosylceramidase) gene that result in loss of function of this lysosomal enzyme (Wenger and Luzi 2020). GALC removes the sugar galactose from galactosylceramide, galactosylsphingosine (psychosine), and other galactolipids (Suzuki and Suzuki 1970; Beltran-Quintero et al., 2019; Komatsuzaki et al., 2019). The inability to catabolize galactosylceramide and galactosylsphingosine leads to their accumulation. On the one hand, galactosylceramide accumulation is postulated to attract macrophages, which phagocytose it, then form multinucleated globoid cells (Komatsuzaki et al., 2019). These globoid cells are associated with severe demyelination, axonopathy, and neuronal death (Wenger and Luzi 2020). On the other hand, psychosine accumulation is cytotoxic to oligodendrocytes (Komatsuzaki et al., 2019) and therefore may be the pathological driver of Krabbe disease symptoms. Indeed, in a human oligodendroglioma cell line, treatment with psychosine caused the mislocalization of fatty acid binding protein 5 (FABP5) to the mitochondria, the formation of mitochondrial pores, and reduced levels of mitochondrial DNA. The authors postulated that this could lead to oxidative stress and apoptosis (Cheng, Kawahata, and Fukunaga 2020). Thus, loss of GALC activity results in aberrant lipid accumulation and various downstream effects.

Surprisingly, of the >70 disease-causing mutations in *GALC*, most are not located in the enzymatic domain. For example, in the D528N mutation, the aberrant asparagine residue leads to hyperglycosylation and misfolding of GALC (Lee et al., 2010). This glycosylation defect is reminiscent of the D32N MPZ (myelin protein zero) mutation in Charcot-Marie-Tooth neuropathy. In the peripheral nervous system (PNS), this mutation leads to hyperglycosylation of MPZ and defects in MPZ trafficking to the plasma membrane (Prada et al., 2012). This is consistent with experiments in cell lines in which mutating the MPZ glycosylation site can lead to a membrane adhesion defect (Filbin and Tennekoon 1993), which is hypothesized to impact myelin compaction. Thus, Krabbe disease mutations can affect both enzymatic activity as well as post-translational modifications (PTMs).

Currently, multiple potential therapeutic strategies for Krabbe disease exist. HSC transplant has been performed and is most successful when it precedes symptom onset. Indeed, to facilitate early diagnosis and treatment, several states (e.g., New York, Ohio, Pennsylvania, Kentucky, Indiana, etc.) require all newborns to be screened within 48 h of birth (Orsini et al., 2016). Unfortunately, long-term outcomes of HSC transplant (regardless of whether the treatment was initiated prior to symptom onset) are poor and high-risk with elevated morbidity rates (Krivit et al., 1998; Escolar et al., 2005; Aldenhoven and Kurtzberg 2015; Wasserstein et al., 2016; Wright et al., 2017).

Ongoing research in mice has focused on another approach: viral delivery of the *Galc* gene. The *twitcher* mouse, which has a *Galc* mutation, is often used to model Krabbe disease. By postnatal day 30, these mice exhibit severe myelin loss, astrocytic gliosis, and the presence of globoid cells (Kobayashi et al., 1980; Li and Sands 2014). Several studies have looked at viral vector delivery of *Galc* to presymptomatic *twitcher* mice. Two studies administered AAV9 encoding mouse *Galc* via intrathecal (Karumuthil-Melethil et al., 2016) and intracisternal injections (Bradbury et al., 2020). Both studies found reduced galactosylsphingosine levels, ameliorated myelin abnormalities, and ultimately prolonged survival of the *twitcher* mice. Another study used a virus with a different serotype (AAVrh10) and a different delivery method (intravenous administration on postnatal day 10). This virus crossed the blood–brain barrier, and prevented both myelin loss and galactosylsphingosine accumulation (Rafi, Luzi, and Wenger 2021). Thus, these promising results in rodents may open the door for future pre-clinical studies on viral delivery of the *Galc* gene.

Metachromatic leukodystrophy (MLD)

MLD is an autosomal recessive demyelinating disorder that can be divided into four subtypes according to age of onset: late infantile, early-juvenile, late-juvenile, and adult-onset (Von Figura, Gieselmann, and Jaeken 2001; Sevin, Aubourg, and Cartier 2007). The most common form of MLD, which comprises ~50% of all cases, is the late infantile subtype, which has symptom onset by ~2 years of age (Cesani et al., 2016). Clinical presentations include muscle wasting, weakness and rigidity, developmental delays, progressive vision loss, seizures, paralysis, and dementia (Gieselmann and Krägeloh-Mann 2010). In the majority of cases, the prognosis is severe and often leads to a persistent vegetative state or death within a few years of symptom onset (Von Figura, Gieselmann, and Jaeken 2001; Gieselmann and Krägeloh-Mann 2010; Aubourg et al., 2011).

Most MLD subtypes can be traced back to >150 mutations in the gene encoding the enzyme arylsulfatase A enzyme (ARSA or ASA) (Von Figura, Gieselmann, and Jaeken 2001; Aubourg et al., 2011; Batzios and Zafeiriou 2012). In rare instances, MLD can also be caused by a mutation in the *PSAP* gene encoding presaposin, the precursor to saposin B (SAP-B), an activator of ARSA (Holtschmidt et al., 1991). Because ARSA is a lysosomal enzyme, MLD is often referred to as a lysosomal storage disorder. Mutations in *ARSA* lead to an enzymatic deficiency, ultimately resulting in the impaired metabolism of sulfatide, a major lipid component of the myelin sheath. Sulfatide can accumulate in microglia, neurons, and oligodendrocytes along with peripheral tissues (Gieselmann 2003; Molander-Melin et al., 2004; Patil and Maegawa 2013). Excess sulfatide triggers an inflammatory response which includes microglial activation, astrogliosis, and recruitment of peripheral macrophages. Together, these events are thought to cause apoptosis of glia and neurons as well as demyelination in the CNS (Sevin, Aubourg, and Cartier 2007; Patil and Maegawa 2013). Loss of function in MLD is also supported by a global *Arsa* knockout mouse that displays many clinical hallmarks of MLD, such as sulfatide accumulation, motor dysfunction, and cognitive impairment. However, these mice lacked shortened lifespans and white matter defects (Hess et al., 1996). Thus, additional research should clarify the mechanistic link between sulfatide accumulation and demyelination.

One therapeutic approach for MLD is enzyme replacement. Recent Phase 1 and 2 clinical trials evaluated the safety and efficacy of intravenous delivery of recombinant human ARSA. 13 children with MLD received ARSA at 50, 100 or 200 U/kg every 2 weeks for 1 year. The results revealed that cerebrospinal fluid (CSF) sulfatide levels significantly decreased in the 100 and 200 U/kg groups, but perplexingly increased in the 50 U/kg group. Nevertheless, despite improvements in sulfatide levels, the other efficacy variables, including MRI, and motor and cognitive function, showed either no change or worsening measurements (Í Dali et al., 2021). It is unclear whether intravenously administered ARSA can cross the blood–brain barrier and this could explain the lack of efficacy in the CNS. This is further confounded by a study indicating that different cell types have varying levels of ARSA uptake. In primary cultures of neurons, microglia, astrocytes, and oligodendrocytes treated with ARSA for 24 h, microglia had the highest uptake, whereas oligodendrocytes had less uptake (Kaminski et al., 2021). Thus, peripheral administration of recombinant ARSA has yet to yield promising results.

Another therapeutic approach for MLD is HSC transplant with the goal for donor cells to secrete functional ARSA (Rosenberg et al., 2016). Early work demonstrated that transplanted bone marrow cells expressing green fluorescent protein (GFP) from transgenic mice could be detected in the brains of wildtype recipients (Brazelton et al., 2000; Mezey et al., 2000) and these engrafted cells expressed microglia markers (Priller et al., 2001). In a clinical trial with three MLD patients, patient-derived HSCs were transduced with a lentivirus expressing a functional copy of ARSA, then reinfusion into patients. This led to functional ARSA expression and halting of disease progression (Biffi et al., 2013). Additional HSC transplant studies also report delays in disease progression (van Egmond et al., 2013; Groeschel et al., 2016; van Rappard et al., 2016). Thus, HSC transplantation is a promising approach for MLD treatment.

Peroxisome defects and fatty acid accumulation

Peroxisomes are organelles that play multiple important roles in lipid metabolism and the building of the myelin sheath. First, peroxisomes perform β-oxidation of fatty acids, such as very-long-chain fatty acids (VLCFAs), pristanic acid, long-chain dicarboxylic acids, and some eicosanoids and polyunsaturated fatty acids (PUFAs). Though mitochondria also perform β-oxidation of fatty acids, each organelle displays substrate exclusivity. Second, peroxisomes synthesize plasmalogens, a type of ether-phospholipid found in myelin (Kassmann 2014). Thus, it is not surprising that multiple leukodystrophies can be attributed to mutations in genes encoding peroxisomal proteins.

D-Bifunctional Protein (DBP) deficiency

DBP deficiency is an autosomal recessive disorder caused by mutations to the *HSD17B4* (hydroxysteroid 17-β dehydrogenase 4) gene that encodes DBP. DBP enzyme catalyzes steps in the peroxisomal β-oxidation of fatty acids. Subtypes of this leukodystrophy are classified according to which DBP domains are affected. Type I, the most severe, is caused by mutations in both the hydratase and dehydrogenase domains; Type II is caused by mutations in the hydratase domain; Type III caused by mutations in the dehydrogenase domain (Ferdinandusse et al., 2006b). The patient phenotype includes abnormal facial features, reduced muscle tone, seizures within the first month of life, intellectual and sensory disability, increased plasma VLCFAs, as well as cerebellar atrophy, progressive white matter dystrophy, and demyelination visualized on MRI (van Grunsven et al., 1999; Ferdinandusse et al., 2006a; Yamamoto et al., 2021).

Several DBP deficient animal models have been generated. Zebrafish embryos lacking DBP display lipid accumulation, general growth delays, aberrant axon development, and reduced myelination (Kim et al., 2014). Interestingly, a neuronal-specific knockout mouse developed motor symptoms and cerebellar atrophy, but an oligodendrocyte-specific knockout mouse had no clinical features (Verheijden et al., 2013). These results hint at intricate neuron-glia interactions and highlight the need to untangle the precise mechanisms by which DBP deficiency causes a range of symptoms.

X-linked adrenoleukodystrophy (X-ALD)

X-ALD encompasses four distinct presentations: a severe childhood type (ALD), the milder adrenomyeloneuropathy (AMN), adrenal insufficiency (Addison's Disease) and an asymptomatic form. The childhood form (ALD) typically begins between ages 4–10 with neurological symptoms that include worsening vision, difficulty swallowing, poor coordination, and seizures. Patient death from ALD typically occurs within a few years. Adult-onset AMN is the most common X-ALD and presents with weakness in the legs (paraparesis), changes in cognitive ability, and urogenital tract disorders. Adrenal insufficiency rarely presents with neurological symptoms (Berger, Forss-Petter, and Eichler 2014; Turk et al., 2020).

X-ALD is caused by mutations on the X chromosome in the *ABCD1* gene that encodes adrenoleukodystrophy protein (ALDP). ALDP is a peroxisomal transmembrane protein involved in the transport of VLCFAs into peroxisomes for their subsequent β-oxidation (Wiesinger et al., 2013). ALDP deficiency causes increased plasma VLCFA levels and VLCFA accumulation in the adrenal cortex, testes, and brain regions preceding demyelination (Theda et al., 1992). However, it is unclear whether increasing levels of VLCFA contribute to disease severity. On the one hand, VLCFAs are toxic to cultured rat neurons, oligodendrocytes, and astrocytes, perhaps by altering inner mitochondrial membrane permeability (Hein et al., 2008). On the other hand, plasma VLCFA levels in ALD and AMN are similar, even though the AMN phenotype is far less severe (Moser et al., 1999; Stradomska and Tylki-Szymańska 2009; Stradomska et al., 2020). Moreover, mouse models expressing truncated deficient ALDP exhibit increased VLCFA levels and impaired β-oxidation, but no demyelination in adulthood (Forss-Petter et al., 1997; Kobayashi et al., 1997; Lu et al., 1997). By contrast, *Abcd1*-null mice display late-onset locomotion defects, and axonal degeneration in the spinal cord and sciatic nerve beginning ~15 months of age (Pujol et al., 2002); therefore, this mouse more appropriately models AMN than ALD.

A number of approaches to treating ALD have been investigated. First, Lorenzo's oil, a mixture of two long-chain fatty acids, can reduce plasma levels of VLCFA by competitively inhibiting their synthesis (Sassa et al., 2014). Second, bone marrow transplantation during the early stage of the disease led to reduced plasma VLCFA levels and stabilization or improvement of demyelinating lesions on MRI scans (Shapiro et al., 2000). Finally, patients transfused with HSCs that were transduced *ex vivo* with *ABCD1* cDNA showed a halt in disease progression and even began to express functional ALDP (Eichler et al., 2017). Thus, basic understanding of peroxisome function and disease mechanism has contributed to promising steps towards the treatment of X-ALDs.

Zellweger syndrome spectrum disorders (ZSDs)

ZSDs are a set of neonatal-onset progressive leukodystrophies that include neonatal adrenoleukodystrophy (NALD) and Infantile Refsum disease. In newborns, symptoms include poor muscle tone, trouble with feeding, seizures, renal cysts, liver dysfunction, skeletal abnormalities, and hearing and vision loss. Children with ZSD have varying levels of symptom severity. Infants with severe ZSD rarely survive past the first year of life. Intermediate cases may show progressive hearing and vision loss as well as fatal myelin degeneration during childhood (Steinberg et al., 2003). Non-progressive cases often result in children surviving until school age with the possibility of normal intellect (Poll-The et al., 2004).

ZSDs are classified as peroxisome biogenesis disorders, because they are caused by autosomal recessive mutations in any of at least 12 peroxin (*PEX*) genes that are responsible for peroxisome assembly. The most commonly mutated genes are *PEX1* and *PEX6*. The most severe cases usually result from loss-of-function mutations, such as large deletions and nonsense mutations (Steinberg et al., 2003). The prevailing hypothesis for the cause of ZSD posits that deficiencies in peroxisome assembly can cause dysregulation of fatty acid metabolism and subsequent accumulation of long-chain fatty acids, which may lead to membrane disruption and cellular toxicity. Indeed, when compared to unaffected brains, ZSD brains have higher levels of certain species of lipids (ceramide monohexosides, cholesterol ester, dipalmitoyl phosphatidylcholine and dipalmitoyl phosphatidylserine) (Steinberg et al., 2006; Saitoh et al., 2007). Interestingly, mouse studies indicate that cholesterol homeostasis and peroxisome assembly may be intricately connected. *Lrp1* knockout mice with dysregulation of cholesterol homeostasis display aberrant peroxisome assembly and impaired oligodendrocyte maturation (Lin et al., 2017).

In mouse models, cell-specific knockout of *Pex5* indicates that many cell types contribute to ZSD pathology. Knockout of *Pex5* in both neurons and glia results in demyelination, axonal degeneration, lack of muscle control (ataxia), tremors, and premature death ~6 months of age (Hulshagen et al., 2008). Knockout of *Pex5* only in oligodendrocytes recapitulates these phenotypes, but mice die later, at ~12 months of age (Kassmann et al., 2007). However, knockout of *Pex5* in either neurons or astrocytes results in high VLCFA and reduced plasmalogens levels, but no behavioral phenotypes and unperturbed axonal integrity (Bottelbergs et al., 2010). Together, these studies show that while peroxisome dysfunction in oligodendrocytes can lead to ZSD phenotypes, contributions by peroxisomes in neurons and astrocytes likely play a role in ZSD pathology as well.

Currently, no cure exists for ZSD and treatments focus on managing symptoms (e.g., gastrostomy to provide nutrition, hearing aids for hearing loss). Unfortunately, dietary supplementation of lipids has not been able to affect disease course. An early study found that ZSD patients had very low levels of docosahexaenoic acid

(DHA) in the brain, retina and other tissues (Martinez 2001). However, in a clinical trial, DHA supplementation for 1 year did not improve the visual function of individuals with peroxisome assembly disorders (Paker et al., 2010). Thus, additional therapeutic approaches should be considered for ZSD.

Mitochondrial protein defects and other metabolic deficiencies

Though mitochondria are commonly known as the "powerhouse of the cell" due to their role in the efficient production of adenosine triphosphate (ATP), they also have additional functions, such as regulation of cell death and metabolism of cholesterol. Several leukodystrophies can be attributed to mutations in genes encoding mitochondrial-specific proteins with diverse functions as well as other genes involved in cellular metabolism.

Cerebrotendinous xanthomatosis (CTX)

CTX is an autosomal recessive disorder caused by mutations in the gene encoding the mitochondrial enzyme sterol 27-hydroxylase (CYP27A1). These mutations result in defective versions of this enzyme with low or undetectable enzyme activity (Cali et al., 1991; Carson and De Jesus 2021). CTX is a lipid storage disease characterized by disruptions in bile acid synthesis. Normally, cholesterol is metabolized into a bile acid called chenodeoxycholic acid (CDCA) by CYP27A1. As a result of reduced feedback (i.e., lack of CDCA), cholesterol synthesis is upregulated, resulting in aberrant accumulation of the byproduct cholestanol in various tissues and organs (Serizawa et al., 1982; Carson and De Jesus 2021).

Sites of localized cholestanol accumulation, such as the brain, eyes, arteries, and tendons, reflect the clinical manifestation of CTX. Around puberty, CTX patients begin to show neurological signs and symptoms, such as cerebellar ataxia, pseudobulbar affect, and brain atrophy (Carson and De Jesus 2021). Furthermore, MRI scans revealed white matter atrophy in the dentate nuclei (Vanrietvelde et al., 2000; Chang et al., 2010). Other clinical features of CTX include cataracts, atherosclerosis, and fatty tumors on tendons and muscles. As the disease progresses, patients can develop paralysis and dementia. Eventually cholestanol deposits affect the brainstem and patient death occurs during mid-to-late adulthood from cardiac arrest (Carson and De Jesus 2021).

Many studies support the mechanistic link between CYP27A1 deficiency and cholestanol accumulation in the brain. An early study of postmortem CTX brains revealed that cholestanol preferentially accumulates in myelin fractions while healthy brain fractions had no detectable cholestanol (Stahl, Sumi, and Swanson 1971). Another study found that feeding mice 1% cholestanol led to significant accumulation of cholestanol in the cerebellum, suggesting that peripheral cholestanol can cross the blood–brain barrier (Byun et al., 1988). *Cyp27a1* knockout mice, which have increased cholesterol synthesis and a two-fold increase in cholestanol levels in peripheral tissues, display a striking 12-fold increase in cholestanol levels in the cerebellum, indicating that cholestanol preferentially accumulates in the brain (Båvner et al., 2010). Indeed, a recent RNA-seq database from mouse brains indicates that *Cyp27a1* mRNA is more highly enriched in oligodendrocytes than other brain cell types (e.g., neurons, astrocytes, microglia/macrophages) (Zhang et al., 2014). Thus, these studies suggest that oligodendrocyte-specific CYP27A1 activity and tissue-specific cholestanol accumulation in the brain play important roles in CTX.

CTX is currently treated through dietary supplementation therapy. CDCA supplementation lowers the accumulation of cholestanol in both plasma and CSF, likely by exerting negative feedback on cholesterol synthesis, and has led to improvements in many clinical symptoms, including cataracts, dementia, neuropathy, and other neurological symptoms (Salen, Meriwether, and Nicolau 1975; Berginer, Salen, and Shefer 1984; Duell et al., 2018). This treatment has shown success when implemented before the age of 25 (Yahalom et al., 2013). However, CDCA is hepatotoxic, prompting some studies to suggest cholic acid as an alternative treatment for patients who tolerate CDCA poorly (Pierre et al., 2008; Koyama et al., 2021). In addition, a recent study in a mouse model of CTX used an AAV to express *CYP27A1* in the liver and this reestablished bile acid metabolism and restored normal plasma bile acid levels (Lumbreras et al., 2021). Thus, promising steps have been made in the management and treatment of this leukodystrophy, though more translational and clinical studies are needed.

Hypomyelination with spondylometaphyseal dysplasia (H-SMD)

H-SMD is a disorder characterized by abnormal growth and development of the vertebrae and bone growth plates (metaphyses), as well as significant lack of myelin on MRI. Beginning between 1 and 2 years of age, patients may start to lose the ability to walk, which may slowly progress into motor deterioration, spasticity and tremors. Other symptoms include mild cognitive impairment, bone and joint issues such as scoliosis, and visual symptoms such as involuntary eye movement (nystagmus) (Kettwig et al., 2015; Miyake et al., 2017).

Multiple studies have found mutations in the *AIFM1* (apoptosis-inducing factor, mitochondria-associated 1) gene in H-SMD. AIFM1 has dual functions: 1) to regulate the assembly of the mitochondrial machinery that participate in oxidative phosphorylation (Vahsen et al., 2004), and 2) to act as a

signal for cell death when it translocates to the nucleus (Susin et al., 1999). An early study discovered mutations in affected sons born to asymptomatic mothers, indicative of X-linked recessive inheritance (Bieganski, Dawydzik, and Kozlowski 1999). Most H-SMD mutations are missense mutations localized to a 70-base-pair region in exon seven of *AIFM1*. However, some cases involve intronic mutations and synonymous variant mutation (a codon substitution that doesn't change the encoded amino acid) (Mierzewska et al., 2017; Edgerley et al., 2021). Conflicting evidence exists on whether *AIFM1* mutations in H-SMD cause loss of function. In one study, patient osteoblast cells displayed significantly reduced *Aifm1* mRNA and protein levels, which the authors suggest could be due to bioinformatically predicted mRNA splicing disruptions (Miyake et al., 2017). However, comparisons of four mutant AIFM1 proteins showed that the extent of structural alterations and changes in redox activity vary by mutation (Sevrioukova 2016), which indicates that only some AIFM1 mutations lead to loss of function. Hence, the molecular mechanisms underlying hypomyelination in H-SMD are still unclear.

2-Hydroxyglutaric aciduria (2HGA)

2HGA is an autosomal recessive neurometabolic disorder characterized by the accumulation of 2-hydroxyglutarate (2-HG). 2-HG is a side product of nonspecific Krebs Cycle enzyme activity and is closely related to the Krebs Cycle intermediate α-ketoglutarate (Rzem et al., 2007). There are three forms of 2HGA; each form is associated with mutations in specific mitochondrial genes and named according to which 2-HG enantiomer (L or D) is affected.

First, L-2-HGA (LHGA) primarily affects the cerebellum, presenting with ataxia, seizures, and an enlarged head (macrocephaly). LHGA is associated with mutations in the *L2HGDH* gene, which codes for a mitochondrial enzyme that converts L-2-HG into α-ketoglutarate. A deficiency in this enzyme causes increased levels of L-2-HG in urine, plasma and CSF (Barth et al., 1993; Rzem et al., 2004).

Second, D-2-HGA (DHGA) falls into two categories. Type I is less severe with later onset and associated with mutations in the *D2HGDH* gene. Type II is more severe with earlier onset and can present with heart enlargement (cardiomyopathy). Unlike other 2HGA's, Type II D-2-HGA is uniquely inherited in an autosomal dominant pattern and associated with mutations in the *IHD2* gene (Struys et al., 2005; Kranendijk et al., 2010).

Finally, D,L-2-HGA is caused by mutations in the *SLC25A1* gene, which encodes a protein that transports citrate across the inner mitochondrial membrane. In cultured patient cells, lack of SLC25A1 activity results in the increased presence of both D-2-HG and L-2-HG (Nota et al., 2013).

The mechanism for 2-HG accumulation leading to symptoms is likely due to two types of toxicity–oxidative damage and excitotoxicity. In primary neuron cultures, both L-2-HG and D-2-HG induce a number of metabolic effects, such as inhibiting mitochondrial creatine kinase and ATP synthase (Kölker et al., 2002; da Silva et al., 2003). In rats, intracerebroventricular administration of D-2-HG resulted in increased oxidative stress and upregulation of markers for reactive astrocytes and microglia (Ribeiro et al., 2021). Indeed, in *L2HGDH* knockout mice, vacuolar lesions appeared in oligodendrocyte and astrocyte cytoplasm as well as in myelin tracts in the cortex and corpus callosum (Rzem et al., 2015). In addition, 2-HG shares chemical structure similarity with the excitatory transmitter glutamate. D-2-HG treatment to cultured neurons led to excitotoxic cell damage (Kölker et al., 2002). In rats, a NMDA glutamate receptor antagonist administration prevented the formation of some oxidative species (Ribeiro et al., 2021). Thus, signs of both excitotoxicity and oxidative damage are observed in cell and animal models of 2HGA and these two types of damage might synergistically exacerbate symptoms in 2HGA.

Treatment of 2HGA primarily focuses on managing symptoms, especially seizures when they are present. One case study successfully managed patient tremors and reduced urinary 2-HG by supplementing with FAD and carnitine (Samuraki et al., 2008). Another found similar effects with riboflavin (Vitamin B2) supplementation (Yilmaz 2009). However, the mechanism of action for these supplements is unclear. Thus, further research is necessary to uncover effective treatments for 2HGA.

Canavan disease

Canavan disease is a progressive, autosomal recessive leukodystrophy. It typically affects infants ~3 months of age, who begin to develop symptoms that include lethargy, poor vision, little-to-no motor development, seizures, and other progressive neurological defects. Symptoms continue to worsen until the child dies ~10 years of age (Bokhari et al., 2022).

Canavan disease results from a mutation in the gene encoding aspartoacylase (ASPA) (Bokhari et al., 2022). ASPA is an oligodendrocyte-enriched enzyme that hydrolyzes *N*-acetyl L-aspartic acid (NAA), which is primarily synthesized in neurons, into acetate and aspartate. Canavan disease patients are unable to catabolize NAA, which progressively accumulates with age in oligodendrocytes. Studies in rodent oligodendrocytes indicate that the products of NAA hydrolysis are important for oligodendrocyte survival and differentiation (Kumar et al., 2009). Indeed, acetate, one of the products of ASPA, is converted to acetyl-CoA, which is an important building block in lipid synthesis. The other product of ASPA, aspartate, can enter cell metabolic pathways (I Amaral et al., 2017), promote oligodendrocyte precursor cell (OPC) differentiation and transcription of myelin basic protein (MBP) (Chakraborty et al., 2001), and may stimulate

myelination and post-injury remyelination through glutamate receptor signaling (de Rosa et al., 2019). In a mouse model for Canavan disease, impaired NAA catabolism results in reduced myelin formation and spongy white matter degeneration (Hoshino and Kubota 2014). Therefore, the function of ASPA in NAA catabolism is important for oligodendrocyte health.

Currently, no treatments exist for Canavan disease, making this a fatal disorder, but recent research has targeted dietary supplementation as well as viral gene delivery. Standard of care is largely palliative and includes gastrostomy tubes that deliver nutrients directly to the stomach, anti-seizure medications, and physical therapy to improve posture and to reduce pressure ulcers (Bokhari et al., 2022). Dietary supplementation with glyceryl triacetate has been proposed to address low acetate levels in Canavan disease. Though this was successful in a mouse model, it has yet to cause improvement in human patients (Segel et al., 2011). Recently, researchers engineered a modified AAV with a capsid that has preferential tropism toward oligodendrocytes to express ASPA. Intracerebroventricular injections of this virus in a mouse model of Canavan disease rescued ASPA activity and motor function (Francis et al., 2021). Thus, ASPA replacement therapy may be a feasible therapeutic approach for human patients.

Cytoskeletal proteins

Cytoskeletal proteins, including microtubules, actin, septin, and intermediate filaments, form the cellular structure of glia. In oligodendrocytes, microtubules mediate long-distance transport and are found in processes that contact axons, as well as inside myelin sheaths (Weigel et al., 2021). Actin dynamics are important for the wrapping of myelin sheaths around axons (Nawaz et al., 2009; Zuchero et al., 2015). Septins also play an important role in oligodendrocyte development (Patzig et al., 2016). In astrocytes, the intermediate filament GFAP (glial fibrillary acidic protein) can play important roles in injury response and can be affected in leukodystrophy.

Alexander disease (AxD)

AxD is a progressive demyelinating leukodystrophy. Children often present with symptoms (e.g., megalencephaly, limb stiffness or rigidity, seizures, and developmental delays) by 2 years of age and have an average life expectancy of 14–25 years (Prust et al., 2011). AxD is a rare disease with an estimated 5-years prevalence of one in 2.7 million in a study in Japan (Yoshida et al., 2011). AxD is caused by autosomal dominant mutations in the *GFAP* gene. To date, over 100 missense variants in coding regions are associated with AxD (Saito et al., 2018). However, most AxD mutations are not inherited, but, instead, are *de novo* mutations (Li et al., 2006).

Many lines of evidence indicate that protein aggregation is a profound component in the AxD pathology due to the striking accumulation of Rosenthal fibers consisting of GFAP. GFAP, an intermediate filament protein, is a major component of astrocytic processes and becomes upregulated in reactive astrocytes responding to injury (Wilhelmsson et al., 2004). Overexpression of human wildtype *GFAP* in mice recapitulated Rosenthal fiber pathology and was lethal (Messing et al., 1998), indicating that GFAP protein levels are important in AxD pathology. Recent research suggests that certain GFAP isoforms or GFAP containing PTMs may be more prone to aggregation. For example, minor isoforms of GFAP (e.g., delta and kappa) preferentially aggregate in Rosenthal fibers (Lin et al., 2021). In addition, severe AxD patients selectively contain GFAP phosphorylated at Ser13, which facilitates GFAP aggregation in patient-derived iPSCs (Battaglia et al., 2019). Thus, many considerations, such as mutations, isoform specificity, and PTMs, may affect GFAP aggregation in AxD.

Though most treatment options for AxD are based on symptom management, researchers are exploring new approaches, such as ASOs to decrease GFAP expression. This approach is supported by results showing that mice lacking GFAP have very mild defects and therefore decreasing GFAP protein levels is unlikely to produce a toxic loss of function phenotype. In experiments in a mutant *GFAP* (R236H) mouse line, ASOs targeted against the 3′UTR of *Gfap* were injected intracerebroventricularly. By 2 weeks after injection, this resulted in less *Gfap* mRNA, near elimination of GFAP protein, fewer Rosenthal fibers, and improved body condition scores (Hagemann et al., 2018). Thus, GFAP-targeting ASOs are a viable therapeutic approach for AxD and additional follow-up studies should be performed.

Autosomal dominant leukodystrophy (ADLD) with autonomic disease

ADLD is an adult-onset leukodystrophy characterized by spasticity, ataxia, and autonomic issues, such as dysregulation of blood pressure and body temperature, and loss of bladder/bowel control (Zerbin-Rudin and Peiffer 1964; Eldridge et al., 1984). Patients display white matter lesions before the onset of symptoms, typically in the fifth decade, which progress over the course of 10–20 years (Finnsson et al., 2015). Most cases are autosomal dominant (Schuster et al., 2011) and caused by duplication of the *LMNB1* gene that encodes lamin B1 (Padiath et al., 2006; Brussino et al., 2009).

Lamins are intermediate filament proteins that form the mesh-like network of the nuclear lamina, which lines the inner nucleoplasmic side of the nuclear envelope. Mutations in lamin A can cause premature aging (progeria), muscular dystrophy, cardiomyopathy, and peripheral neuropathy (Shin

and Worman 2022). Patient fibroblasts overexpress lamin B1, which leads to increased nuclear rigidity, misshapen nuclei, and possible changes in nuclear signaling (Ferrera et al., 2014). Furthermore, a glioma cell line overexpressing *LMNB1* also has misshapen nuclei with many aberrant layers of nuclear membranes (Ratti et al., 2021). Mouse models have shown that both cell-autonomous and non-cell-autonomous effects occur. Mice globally overexpressing lamin B1 show downregulation of PLP1 (Heng et al., 2013). Mice with oligodendrocyte-specific overexpression of lamin B1 show astrogliosis, microglia infiltration, decreased expression of genes that regulate lipid synthesis in oligodendrocytes, age-dependent demyelination (Rolyan et al., 2015), and motor dysfunction, but no autonomic phenotype (Lo Martire et al., 2018).

Recently, a drug screen in ADLD fibroblasts identified an inhibitor of heat shock protein 90 as a possible modulator of lamin B1 expression (Giorgio et al., 2021). Thus, therapeutic strategies for ADLD treatment are beginning to be identified.

Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)

H-ABC is a leukodystrophy inherited in an autosomal dominant manner. Beginning in infancy to early childhood, patients present with movement and speech abnormalities, including ataxia and spasticity, and may never develop fine motor skills. MRI studies have revealed atrophy of the basal ganglia, putamen, and cerebellum, and histology studies have confirmed hypomyelination (van der Knaap et al., 2002; van der Knaap et al., 2007).

H-ABC is caused by mutations in the *TUBB4A* gene which codes for β-tubulin, a major structural protein that dimerizes with α-tubulin to form heterodimers that are the building blocks of the microtubule cytoskeleton. Compared to other β-tubulin genes, *TUBB4A* is highly expressed by oligodendrocytes and its expression increases postnatally, consistent with a role in myelination (Zhang et al., 2014; Park et al., 2021). In oligodendrocytes, microtubules play important roles in building the structure of oligodendrocyte branches and myelin sheaths (Fu et al., 2019) as well as in transporting mRNA and other cargos (Carson et al., 1997; Herbert et al., 2017). Loss of the microtubule nucleation protein TPPP (tubulin polymerization promoting protein) results in shorter and thinner myelin sheaths as well as behavioral defects in motor coordination (Fu et al., 2019) and in innate and memory-dependent fear responses (Nguyen et al., 2020).

H-ABC can be caused by many different point mutations in *TUBB4A*. *TUBB4A* mutations can affect microtubule stability and growth, and interfere with motor protein binding to microtubules (Vulinovic et al., 2018). One example is a *de novo* point mutation (D249N) at a highly conserved aspartic acid residue that is located on the dimer interface between α-tubulin and β-tubulin and is important for heterodimer formation (Simons et al., 2013). Indeed, a mouse model of the D249N mutation recapitulates disease-like motor dysfunction and hypomyelination and indicates that both neurons and oligodendrocytes are affected. Cultured cerebellar granule neurons expressing this mutation displayed a variety of morphological defects, including shorter axons, fewer dendrites, and less dendritic branching. Similarly, in the differentiated oligodendrocyte-like cell line Oli-neu, expression of this mutation resulted in lack of complex branching morphology (Curiel et al., 2017). Furthermore, this mouse model also displays fewer mature oligodendrocytes, striatal neurons, and cerebellar granular neurons, as well as more caspase-3-positive apoptotic OPCs and cerebellar granular neurons (Sase et al., 2020).

There are currently no treatments for H-ABC, though rehabilitation and other management strategies are often utilized (Rossi et al., 2018). However, *Tubb4a* knockout mice do not exhibit any deleterious effects (Sase et al., 2020), indicating that H-ABC may be an ideal target for ASO therapy that aims to decrease expression of mutant *TUBB4A* mRNAs.

Transcription defects

4H leukodystrophy

4H leukodystrophy is so named due to its alliterative primary clinical manifestations: hypomyelination, hypodontia, and hypogonadotropic hypogonadism (Bernard and Vanderver 1993). This leukodystrophy is also known as RNA polymerase III (*POLR3*)-related leukodystrophy due to mutations in *POLR3A*, *POLR3B*, and *POLR3K genes* (Bernard et al., 2011; Tétreault et al., 2011; Dorboz et al., 2018). The autosomal recessive inheritance pattern of 4H leukodystrophy requires biallelic expression of the pathogenic variant (e.g., homozygous or compound heterozygous mutations). Consistent with this inheritance pattern, a homozygous conditional knock-in mice expressing mutant *Polr3a* under the *Olig2* promoter displays hypomyelination as well as a range of cognitive, sensory, and sensorimotor defects (Merheb et al., 2021).

Despite the existence of a mouse model for 4H leukodystrophy, the mechanism for how *POLR3* mutations cause hypomyelination remains unclear. Multiple hypotheses have emerged in the literature. First, *POLR3* mutations may lead to tRNA deficits that impact global translation. Indeed, POLR3 transcribes more than 100 tRNA genes (Goffeau et al., 1996), and mutations in *POLR3* result in decreased tRNA transcription and increased tRNA post-translational modifications (Arimbasseri et al., 2015). In addition,

oligodendrocytes may be more vulnerable to tRNA deficits due to their heavy reliance on local translation. For example, MBP is locally translated within the myelin sheath and many mRNAs are found locally in myelin fractions by RNA-seq (Thakurela et al., 2016; Herbert et al., 2017; Meservey, Topkar, and Fu 2021). Second, in a human oligodendrocyte-like cell line, *POLR3* mutation can impair production of a non-coding RNA (ncRNA) that may be important for myelin formation and expression of myelin transcripts like *MBP* mRNA (Choquet et al., 2019). However, it is not clear which downstream RNAs could be feasible therapeutic targets for restoring myelination. Thus, future research elucidating the cellular pathology of oligodendrocytes in 4H leukodystrophy models will be important for uncovering logical therapeutic approaches.

NKX6-2-related spastic ataxia with hypomyelination (SPAX8)

De novo mutations in the *NKX6-2* gene are associated with spastic cerebellar ataxia that presents with hypomyelination on MRI. While neonatal-onset SPAX8 is associated with global delays, childhood-onset SPAX8 typically results in only motor delays (Chelban et al., 2017; 2020). NKX6-2 is a homeobox transcription factor that is important for oligodendrocyte differentiation and myelination in the hindbrain and spinal cord (Vallstedt, Klos, and Ericson 2005; Cai et al., 2010). Indeed, transcription factors NKX6-2, SOX10, and OLIG2 can be used to reprogram human fibroblasts into O4-positive OPC-like cells that can differentiate into MBP-positive oligodendrocyte-like cells (Ehrlich et al., 2017). Specifically, NKX6-2 can regulate expression of the microtubule severing protein stathmin and paranodal cell adhesion molecules neurofascin and contactin (Southwood et al., 2004), which highlight a role for NKX6-2 in regulating oligodendrocyte cytoskeleton and paranodal structures. Currently, no animal model for this disease exists, though one may prove useful to determine disease mechanisms and investigate treatments.

Waardenburg-hirschsprung disease (WS4)

Mutations in the gene encoding the transcription factor SOX10 are associated with WS4 (Pingault et al., 1998), which is a subtype of a family of Waardenburg syndromes. WS4 is characterized by deafness, reduced pigmentation, skull and intestine abnormalities, and reduced myelin production by both oligodendrocytes and Schwann cells (Inoue et al., 1999; Inoue et al., 2002). In addition to its roles in the development of the colon and of melanocytes, SOX10 is important for the development of both CNS and PNS glia. *In vivo*, *SOX10*-null mice show impaired development of Schwann cells and other PNS glia (Britsch et al., 2001) and diminished oligodendrocyte differentiation in the CNS (Stolt et al., 2002).

Biochemical studies indicate that mutant SOX10 acquires a toxic gain of function. Though many *SOX10* mutations result in truncated mRNA transcripts, they are not downregulated by the nonsense-mediated decay pathway. In fact, mutant SOX10 proteins surprisingly outcompete wildtype SOX10 for DNA binding when co-expressed in glioblastoma cells (Inoue et al., 2004). Thus, this dominant-negative mechanism indicates that WS4 may be best therapeutically targeted by decreasing mutant *SOX10* mRNA expression or decreasing mutant SOX10 protein activity.

Translation machinery defects

tRNA synthetase-related leukodystrophies

Mutations in genes that encode components of the tRNA multisynthetase complex (DARS1, RARS1, EPRS1) are implicated in hypomyelination. These mutations cause a spectrum of clinical phenotypes, from severe seizures and brain atrophy within the first 3 months of age, to mild ataxia and cognitive deficits beginning at 1 year old or later (Taft et al., 2013; Mendes et al., 2020).

tRNA synthetases function to join the proper amino acid to each tRNA molecule. Though it is unclear how mutations in this mechanism cause hypomyelination, studies have shown reduced EPRS protein levels and activity in patients with *EPRS* mutations (Mendes et al., 2018). For *RARS*, the most common mutation is associated with mild disease, while truncation mutations and mutations located in the enzymatic domain are associated with severe disease (Mendes et al., 2020). These findings suggest that disruption in tRNA complex assembly, reduced tRNA synthetase activity, and translation disruption result in insufficient myelination in the developing brain.

Researchers have questioned whether tRNA synthetase mutations cause hypomyelination via oligodendrocyte dysfunction or neuron dysfunction (Mendes et al., 2020; Wolf, ffrench-Constant et al., 2018). Indeed, mutations in tRNA synthetase genes *VARS* (Friedman et al., 2019; Siekierska et al., 2019) and *AIMP2* (Shukla et al., 2018) have been implicated in neuronal disorders with shared phenotypes in severely affected patients, such as cerebral atrophy and seizures. Thus, more research to dissect the cell-specific effects of mutations in tRNA synthetase machinery is important for better mechanistic understanding of these leukodystrophies.

Vanishing white matter (VWM) disease or childhood ataxia and cerebral hypomyelination (CACH)

VWM disease, also known as CACH, is one of the more prevalent leukodystrophies, with an estimated incidence of one in 80,000–100,000 live births (van der Knaap et al., 2022). VWM is highly variable in age of onset, severity, and progression. In some cases, children exhibit normal early development, whereas others experience ataxia, and delayed speech and cognitive milestones (Schiffmann et al., 1994; van der Knaap et al., 2003). MRI imaging of VWM patients shows distinct patterns of diffuse white matter signal (Schiffmann et al., 1994; van der Knaap et al., 1997). These signs of hypomyelination are present even prior to symptom onset (Schiffmann et al., 2003). As white matter MRI signals decrease and white matter tract deterioration progresses, neurological symptoms worsen. Unfortunately, this hypomyelination can become so severe that it can result in death around the first or second decade of life (van der Knaap et al., 2022).

A number of studies in postmortem brains have described the histopathological characteristics of VWM. First, one study observed oligodendrocytes with "foamy" cytoplasm, which was hypothesized to indicate abnormal glycosylation (Fogli et al., 2002). Second, a thorough literature review of VWM brain pathology studies highlighted a pattern of disproportionately high number of OPCs compared to mature oligodendrocytes. Lastly, oligodendrocytes in VWM brains have abnormal mitochondrial morphology (Wong et al., 2000), and increased rates of apoptosis (Brück et al., 2001; Van Haren et al., 2004). Thus, these histology results indicate that oligodendrocytes in VWM have maturation defects and cell health issues.

Genetics studies of VWM have revealed mutations in the genes encoding the five subunits of the eukaryotic initiation factor 2B (*EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5*). EIF2B regulates the first stage of translation initiation: the recruitment of ribosomes and proper identification of the start codon (Bogorad et al., 2018). While mutations can occur in any of the five subunits, 80% are missense mutations occuring in gene encoding the ε-subunit (*EIF2B5*) (van der Knaap et al., 2002). Since eIF2B is a guanine nucleotide exchange factor, *EIF2B* mutants display reduced GTP hydrolysis due to conformational changes, and therefore may adversely impact global mRNA translation (Fogli et al., 2004). These changes can trigger downstream activation of the integrated stress response, a system that regulates protein translation and folding in response to both intracellular and extracellular stress (van der Knaap et al., 2022).

Studies to elucidate the cellular mechanisms of VWM have uncovered both cell-autonomous and non-cell-autonomous mechanisms. Mutant-*Eif2b5* mice exhibit delayed white matter development (Geva et al., 2010), and purified OPCs cultured from these mice had mitochondrial defects, as well as impaired differentiation and morphology (Herrero, Mandelboum, and Elroy-Stein 2019). However, in a co-culture system using glial cells isolated from wildtype and mutant-*Eif2b5* mice, mutant astrocytes secreted factors that inhibited wildtype OPCs from differentiating into mature oligodendrocytes (Dooves et al., 2016). Thus hypomyelination in VWM likely involves defects in both OPCs and astrocytes.

Although there are no treatment options available for VWM, a recent study performed an ambitious small molecule drug screen. The authors conducted a screen of 2400 FDA-approved drugs using iPSC-derived astrocytes from a patient harboring mutations in two subunits of eIF2B. They identified 113 anti-inflammatory drugs with cytoprotective effects, including ursodiol, berberine, deflazacort, and zileuton. Of these, ursodiol rescued oxidative stress and mitochondrial dysfunction in VWM patient iPSC-derived astrocytes (Ng et al., 2020). However, for all the drugs identified, further *in vivo* animal testing is needed prior to moving to any clinical studies.

Cell junction defects

Megalencephalic leukoencephalopathy with subcortical cysts (MLC)

MLC is an autosomal-recessive vacuolating leukodystrophy that is also known as van der Knaap disease, after the pediatric neurologist who first described the condition (Bosch and Estévez 2021). MLC is characterized by prominent macrocephaly that progressively develops within the first year of life (van der Knaap et al., 2012). Due to the macrocephaly, children exhibit difficulty walking, while gradual onset of ataxia and spasticity further contribute to gross motor delays and difficulties. Typically, children have normal cognition, though mild mental deterioration can occur later during development. Computed tomography (CT) and MRI scans revealed that MLC patients have mild-to-severe swelling or edema, vacuolization of white matter, and subcortical cysts (van der Knaap et al., 1995; van der Knaap et al., 2002; Dash, Raj, and Sahu 2015).

MLC can be categorized into different subtypes based on the specific genes mutated. MLC1 subtype results from a missense mutation in the *MLC1* gene. *Mlc1* mRNA is expressed exclusively by astrocytes, but not by oligodendrocytes (Schmitt et al., 2003; Dubey et al., 2015). *MLC1* encodes a transmembrane protein (Leegwater et al., 2001) that participates in osmoregulation by astrocytes. In astrocytoma cells, wildtype MLC1 localizes to the plasma membrane in a complex with aquaporin, the potassium channel Kir4.1, and the TRPV4 channel. By contrast, mutant MLC1 localizes intracellularly and this disrupts osmolarity homeostasis (Lanciotti et al., 2012). Consistent with this, a study in HeLa cells demonstrated that mutant MLC1 protein was retained in the ER (Duarri et al., 2008), likely due to protein misfolding. Both mouse and zebrafish models recapitulate human phenotypes, including macrocephaly and edema (Sirisi

et al., 2014). A *Mlc1*-null mouse model unveiled morphologically abnormal astrocytes present in the swollen white matter. These astrocytes express lower levels of the adhesion molecule GLIALCAM, which is also known as HEPACAM (hepatocyte cell adhesion molecule). No neuronal or oligodendrocyte defects were observed, because MLC-null axons were fully myelinated in EMs and oligodendrocyte-specific transcripts were expressed at normal levels (Dubey et al., 2015).

MLC2a subtype is caused by mutations in the *HEPACAM* gene, which encodes a cell adhesion molecule in the immunoglobulin family (Sirisi et al., 2014). *Hepacam* mRNA is present in both astrocytes and oligodendrocytes (Hoegg-Beiler et al., 2014; Bugiani et al., 2017). Recent work indicates that HEPACAM plays a crucial role in gap junction coupling between adjacent astrocytes (Baldwin et al., 2021). Mutations in this gene have been shown to cause protein mislocalization (Elorza-Vidal et al., 2020).

MLC1 and HEPACAM likely function in a complex to mediate cell-cell interactions. In mouse models, MLC1 and HEPACAM mutually affect each other's localization. Knockout of *Hepacam* affects *Mlc1* expression and MLC protein localization (Hoegg-Beiler et al., 2014; Bugiani et al., 2017), while knockout of *Mlc1* decreases HEPACAM levels and leads to its mislocalization (Dubey et al., 2015). A recent study showed that astrocytes in *Mlc1* knockout mice are more branched, but their endfeet make fewer contacts with vasculature. In addition, *Mlc1* knockout mice have high incidence of neurons aberrantly contacting vasculature (Gilbert et al., 2021). These defects in gliovascular coupling may underlie the fluid buildup and macrocephaly observed in MLC patients (van der Knaap et al., 2012; Dubey et al., 2015).

Although there are no treatments for MLC, recent work has provided some preclinical insight into viral replacement therapy. Using *Mlc1* knockout mice, researchers demonstrated that cerebellar subarachnoid administration of an AAV expressing human *MLC1* under a GFAP promoter increased MLC1 protein expression in the cerebellum and decreased white matter vacuolation in a dose-dependent manner (Bosch and Estévez 2021). This study indicates that replacement therapy is a feasible therapeutic approach for MLC.

Oculodentodigital dysplasia (ODDD)

ODDD is a multisystem syndrome whose symptoms present in three major categories: ocular, dental, and digital. Ocular symptoms include very small corneas (microcornea), eyes that do not look in the same direction (strabismus), and fluid buildup in the eye (glaucoma). Dental symptoms include abnormally small teeth, defective enamel, and a thickened lower jaw. Digital symptoms usually present as webbing between the fourth and fifth fingers and third, fourth, and fifth toes (syndactyly) (Traboulsi, Faris, and Der Kaloustian 1986). The neurological symptoms of ODDD are wide-ranging and include lower limb spasticity or paralysis (paraparesis), ataxia, bladder disturbances, and seizures. MRI imaging has shown decreased white matter intensity in the CNS, which likely contributes to motor symptoms in ODDD (Loddenkemper et al., 2002).

ODDD is caused by mutations in *GJA1* (also known as *Cx43*), which encodes the gap junction α-1 protein (connexin 43). Mutations causing ODDD are typically inherited in an autosomal-dominant fashion (Paznekas et al., 2003). One screen of 17 families found 16 unique missense mutations and one codon duplication; these mutations were present only in affected individuals, indicating an autosomal-dominant pattern of inheritance (Paznekas et al., 2003). However, there are also documented cases of autosomal-recessive inheritance (Joss et al., 2008) and novel *de novo* mutations (Choi et al., 2018; Pace et al., 2019). Thus, ODDD displays a variety of inheritance patterns.

Cx43 is one protein component comprising gap junctions between astrocytes and other glial cells (Orthmann-Murphy et al., 2007). A mouse model deficient in the *Cx43* and *Cx30* genes had a complete loss of astrocyte–astrocyte gap junctions, which reduced the rate of potassium clearance and increased the probability of seizure-like activity in hippocampal neurons *in vitro* (Wallraff et al., 2006). Cx43 has also been shown to be involved in astrocyte–oligodendrocyte gap junctions (Nagy et al., 2003). Double knockout mice with astrocyte-specific deletion of *Cx43* and global deletion of *Cx30* displayed demyelination in multiple regions (corpus callosum, cerebellum, corticospinal and other tracts) and edema within myelin. These mice also performed worse on the rotarod motor coordination assay, which is consistent with ODDD neurological motor symptoms (Lutz et al., 2009).

Treatments for ODDD are symptomatic and supportive. For instance, an eye patch over the stronger eye can correct strabismus, corrective surgery can address defects in the fingers and toes, and antispastic medication can ameliorate neurological symptoms (Shinya et al., 2021). Thus, additional basic research is needed to elucidate the role of gap junctions in astrocytes and oligodendrocytes.

Connexin-47-related Pelizaeus-Merzbacher-like disease (PMLD)

PMLD presents with similar symptoms as Pelizaeus–Merzbacher Disease (PMD), including nystagmus, spasticity, head tremors, poor muscle tone, and progressive spasticity, but PMLD symptoms are less severe than PMD symptoms. PMLD is autosomal recessive and associated with mutations in connexin 47 (Cx47), which also known as connexin 46.6, gap junction protein γ2 (GJC2), and gap junction protein α12 (GJA12) (Uhlenberg et al., 2004; Bilir et al., 2013; Abrams et al., 2014; Owczarek-Lipska et al., 2019). Many patients present with biallelic (compound heterozygous) mutations in combination (Owczarek-Lipska et al., 2019).

Whether mutant Cx47 causes leukodystrophy via loss or gain of function remains unclear. In one study that treated HeLa cells with mutant Cx47, gap junction formation was normal, but electrical coupling was disrupted (Abrams et al., 2014). In a bulk RNA-seq transcriptome, Cx47 is expressed very highly and specifically in oligodendrocytes (Zhang et al., 2014). However, a *Cx47* knockout mouse did not display any clinical symptoms (Odermatt et al., 2003), which hints that *Cx47* mutations in PMLD patients may exert a toxic gain-of-function effect. Thus, elucidation of PMLD disease mechanisms is needed to lay the important groundwork for the road toward translational studies.

Myelin structural protein defects

Proteomic analysis of human myelin shows that the protein composition of myelin largely consists of two proteins - PLP1 (45%) and MBP (28%). Additional myelin proteins include CNP (4.5%), MOG (0.8%), MAG (0.3%), MOBP (0.1%), and others (Gargareta et al., 2022). Many of these proteins play a role in compaction, the formation of efficient myelin insulation by bringing together adjacent layers of membrane. Compaction happens both intracellularly (between membranes from the same wrap) and extracellularly (between membranes from different but juxtaposed wraps). While intracellular compaction largely relies on MBP, extracellular compaction relies on PLP. Additional transmembrane proteins, like MAG and MOG, are found in non-compact regions of the myelin sheath (Raasakka and Kursula 2020).

CNP-related hypomyelinating leukodystrophy

A recent study of multiple members of a consanguineous family found a homozygous mutation in the *CNP* (2′,3′-cyclic nucleotide-3′-phosphodiesterase) gene. Symptoms began ~1 year of age and include arrest then regression in motor skill development, dystonia, irritability, microcephaly, scoliosis and hirsutism. MRI imaging showed hypomyelination, especially of periventricular and subcortical white matter. Ultimately these children passed away ~five to eight years of age. This mutant CNP is unstable and has barely detectable protein levels by Western blot of patient fibroblast lysates (Al-Abdi et al., 2020). CNP plays an important role in establishment of the cytoplasmic channels in myelin sheaths that allow transport between outer to inner layers of myelin (Snaidero et al., 2017).

MAG-related PMLD

Another gene associated with PMLD is *MAG* (myelin-associated glycoprotein). Three siblings from a consanguineous family presented with infantile-onset PMLD that later in adulthood developed into additional symptoms of mental retardation, dysarthria, optic atrophy, and peripheral neuropathy. They share a homozygous missense mutation in *MAG* that results in mutant MAG retention in the ER, misshapen paranodal junctions, and thin myelin sheaths (Lossos et al., 2015).

MAL-related leukodystrophy

A recent report found that a patient presenting with PMLD had a novel missense mutation (A109D) in the gene encoding myelin and lymphocyte protein (MAL) (Elpidorou et al., 2022). MAL is a four-pass transmembrane protein that is important for the structure of paranodal loops, which are located at the ends of myelin sheaths and flank the nodes of Ranvier. In *Mal* knockout mice, paranodal loops are aberrantly oriented facing away from the axon (Schaeren-Wimers et al., 2004). Experiments in cultured kidney cells demonstrated that mutant MAL aggregates in the ER, likely due to a protein misfolding defect. Treatment with 4-phenylbutyrate, a chemical chaperone, appeared to restore MAL trafficking out of the ER (Elpidorou et al., 2022), which supports targeting protein misfolding as a putative therapeutic strategy for this leukodystrophy.

Pelizaeus–Merzbacher disease (PMD)

PMD is an X-linked, dysmyelinating leukodystrophy characterized by involuntary eye movement, head tremors, and systematically poor muscle tone. Symptom onset usually occurs within the first year of age (Laukka et al., 2016). PMD is caused by mutations in the gene encoding PLP1, one of the most abundant membrane-associated myelin proteins in the CNS. Many types of *PLP1* mutations can cause PMD. These include duplications (Inoue et al., 1996), deletions (Raskind et al., 1991), and missense mutations. Of these, *PLP1* gene duplication is the most common cause of PMD (Sistermans et al., 1998; Mimault et al., 1999), while missense point mutations in *PLP1* also result in axonal degeneration in the CNS (Garbern et al., 2002).

Both loss-of-function and gain-of-function mechanisms have been suggested for how *PLP1* mutations cause PMD. Early neuropathology studies of PMD brains revealed significant deficiencies in myelination as well as decreased levels of myelin proteins (MBP, MAG, and CNP) and lipids (cerebroside, sulfatides, and sphingomyelin) (Bourre et al., 1978). As a four-pass transmembrane protein, PLP1 functions in myelin compaction, bringing together adjacent extracellular layers of myelin. Indeed, *PLP1*-null mice exhibit myelin structural defects, such as incomplete compaction, and axonal accumulation of organelles (Klugmann et al., 1997; Edgar et al., 2004), which is indicative of axonal transport defects. Additional studies suggest that PMD mutations may lead to toxic gain of function. In patient-derived iPSCs differentiated into oligodendrocytes,

mutant PLP1 proteins misfold and mislocalize to the ER (Numasawa-Kuroiwa et al., 2014) and can contribute to iron toxicity. These mechanisms may contribute to oligodendrocyte cell death and iron chelation therapy has even been suggested to prevent cell death (Nobuta et al., 2019). Thus, determining the disease-causing mechanisms for different PLP1 mutations will be crucial for assessing therapeutic rationales for different patient cohorts.

Recently, promising experiments in mice indicate that ASOs may be a feasible therapeutic approach for PMD. First, researchers ensured that decreasing PLP1 levels does not have detrimental effects. The *jimpy* mouse model expresses a truncated defective copy of PLP1 and shares similar cellular and neurological phenotypes with severe PMD patients. Interestingly, targeted germline deletion of the *PLP1* gene improved the lifespan of this mouse and eliminated tremors, ataxia, and seizures. Thus, to recapitulate this positive effect, ASOs targeting *Plp1* mRNA were administered to *jimpy* mice. This resulted in silencing of *Plp1*, restored white matter volume, and astonishingly improved survival rate (Elitt et al., 2020). However, it should be noted that *jimpy* is a spontaneously occurring *PLP1* mutation in mice and does not directly model PMD mutations. Moreover, *PLP1*-null adult mice have myelin and axon defects (Klugmann et al., 1997; Edgar et al., 2004), indicating that complete loss of PLP1 can also be deleterious. Thus, it will be important for future research to focus on long-term effects of administering *Plp1*-targeted ASOs.

Another possible cause of PMD pathology is mutations causing aberrant splicing. *Plp* mRNA can be spliced into two isoforms: *Plp1* and the shorter *Dm20* (Nave et al., 1987). Some PMD patients have mutations in *PLP1* Intron 3, which contains an alternative splicing site, (Taube et al., 2014; Kevelam et al., 2015). These mutations alter alternative splicing and disrupt the ratio of PLP1/DM20 protein in oligodendrocyte cultures (Hobson et al., 2006; Taube et al., 2014). In an attempt to target disease-causing mutations, morpholino oligomers blocking the DM20 splice site successfully shifted alternative splicing towards PLP1 in oligodendrocyte culture. In addition, intracerebroventricular delivery of the same oligomer to neonatal mice modeling this mutation rescued both *Plp* mRNA and PLP protein levels (Tantzer et al., 2018). Thus, approaches targeting both PLP overexpression and splicing defects are being developed and show promising results in animal models.

Other transmembrane protein defects

CNTNAP1-related arthrogryposis and leukodystrophy

Two children presenting with arthrogryposis (joint stiffness and muscle weakness) and hypomyelination by MRI were found to have either homozygous or compound heterozygous mutations in the *CNTNAP1* gene, which encodes contactin-associated protein 1 (Caspr1). Caspr1 is a paranodal cell-adhesion protein in the axon that interacts with neurofascin 155 to form paranodal junctions. EM of sural nerve biopsies showed a striking absence of paranodal loop structures (Conant et al., 2018).

Hypomyelination with congenital cataracts (HCC)

HCC is characterized by the appearance of cataracts within the first year of life, followed by progressive neurological and cognitive impairment, and hypomyelination in the CNS and PNS (Biancheri et al., 2011; Wolf et al., 2021). HCC is caused by mutations in *FAM126A* gene that encodes the membrane protein hyccin, which is expressed ubiquitously in the adult brain and also in the lens of the eye (Zara et al., 2006).

Hyccin function may be important for myelin sheath development. Hyccin is a component of the PI4K (phosphatidylinositol 4-kinase) complex that synthesizes phosphatidylinositol 4-phosphate (PI4P). Absence of hyccin destabilizes the PI4K complex (Baskin et al., 2016), which may result in fewer PI4P and other phosphoinositides intermediates that are important for myelin formation. Indeed, phosphoinositides are important both for the association of MBP with adjacent myelin sheath plasma membranes (Nawaz et al., 2009; Zuchero et al., 2015), and for opening cytoplasmic channels that are found from outer to inner myelin sheath layers as they grow and wrap around the axon (Snaidero et al., 2014). More research on how hyccin mutations affect myelination are needed in order to better design novel therapeutic treatments for this leukodystrophy.

SLC35B2-related chondrodysplasia with hypomyelinating leukodystrophy

Homozygous mutations in *SLC35B2* were found in two patients presenting with chondrodysplasia (disrupted growth of cartilage), intellectual disability, and hypomyelination on brain MRI (Guasto et al., 2022). The *SLC35B2* gene (also known as *PAPST1*) encodes a 3′-phosphoadenosine 5′-phosphosulfate (PAPS) transporter that moves PAPS from the cytoplasm into the Golgi apparatus. In the Golgi, sulfotransferases add PAPS to proteins already modified with GAGs (glycosaminoglycan chains). This process generates sulfated proteoglycans (PGs), which are important in the extracellular matrix for building and maintaining connective tissues in bones, cartilage, and even brains (Schwartz and Domowicz, 2018). Biochemical analyses of sulfated proteins in both patient fibroblasts and serum indicate reductions in protein

sulfation (Guasto et al., 2022). Moreover, in a transfected kidney cell line, mutant SLC35B2 lost its Golgi-specific localization and instead appeared throughout the cell. These results suggest that mutant SLC35B2 may act through a loss-of-function mechanism. Though the role of PAPS transporters in myelination is still unclear, the discovery of these mutations open the door toward exciting future research.

Transient infantile hypomyelinating leukodystrophy-19 (HLD19)

Recently, heterozygous missense mutations in the transmembrane protein 63A (*TMEM63A*) gene were identified in a hypomyelinating leukodystrophy that usually presents in the first weeks of life with nystagmus, neurological abnormalities, and hypomyelination by MRI. Surprisingly, all patients showed neurological improvement and nearly recovered hypomyelination by 4 years of age. TMEM63A is a mechanosensitive ion channel (Yan et al., 2019) that is preferentially expressed in oligodendrocytes and microglia (Zhang et al., 2014). While cultured cells expressing wildtype TMEM63A exhibited stretch-activated currents upon mechanical stimulation, cells expressing mutant TMEM63A did not (Yan et al., 2019). Though the mechanism leading to leukodystrophy is yet unknown, this discovery highlights an interesting finding that mechanosensitive ion channels play a role in myelination.

TMEM106B-related hypomyelinating leukodystrophy

Recently, a hypomyelinating leukodystrophy with relatively mild phenotypes was attributed to a single *de novo* mutation in the gene encoding transmembrane protein 106B (*TMEM106B*) leading to a D252N residue change. In 4 unrelated patients, symptoms include nystagmus, delays in motor skills development, and intellectual impairment (Simons et al., 2017).

Multiple studies support a role for TMEM106B in regulating both lysosomal function and acidification as well as myelin sheath structure. First, TMEM106B binds to the lysosomal protein vacuolar-ATPase accessory protein 1 (AP1). Loss of TMEM106B leads to fewer lysosomes in cultured neurons and decreased levels of lysosomal enzymes in mice (Klein et al., 2017). Second, early studies indicate that late endosomes and lysosomes transport the transmembrane protein PLP to the myelin sheath (Trajkovic et al., 2006). Indeed, *Tmem106b* knockout mice have reduced PLP and MOG levels by Western blot and their myelin sheaths contain vacuoles in between myelin layers visible by EM (Feng et al., 2020). Furthermore, *Tmem106b* knockout mice are more susceptible to cuprizone-induced demyelination damage and have poorer ability to remyelinate. Primary oligodendrocytes cultured from *Tmem106b* knockout mice contain clusters of PLP-positive lysosomes inside the cell body and decreased distribution of PLP outside of the cell body (Zhou et al., 2020). Together, these experiments indicate that TMEM106B dysfunction can lead to lysosomal defects in neurons as well as aberrant vacuoles and PLP trafficking defects in the myelin sheath.

Interestingly, TMEM106B dysfunction is also implicated in neurodegenerative diseases in elderly patients. Polymorphisms of *TMEM106B* were identified as a risk factor for frontotemporal degeneration (FTD) (Van Deerlin et al., 2010). Very recently, TMEM106B amyloid filaments were discovered in the brains of older patients with various neurodegenerative diseases, including tauopathies, synucleinopathies, Aβ-amyloidoses and TDP-43 proteinopathies. Similar TMEM106B filaments were also found in older but neurologically normal patients, indicating that TMEM106B is prone to forming filaments in aging brains. The D252N leukodystrophy mutation (Simons et al., 2017) resides within the amyloidogenic region in TMEM106B (residues 120–254) (Schweighauser et al., 2022), but it is unclear whether the D252N mutation could be more amyloidogenic than wildtype TMEM106B. Surprisingly, polymorphisms in other leukodystrophy genes, including *ARSA* and *CYP27A1*, are also linked to FTD (Lok and Kwok 2021). Thus, these connections between FTD and leukodystrophies hint at common mechanisms and an interesting topic for future research.

TMEM163-related hypomyelinating leukodystrophy

Recently, two patients with hypomyelinating leukodystrophy were found to carry two unique *de novo* variants of *TMEM163* (Yan et al., 2022). Both patients presented initially with symptoms consistent with PMLD, such as nystagmus, motor deficits, and hypomyelination on MRI. Similarly to transient infantile HLD19, hypomyelination on MRI improved with age.

TMEM163 is a small protein with six predicted transmembrane domains. It is a member of the ZNT/SLC30 zinc efflux transporter family (Sanchez et al., 2019). In cultured cells exposed to the zinc indicator Newport Green (NPG), expression of wildtype TMEM163 leads to decreased NPG fluorescence, but expression of mutant L76P TMEM163 leads to even lower NPG signal, indicating that mutant TMEM163 has hyperactive zinc efflux activity. Zebrafish in which *tmem163a* and *b* were knocked down and replaced with mutant human *TMEM163* had locomotion defects and decreased myelin protein expression (Yan et al., 2022), which recapitulates the motor deficits and hypomyelination seen in patients. These mutations raise the interesting hypothesis that dysregulation of zinc homeostasis can preferentially disrupt myelination. Consequently, further research should investigate how zinc efflux affects myelin growth and how this process is affected by these novel mutations.

Immune system activation

Aicardi-Goutieres syndrome (AGS)

AGS is an autosomal-recessive disorder that mainly affects the brain and the immune system. In the brain, there is a loss of white matter and the appearance of abnormal calcium deposits. Together, hypomyelination and calcification lead to severe disabilities, including joint and muscle rigidity, involuntary muscle contractions, and poor muscle tone. In the immune system, one case report found lymphocytes in the CSF, a 25-fold increase in CSF interferon α (IFNα) levels, and autoantibodies against phospholipids (Olivieri et al., 2013).

AGS is linked to mutations in genes encoding intracellular nucleic acid–sensor machinery, including *ADAR1, IFIH1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1,* and *TREX1* (Crow 2013; Livingston and Crow 2016). Nucleic-acid sensors play an integral role in the innate immune response by inducing apoptosis, necroptosis, and pyroptosis when foreign or defective DNA and RNA are detected (Maelfait, Liverpool, and Rehwinkel 2020). Once these sensors are activated, they initiate induction of cytokines, leading to the transcriptional upregulation of type I interferons (McNab et al., 2015). AGS mutations lead to the accumulation of unusual double-stranded DNA species, which triggers chronic type I interferon release by astrocytes, and ultimately leads to autoimmunity. Indeed, elevated IFNα level is a clinical marker for AGS (Crow et al., 2006).

Astrocytic release of type I interferon, specifically IFNα, may cause hypomyelination via multiple mechanisms. High levels of IFNα adversely affect astrocytes, which may ultimately lead to insufficient trophic support for oligodendrocytes. Indeed, AGS patients have low astrocyte cell counts and chronic IFNα exposure has deleterious effects on astrocytes, including reduced proliferation, increased reactivity, and gene dysregulation (Sase et al., 2018). Chronic IFNα levels in AGS may also lead to hypomyelination by directly causing oligodendrocyte death. The type II interferon, interferon γ (IFNγ), harms cultured primary (*in vitro*) and *in vivo* oligodendrocytes by disrupting cellular bioenergetics pathways, such as glycolysis and mitochondrial respiration (Minchenberg and Massa 2019). However, currently there are no studies investigating the direct link between IFNα and oligodendrocyte death (de Waard and Bugiani 2020).

The rarity of AGS presents difficulties in recruitment for clinical studies; however, anecdotal reports suggest that the kinase inhibitor Ruxolitinib may result in clinical improvements (Crow, Shetty, and Livingston 2020). Clearly, more basic research on cellular nucleic acid–sensor machinery and translation studies are needed in order to identify therapeutic targets in AGS.

Hereditary diffuse leukoencephalopathy with spheroids (HDLS)

HDLS is an adult-onset disorder typically beginning in the fourth decade of life; therefore, it likely represents a demyelinating disease rather than a developmental disease. HDLS is characterized by various neurological (seizures and parkinsonism), psychiatric (personality changes and dementia), and somatic symptoms (arthritis and gastrointestinal pain). Histopathological studies have found demyelination in the cerebral cortex, axonal spheroids containing aggregates of phosphorylated neurofilament and amyloid precursor protein, and oxidative damage in glia (Axelsson et al., 1984; Baba et al., 2006; Ali et al., 2007). HDLS is an autosomal-dominant disorder and whole-exome sequencing revealed that it is caused by mutations in the gene encoding colony stimulating factor 1 receptor (CSF1R) (Rademakers et al., 2011).

Multiple sources of evidence indicate that microglia defects cause HDLS. CSF1R is the receptor for the cytokine CSF-1, which regulates the proliferation and differentiation of microglia in the CNS (Stanley et al., 1997). Upon ligand binding, wildtype CSF1R homodimerizes and auto-phosphorylates tyrosines in its cytoplasmic domain, but mutant HDLS CSF1R does not (Rademakers et al., 2011). Moreover, a mouse model with reduced CSF1R expression in microglia displays memory deficits, microglial activation, and demyelination (Biundo et al., 2021). Thus, CSF1R inactivating mutations likely contribute to HDLS myelin pathology through microglia.

Though no treatment currently exists, microglia replacement therapy has been proposed for HDLS. This would involve microglia depletion followed by replacement with either HSCs or engineered microglia expressing wildtype CSF1R (Han et al., 2020). Indeed *Csf1r* knockout mice can be partially rescued by bone marrow transplants and donor-derived cells engraft into the brain and adopt signature microglial genes (Bennett et al., 2018). Though more validation of this approach is needed, it presents a promising avenue for treatment of this leukodystrophy.

Conclusion

The field of leukodystrophies is exemplary in identifying underlying genetic mutations. Perhaps due to decreased sequencing costs, many novel mutations are being discovered each year. This wealth of genetic information has provided not only a rich foundation for understanding the mechanistic underpinnings of leukodystrophies, but also insights into normal oligodendrocyte and myelin development, astrocyte cell biology, as well as glia–glia and glia–neuron interactions. Cellular mechanisms attributed to hypomyelination in leukodystrophies include contributions to lipid

metabolism and myelin biogenesis by various organelles, such as lysosomes, peroxisomes, and mitochondria, as well as enzymes like ASPA. In addition, astrocytes may contribute to etiologies in leukodystrophies such as AxD, VWM, and AGS.

Selection of therapeutic strategies in translational studies of leukodystrophy have relied on basic research results that determined mode of genetic inheritance as well as cellular mechanisms. For autosomal recessive and X-linked leukodystrophies, replacement therapies and other therapies targeted at restoring loss of function have been validated for certain disorders. For autosomal dominant leukodystrophies, therapies aim to decrease expression of mutant or overexpressed proteins. ASOs, a new generation of neurotherapeutic that binds to RNA targeting sequences in order to achieve gene silencing, hold great promise. ASOs have been FDA-approved and are successful in targeting other genetic neurological diseases like SMA. Such applications would require careful validation in cell and animal models, but having a strong base of cellular targets and mechanisms is an important first step.

Future clinical studies in humans may face multiple challenges, including adverse or toxic effects, reproducibility in humans, and small sample sizes in rarer leukodystrophies. However, a solid foundation of many translational studies will hopefully lead to promising therapeutics approaches that may 1 day help patients affected by leukodystrophies.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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