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OVERVIEW

Role of epigenetics and alterations in RNA metabolism in leukodystrophies

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Abstract

Leukodystrophies are a class of rare heterogeneous disorders which affect the white matter of the brain, ultimately leading to a disruption in brain development and a damaging effect on cognitive, motor and social-communicative development. These disorders present a great clinical heterogeneity, along with a phenotypic overlap and this could be partially due to contributions from environmental stimuli. It is in this context that there is a great need to investigate what other factors may contribute to both disease insurgence and phenotypical heterogeneity, and novel evidence are raising the attention toward the study of epigenetics and transcription mechanisms that can influence the disease phenotype beyond genetics. Modulation in the epigenetics machinery including histone modifications, DNA methylation and non-coding RNAs dysregulation, could be crucial players in the development of these disorders, and moreover an aberrant RNA maturation process has been linked to leukodystrophies. Here, we provide an overview of these mechanisms hoping to supply a closer step toward the analysis of leukodystrophies not only as genetically determined but also with an added level of complexity where epigenetic dysregulation is of key relevance.

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Regulatory RNAs/RNAi/Riboswitches > Regulatory RNA
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KEYWORDS

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1 | INTRODUCTION

Leukodystrophies are a rare group of inherited disorders that primarily affect the white matter of the Central Nervous System (CNS). The term "leukodystrophy" originates from histopathological analysis, but it has been adopted by the medical imaging community because MRI patterns demonstrated normal or abnormal white matter and changes in myelination (e.g. myelin build-up and breakdown) (Stellingwerff et al., 2023). In leukodystrophies, there is a disruption in the development, maintenance or destruction of white matter, leading to progressive and often debilitating neurological symptoms (Ashrafi et al., 2020; Wolf et al., 2021). The white matter consists of glial cells, including astrocytes, microglia, ependymal cells and oligodendrocytes. The latest are involved in the production of myelin, a fatty substance that surrounds nerve fibers enabling efficient signal transmission (Poitelon et al., 2020).

All inheritance patterns are possible, and symptoms can manifest in infancy, childhood, or even adulthood (Pouwels et al., 2014; Wolf et al., 2021). Arising from dysfunction in any components of the cerebral white matter, leukodystrophies can be classified based on the affected cell type: (1) Myelin disorders, characterized by a primary involvement of oligodendrocytes and myelin sheath; (2) Astrocytopathies, that result from astrocytes dysfunctions; (3) Leuko-axonopathies, caused by impaired interaction between axons and glial cells; (4) Microgliopathies due to dysfunction of microglial cells; (5) Leukovasculopathies: characterized by a primary genetic abnormality in blood vessels within the brain white matter (Muthusamy et al., 2023; Pouwels et al., 2014; van der Knaap & Bugiani, 2017). Neuroradiological patterns further classify leukodystrophies in demyelinating disorders, where myelin is initially formed but later degenerates, and hypomyelinating disorders, in which myelination stalls prematurely, hindering further development (Muthusamy et al., 2023).

Clinical presentations are highly variable. Hypomyelinating disorders typically have a slow course with onset at birth, while demyelinating disorders often have a more abrupt onset, rapid progression, and a poorer prognosis, following a period of seemingly normal development. Symptoms include motor and cognitive impairments, vision and hearing loss, seizures, and deteriorating neurological functions (Ashrafi et al., 2020; Köhler et al., 2018; Vanderver et al., 2015). Pyramidal and cerebellar signs are frequent, with motor impairment typically more severe than cognitive decline. Seizures are more common in advanced stages, except in astrocytopathies where they may occur early. Movement disorders are uncommon but can occur in specific conditions affecting the basal ganglia. Involvement of peripheral nerves, muscles, retinas, or other organs can also be seen (Muthusamy et al., 2023).

It is clear that, behind the heterogenous group of leukodystrophies, imaging pattern abnormalities can be revealed by MRI (La Piana et al., 2014; Steenweg et al., 2010). Almost half of the brain is composed of myelinated axons in the white matter; it is, therefore, not surprising that leukodystrophies have a significant functional effect.

While there is currently no cure for most leukodystrophies, ongoing research aims to unravel their underlying mechanisms, improve diagnostic methods and explore potential therapeutic strategies to alleviate symptoms and improve the quality of life for affected individuals (Ashrafi et al., 2020; Pouwels et al., 2014). These disorders present great heterogeneity, and identifying common epigenetic regulators could be of crucial interest.

The primary genetic mutations associated with leukodystrophies have been widely studied (Guerreiro et al., 2013; Mahdieh et al., 2021; Sarret, 2020). Although research is still ongoing to identify novel causative genes, recent advances are highlighting how, along with a canonical genetic mutation, epigenetics and alterations in gene expression process could impact the pathogenesis of these disorders (Bradbury & Ream, 2021; Chen et al., 2018; Schlüter et al., 2018). Epigenetic modifications include DNA methylation, histone modifications, and non-coding RNA expression, which altogether play a pivotal role in regulating gene expression patterns without altering the underlying DNA sequence (Bure et al., 2022). Moreover, transcriptional and translational mechanisms can also be finely regulated, and RNAs themselves could present an impaired metabolism which could lead to alterations in gene expression (Casamassimi & Ciccodicola, 2019; Chatterjee et al., 2021). The aim of this review is to summarize all recent advances made in epigenetics (DNA methylation, histone modifications, non-coding RNA expression), RNA metabolism, and RNA processing in the context of gene expression (RNA transcription, RNA editing, translation), linking these molecular mechanisms to leukodystrophies.

2 | EPIGENETICS ALTERATIONS IN LEUKODYSTROPHIES

2.1 | Epigenetics alterations at DNA level

Epigenetic changes at DNA level are caused by chemical modifications to the DNA that do not alter the genome, but may influence gene transcription. These changes can explain many cases in which medical observations conflict

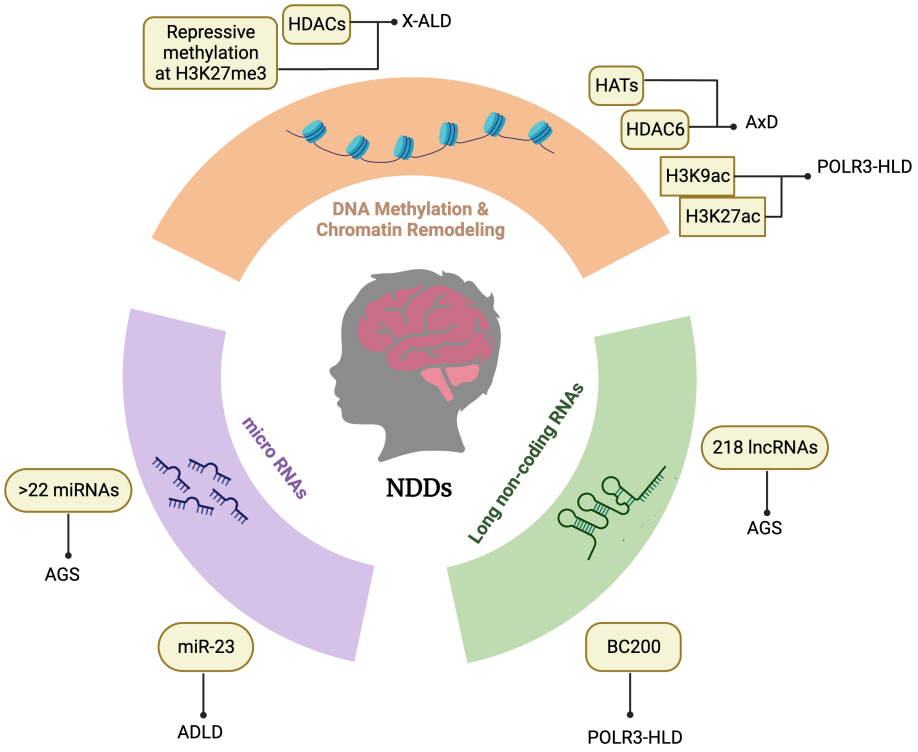

FIGURE 1 Possible impact of epigenetic alterations in some Leukodystrophies. Schematic overview of how epigenetic changes, including alterations at DNA level and non-coding RNAs (lncRNAs and miRNAs) combine and are related in the etiology of Leukodystrophies. AGS, Aicardi-Goutières syndrome; ADLD, adult-onset autosomal dominant leukodystrophy; AxD, Alexander disease; POLR3-HLD, POLR3-related hypomyelinating Leukodystrophy; X-ALD, X-linked adrenoleukodystrophy. Created with Biorender.com.

the prevision of Mendelian genetics. At DNA level, two main mechanisms arise: DNA methylation and histone modifications (Zhang et al., 2020). DNA methylation consists in the covalent addition of a methyl group at the 5-position of cytosine and, particularly in mammals, it is common in the symmetric dinucleotide CpG. Methylation is associated with a reduced accessibility of the chromatin and, as a consequence, reduced transcription. In addition to DNA methylation, Post-Translational Modifications (PTMs) of histones increase chromatin complexity. PTMs are covalent modifications of specific residues in the histone N- or C- terminus or tails that can be either stable or highly dynamic, specific for each gene, cell type and stage (Liu et al., 2023). Specific enzymes regulate PTMs: the balance of both histone acetyltransferase (HAT) and histone deacetylase (HDAC) activity strictly controls the levels of histone acetylation, whereas the histone methylation is regulated by a fine balance between specific lysine methyltransferases (KMTs) and lysine demethylases (Liu et al., 2023; Peixoto & Abel, 2013). Abnormalities in the molecules involved in these mechanisms, belonging to the category of transcriptional regulators or chromatin remodelers, are known to be associated with some leukodystrophies with variable clinical severity (Gómez-Pinedo et al., 2018) (Figure 1).

2.1.1 | Epigenetic alterations at DNA level in leukodystrophies

Recent studies highlighted a solid association between epigenetic alterations and the insurgence of leukodystrophies (Gómez-Pinedo et al., 2018). An example is represented by DNA methylation signatures found in PBMCs of patients with Aicardi-Goutières Syndrome (AGS) that explain the phenotypic heterogeneity in patients with mutations in RNASEH2B (Garau et al., 2023). AGS is a leukodystrophy associated with mutations in key genetic factors implicated in nucleic acids metabolism at different levels. It is also classified as interferonopathy (Liu & Ying, 2023; Pulliero et al., 2011) and is a severe childhood autoinflammatory disease that has a genetic basis and severe clinical features (Crow & Manel, 2015). This disorder was first discovered and described in 1984 by the two neurologists from whom it is named, Jean Aicardi and Françoise Goutières. In their work, they described eight children, coming from five

different families, affected by a progressive disorder of the CNS with early onset familial encephalopathy and chronic lymphocytosis in the CSF (Aicardi & Goutières, 1984). AGS patients displayed reduced methylation levels in interferon-stimulated genes (ISGs) and distinctive methylation variations in genes related to the activation of neutrophils and platelets. Those with less severe symptoms showed methylation differences in genes implicated in DNA damage and repair, while individuals with more severe symptoms exhibited methylation variations in genes linked to cell fate determination and organ development. Notably, alterations in the methylation of two ISGs (IFI44L and RSAD2) were associated with heightened gene expression in patients with severe symptoms compared to those with milder ones (Garau et al., 2023).

Another relevant example is represented by the fact Alexander disease (AxD), a leukodystrophy caused by mutations in the *GFAP* gene that is related to astrocytic dysfunction (Mignot et al., 2004). *GFAP* encodes for fibrillary acidic protein (GFAP), and presents alternative splicing, with 10 different isoforms discovered in the human brain. The canonical isoform is GFAPα, whilst the most abundant alternatively spliced variant is GFAPδ in glioma cells (Radu et al., 2022). During astrogenesis, *GFAP* transcription is regulated by either GFAP promoter demethylation and histone acetylation managed by HATs (Histone acetyltransferases) and HDACs (Histone deacetylases). Both enzymes are implicated in GFAP-δ expression in astrocytes and astrocytoma cells (Kanski, Sneeboer, et al., 2014). The recruitment of splicing factors and transcriptional regulators such as HDACs may affect the splicing process of pre-mRNA transcription, resulting in alternatively spliced forms GFAP-δ (Rahhal & Seto, 2019).

Several studies have reported that the activity of GFAP promoter controls the expression levels of *GFAP*, demonstrating the centrality of epigenetic modifications in this process. Particularly, during the astrogenesis process in neural stem cells (NSCs) differentiation, the expression of *GFAP* is activated after the demethylation of its promoter (Kanski, van Strien, et al., 2014; Nakagawa et al., 2020).

Epigenetic alterations, such as histone acetylation and deacetylation as well as methylation, largely control GFAP-δ expression in reactive patients' glial cells, which in AxD lead to cytoplasmic inclusions of the protein (Mignot et al., 2004).

Interestingly, the inhibition of HDAC6 activity is associated with a dysregulation of the microtubule-organizing center in AxD (Huyghe et al., 2012; Melchionda et al., 2013). Indeed, *HDAC6* mutations or variation in HDAC6 activity influence the acetylation of microtubules leading to a reorganization of the vimentin network. Therefore, dependent on HDAC6 functionality in astrocytes, mutations in both *HDAC6* and *GFAP* in AxD patients may trigger a reorganization of GFAP network causing an abnormal morphology of astrocytes (Yasuda et al., 2019).

Epigenetic mechanisms are also implicated in the pathophysiology of X-linked adrenoleukodystrophy (X-ALD). Histone modifications depend on the cell's stage of differentiation in neural stem-cell (Schlüter et al., 2018). As a consequence of the recruitment of HDACs and repressive histone methyl transferases, oligodendrocytes differentiation inhibitors are downregulated, preceding the new myelin synthesis (Liu et al., 2006). In this context, increased levels of transcriptional inhibitors of myelin gene expression are related to different clinical phenotypes of X-ALD. This phenomenon makes us understand how PMTs of lysine residues on histones and changes in both DNA methylation and acetylation can affect the remyelinating capacity of oligodendrocytes (Schlüter et al., 2018).

Generally, histone acetylation plays a crucial role in gene expression regulation allowing the transcriptional machinery to access the DNA and initiate gene transcription more easily (Lee et al., 2020). Particularly, histone H3 acetylated at the lysin residues 9 and 27 (H3K9ac and H3K27ac) was observed in Polymerase III (Pol III) genes whose mutation have been implicated in the cause of hypomyelinating leukodystrophies (Kenneth et al., 2007; Thomas & Thomas, 2019). ChIP-seq data showed that loci occupied by Pol III are commonly marked with H3K9ac and H3K27ac, defining the TSS of Pol III genes (Barski et al., 2010). Moreover, similarly to what was observed in Pol II genes, histone H3 trimethylated at lysine residue 27 (H3K9me27) is enriched in Pol III genes, leading to a repressive chromatin state (Moqtaderi et al., 2010). Pol III transcription seems to play an active role in determining chromatin structure rather than being passively subjected to epigenetic alterations. Taken together, all of the above evidences highlight that the effect of histone modifications and epigenetic alterations is very different in the three Pol III subtypes. This could suggest a possible relation with the different severity levels of the disease.

These studies emphasize a more and more evident role of epigenetic alterations in the etiopathogenesis of leukodystrophies. Nonetheless, further investigations need to be carried out in this field to clarify how alterations at DNA level impact on chromatin accessibility and cellular pathways of each specific disorder and whether there is a common trend of dysregulation shared amongst leukodystrophies.

2.2 | Epigenetic inheritance and environmental contributors

Epigenetic modulation provides a rapid and adaptive mechanism in response to different environmental influences, creating an individual molecular signature, also called epigenetic memory (Espinosa-Martínez et al., 2024; Ge & Brickner, 2024). These molecular marks induced by environmental triggers may be transmitted to future generations via intergenerational or transgenerational epigenetic inheritance. The intergenerational inheritance involves in utero epigenetic changes acquired due to parental exposure to environmental stimuli (e.g. stress, nutrition, and toxins) (Perera & Silvestre, 2023). On the other hand, transgenerational transmission includes epigenetic information transmitted to new generations by germline cells and resist to both epigenetic reprograming events (van Otterdijk & Michels, 2016). Environmentally induced modifications that fail to be corrected by epigenetic maintenance processes or reprogramming events may lead to severe consequences affecting the phenotype. In this context, gene–environment interactions play a significant role on neurological outcomes in utero period and during the first 1000 days (Scher, 2022).

The DOHaD hypothesis (Developmental Origin of Health and Disease) formulated by Barker suggests that, during periods of embryonic development or early life, the exposure to environmental influences (the two major susceptibility windows) might predispose an organism to diseases in adult life (Barker, 1990). Peaks of histone modifications (H3K27ac, H3K4me3 and H3K27me3) and DNA modifications are found at specific loci in the brain, regulating neurogenesis (Kerimoglu et al., 2017). Thus, acquired or inherited epigenetic alterations can affect the brain development, changing responses to environmental triggers (Scher, 2022). To date, there are several clinical studies that suggest the intergenerational role of epigenetics in autism inheritance (Furukawa et al., 2023; Yasuda et al., 2023). Some studies have showed that maternal exposure to antidepressants, antibiotics and infections may influence the predisposition to autism spectrum disorders in the offspring (Zhu et al., 2019). In addition to that, the hypothesis that inflammatory perturbations in utero provide fetal brain injures is supported by epidemiological studies associating a maternal inflammation state during pregnancy and offspring conditions, where maternal factors such as obesity, asthma, autoimmune disease, infections and psychosocial stress are correlated to highest risk of diseases in the newborn (Han et al., 2021). Even so, a mechanistical link between these phenomena is yet to be defined, and experimental studies concerning their roles in leukodystrophies are currently still absent.

2.3 | Epigenetics regulation mediated by non-coding RNAs

2.3.1 | Role of non-coding RNAs

Numerous molecular mechanisms can influence gene expression, and non-coding RNAs play a fundamental role. Indeed, as only 1%–2% of the human genome codes for protein, the question of "what" the remaining part of the genome does is gaining more and more relevance. For this reason, RNAs can be classified for their coding potential in coding RNAs (transcripts that will subsequently be translated into proteins) and non-coding RNAs, transcripts that do not code for a polypeptide and that could thus have a role in modulation of gene expression (Mattick, 2009; St Laurent et al., 2015; Statello et al., 2021; Yao et al., 2019). Amongst the non-coding RNAs, it is possible to distinguish two subclasses: small non-coding RNAs, molecules smaller than 200 bp, and long non-coding RNAs (lncRNAs), defined as non-coding RNA molecules longer than 200 bp (Statello et al., 2021). These molecules are implicated in a wide range of clinical conditions, including leukodystrophies, proving to be key regulators of disease progression (Chen et al., 2020; Choquet et al., 2019; Ji et al., 2020; Rey, Pandini, et al., 2021; Rey, Urrata, et al., 2021; Rey, Zuccotti, & Carelli, 2021).

2.3.2 | Small non-coding RNAs and leukodystrophies

Amongst the numerous small non-coding RNAs, the most abundantly characterized sub-class is represented by microRNAs (miRNAs). These is a class of RNA regulators composed of approximately 22 nucleotides, able to control gene expression, influencing mRNA stability and translation in the cytoplasm (Ma et al., 2023). miRNAs are processed starting from precursor molecules named pre-miRNAs, transcribed from independent genes or from introns of protein coding RNAs. The precursors are processed into two steps by two endonucleases, namely Drosha and Dicer. Drosha reduces the pre-miRNAs to hairpin structures of nearly 70 nucleotides known as pre-miRNAs. The pre-miRNAs are

then exported in the cytoplasm where they are cleaved by Dicer in ~20 bp miRNA duplexes. One of the two strands is then selected as mature miRNA, while the other is degraded (Vishnoi & Rani, 2023). In the human brain, miRNAs have proven to be abundantly expressed and to exert fundamental control over development of the brain architecture and neuronal plasticity (Ma et al., 2023).

To date, the precise role of small non-coding RNAs in leukodystrophies is an active area of research and very few information is present in pediatric forms of leukodystrophies. For instance, the demyelination occurring in adult-onset autosomal dominant leukodystrophy (ADLD) is caused by over expression of lamin B1, a component of nuclear lamina, due to a duplication of *LMNB1* gene, resulting in increased gene dosage in brain (Lin et al., 2011). Lamin B1 plays at pivotal and indispensable role in the physiological neural development and maturation (Mahajani et al., 2017). When lamin B1 is not working properly, neural cell development is disrupted, leading to aberrant cellular growth and impaired cell function (Koufi et al., 2023). In vitro models showed as the excessive lamin B1 caused the reduction of myelin gene transcription, ultimately resulting in the premature block of oligodendrocyte differentiation (Lin et al., 2014). Lamin B1 is finely regulated, and one of these regulators is represented by miRNAs. In fact, miR-23, one of the most abundant miRNAs in oligodendrocytes, has been predicted to target *LMNB1* and counteract the expression of *Lmnb1*. Indeed, the trend of the expression of miR-23 has been demonstrated to be inversely correlated with that of *Lmnb1* (Lin et al., 2011; Lin et al., 2014; Takamori et al., 2018). Moreover, miR-23 is able to enhance oligodendrocyte differentiation in glial cells cultured in vitro, as reported by the increased expression of markers of mature oligodendrocytes along with an increase in myelin proteins (Lin & Fu, 2009).

However, since the abnormal development or progressive degeneration of myelin is a feature of some leukodystrophies, we might only suppose and thus propose that miRNAs involved in oligodendrocyte differentiation or myelination can modulate somehow either the onset or the development of these leukodystrophies. For example, miR-219 and miR-338 are two oligodendrocyte-specific miRNAs. Their expression seems to tightly regulate the progression through the oligodendrocyte lineage, enhancing the differentiation of neural progenitor cells to oligodendroglia cells (Ngo & Kothary, 2022). Differently, the expression of miR-124 drives the specific maturation of neurons (Makeyev et al., 2007) and its in vitro administration contributes to the direct neurogenic conversion from astrocytes (Papadimitriou et al., 2023). Moreover, the up-regulation of mir-124 has been associated with demyelination of the human hippocampal biopsies (Dutta et al., 2013).

In recent years, RNA-sequencing studies are highlighting also a dysregulation in miRNAs expression in the pathology of AGS (Al Wardat et al., 2024; Pulliero et al., 2011; Pulliero et al., 2014). Specifically, one study evaluated the expression of 957 miRNAs in lymphocytes from AGS patients versus control, highlighting a miRNA overload in AGS patients, with 22 miRNAs being up-regulated by more than fourfold (Pulliero et al., 2011). On the contrary, miR-219 was found down-regulated in all investigated AGS patients, and its transfection in astrocytes induced an increase in viability, growth and differentiation (Pulliero et al., 2014). Moreover, another study conducted in lymphoblastoid cells harboring mutations in the ADAR1 enzyme highlighted 27 differentially expressed miRNAs, including miR-320c and miR-181a-2-3p (Al Wardat et al., 2024). Lastly, also *mir-3614-5p* was recently associated to the inhibition of ADAR1 proteins and RNA editing in HeLa cells (Vuillier et al., 2022). Specifically, *miR-3614-5p* directly targets both ADAR1 transcripts (p110 and p150) by binding to specific sites in the 3′ UTR, and consequently reduces IFN-induced A→I. However, the current state of research in this field is still at a nascent stage, where studies and experiments are just at the beginning. Further investigations, such as miRNome analysis as well as predictive studies, are needed to better clarify the molecular mechanisms implicated in the relationship between non-coding RNAs regulations and leukodystrophies pathogenesis.

2.3.3 | Long non-coding RNAs and leukodystrophies

LncRNAs were found to be partially responsible for the definition of the complex architecture and function of the CNS (Roberts et al., 2014). Indeed, these molecules regulate both pluripotency and neuronal-glial differentiation, either maintaining pluripotency in the early phases or modulating gene expression of neural/glial specific genes upon lineage commitment (Carelli et al., 2019; Goff et al., 2015; Roberts et al., 2014; Sauvageau et al., 2013). It is thus easy to infer that aberrations in the expression of these molecules could be of great relevance in the development of leukodystrophies, either through their single mode of action or through a combinatorial network dysregulation (Choquet et al., 2019; He et al., 2017; Wang et al., 2017).

Recent studies revealed that a dysregulation of lncRNAs could also contribute to the key processes involved in the pathogenesis of leukodystrophies (Al Wardat et al., 2024; Choquet et al., 2019), suggesting a role for the molecules in these diseases. These molecules are dynamically expressed during oligodendrocyte maturation and neuronal-glial fate switches, influencing myelination processes (Wang et al., 2017). Indeed, an integrative analysis using transcriptomic and epigenetic data was conducted in murine NSCs to investigate the role of lncRNAs in oligodendrocyte precursor cell differentiation and oligodendrogenesis, associating distinct clusters of lncRNAs with protein-coding genes, providing insights into the functions of these lncRNAs in oligodendrocyte myelination (Dong et al., 2015). Moreover, genetic ablation of the lncRNA lncOL1 highlighted that this lncRNA binds to SUZ12, a core component of the Polycomb Repressive Complex 2 (PRC2) contributing to oligodendrocyte maturation (He et al., 2017). As per miRNAs, identifying finely-tuned lncRNAs-expression patterns which are induced during oligodendrocyte differentiation could give insights into the global machinery governing oligodendrogenesis, which could then be exploited to identify patterns divergent or shared amongst leukodystrophies.

Even so, direct evidence of lncRNAs involved in specific leukodystrophies is currently lacking. Only the BC200 RNA (BCYRN1), involved in translation regulation, was found to be implicated POLR3-related leukodystrophy (POLR3-HLD) by performing RNA-Sequencing experiments in HEK293 cells where the CRISPR-Cas9 system was used to introduce the POLR3A mutation c.2554A→G (p.M852V). Indeed, genetic ablation of BC200 in oligodendroglial cells leads to a profound disruption in transcriptomic and proteomic profile, and interestingly this lncRNA was found impacted in all POLR3-HLD cell models and patients-derived cell lines (Choquet et al., 2019). Evidence of BC200 mechanism of action in leukodystrophies is currently lacking, but a BC200 in vitro knock-out model led to an up-regulation of different set of proteins located in the plasma membrane, endoplasmic reticulum and cytoskeleton; this is interesting considering also the hypothesis correlating POLR3-HLD with translational dysfunctions (see below). Moreover, for AGS, a study conducted in lymphoblastoid cells harboring mutations in the ADAR enzyme highlighted 218 differentially expressed lncRNAs, 183 of which were down-regulated (Al Wardat et al., 2024). Also in this case, no functional characterization of these lncRNAs is performed, but a difference in 3′ UTR length in AGS-RNA-sequencing transcripts suggests alterations in RNA–RNA binding patterns (Al Wardat et al., 2024).

3 | DYSFUNCTIONS IN RNA METABOLISM AND LEUKODYSTROPHIES

The molecular complexity of the human brain is substantially based on the dynamic nature of gene expression (Piwecka et al., 2023). Gene expression is composed of multiple steps, which canonically initiate with RNA transcription, its maturation and its subsequent translation in proteins. Of course, there are exceptions to this process (e.g. non-coding RNAs), but a correct functioning of all these steps is necessary for the correct physiology of cells. Indeed, disruptions in these mechanisms or mutations in genes involved in these processes has been described as causative of leukodystrophies (Figure 2).

3.1 | Association between RNA transcription dysfunction and leukodystrophies

Transcription is the essential process that makes genome-encoded information accessible. It represents the first step in gene expression, in which information from a gene is used to construct a functional product allowing cells to respond to their needs (de Klerk & Hoen, 2015). The main enzyme involved in transcription is RNA polymerase which is responsible for the transcription of genomic DNA into RNA. In eukaryotic cells five different nuclear DNA-dependent RNA polymerases (Pol I-V) have been recognized, each of which transcribes several classes of genes (Barba-Aliaga et al., 2021).

In the past decade, several studies have discovered that pathogenic variants in genes encoding distinct subunits of Pol III cause tissue-specific diseases and a wide spectrum of neurodegenerative disorders (Beauregard-Lacroix et al., 2020; Terhal et al., 2020). Amongst the three nuclear RNA polymerases, Pol III particularly is composed of 17 subunits and represents the most complex enzyme performing DNA-dependent transcription. It is responsible for the transcription of different noncoding genes, including small (<350 nt) and highly expressed RNAs such as 5S rRNA, U6 RNA and transfer RNA (tRNA), whose products play a key role in well-defined functions in translation and other cellular processes (Dieci & Sentenac, 1996). In this context, Pol III is emerging as a crucial factor in the pathogenetic

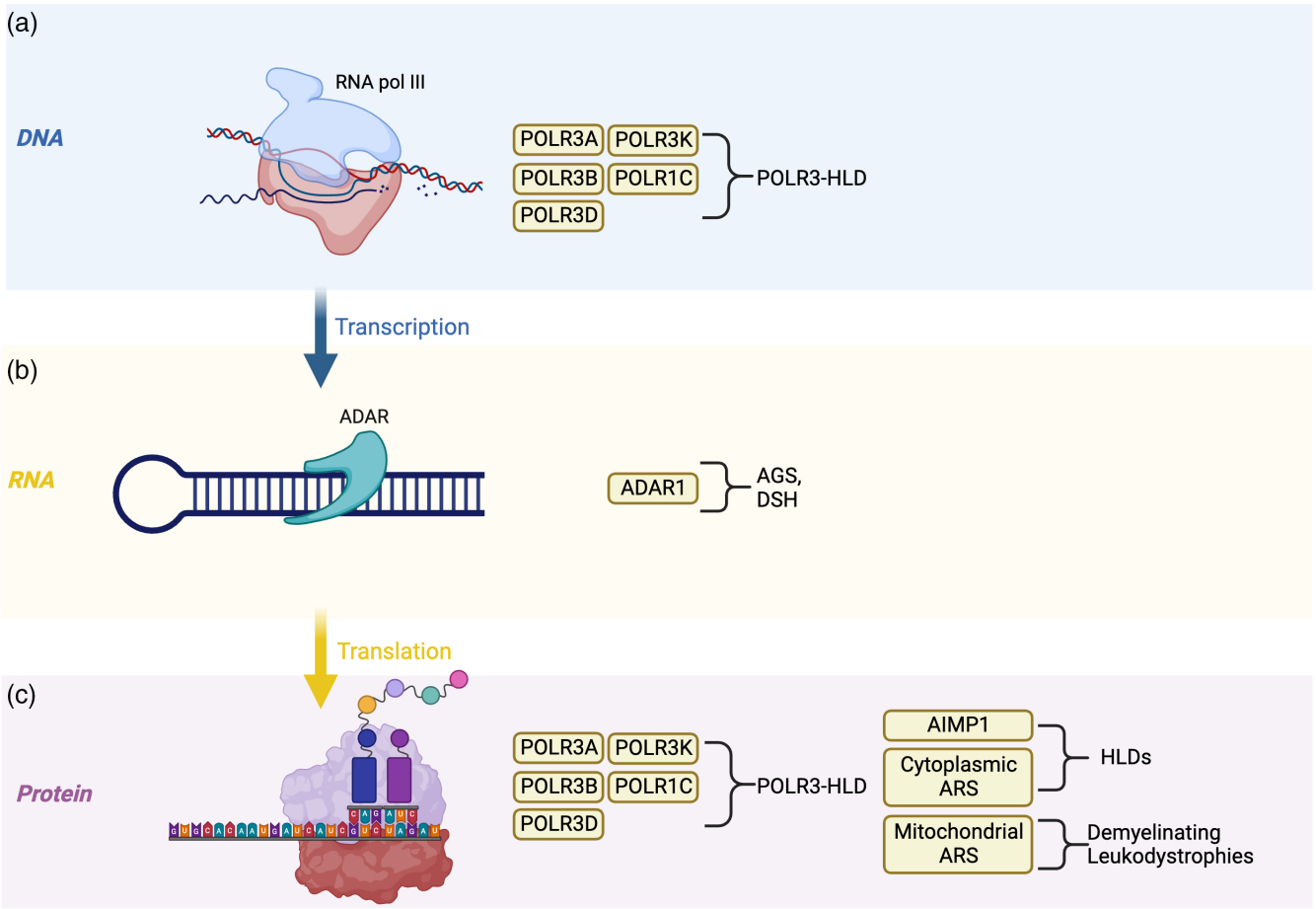

FIGURE 2 Association between defective mechanisms in gene expression and Leukodystrophies. Molecular mechanisms underlying gene expression are composed of multiple steps, which initiate with RNA transcription, its maturation and its subsequent translation in proteins. Mutations in genes encoding for subunits of the RNA-Polymerase III complex can present deficits in transcription of RNA-Polymerase III substrates impacting both transcription and translation (as part of these targets are tRNAs and rRNAs). Moreover, ADAR1 mutations impact the RNA editing processes and mutations in other key components regulating tRNAs biology can lead to leukodystrophies. AGS, Aicardi-Goutières syndrome; ARS, aminoacyl tRNA synthetase; DSH, dyschromatosis symmetrica hereditaria; HLD, hypomyelinating leukodystrophies; POLR3-HLD, POLR3-related leukodystrophy. Created with Biorender.com.

mechanism of several rare debilitating diseases, including both neurodegenerative diseases and rare forms of impaired puberty and premature aging, giving rise to the so-called "POLR3-related disorders" (Lata et al., 2021).

Mutations in component of the Pol III transcription apparatus, including subunits of the enzyme itself, have been correlated to various disorders such as the HLD, identified as the first and the most common disease linked to Pol III dysfunction (Yeganeh & Hernandez, 2020). POLR3-HLD (RNA polymerase III-related leukodystrophy) is now considered as one of the most common HLD involving a combination of neurologic and non-neurologic manifestations (Schmidt et al., 2020). Within the past decade, several studies have revealed the most commonly mutated genes linked to POLR3-HLD: *POLR3A*, *POLR3B*, *POLR1C*, *POLR3K* and *POLR3D* (Bernard et al., 2011; Daoud et al., 2013; Macintosh et al., 2023; Thiffault et al., 2015). Particularly implicated in the transcription initiation and termination is the *POLR3D* gene (Girbig et al., 2021). *POLR3D, POLR3E and POLR3B* encode for RPC4, RPC5 and RPC2 subunits of Pol III complex, respectively. It has been reported that *POLR3*-related leukodystrophy variants in the *POLR3B* gene result in the destabilization of RPC4/RPC5 dimer disassembly. This demonstrates that variants in different subunits of the Pol III complex modify the global activity of the enzyme (Ramsay et al., 2020). Furthermore, RPC4 is characterized by numerous sumoylation sites which, in yeast, induce proteasomal degradation of the complex (Wang et al., 2018). As recently reported, the stoichiometric balance of Pol III complex is crucial; indeed, when *POLR3D* transcription is reduced, non-affected Pol III genes may be also damped to avoid an unbalancing in the transcription of each subunit (Macintosh et al., 2023).

To date, there are two main pathophysiological hypotheses representing possible mechanisms involved in POLR3-related disorders insurgence. The first hypothesis postulates that mutations in genes encoding Pol III subunits (POLR3A, POLR3B, POLR1C, POLR3K or POLR3D) result in reduced Pol III transcription leading to reduced levels of tRNAs and/or small ncRNAs. Therefore, it is easy to predict that the dysregulation of Pol III could influence relative levels of certain tRNAs that are known to be more abundant in the CNS given their importance for translation in a critical developmental period such as myelination (Anitei & Pfeiffer, 2006). In addition, or alternatively, the second hypothesis states that Pol III hypofunction leads to decreased levels of other Pol III transcripts (such as those involved in RNA processing and/or translation of mRNAs) that are crucial for the development and function of neurons and/or oligodendrocytes (Minnerop et al., 2017). An example is represented by 7SL RNA, a ncRNA which is a component of the large subunit of the ribosome and, therefore, fundamental for ribosomal functioning. Particularly, 7SL RNA is responsible for the signal recognition particle required for associating the nascent peptide chain linked to the ribosome with the endoplasmic reticulum. Its reduced levels could impair translocation of secreted or transmembrane proteins to the ER, which could impact production of myelin, causing the hypomyelination phenotype (Azmanov et al., 2016). During neural differentiation of mouse embryonic stem cells into a population of neurons and glial cells, the expression of 7SL was shown to be significantly up-regulated. This could suggest that the expression of 7SL may have an impact on protein expression and cell differentiation (Skreka et al., 2012). In a human oligodendroglial cell line, quantitative proteomics have shown that both the *POLR3A* M852 V mutation and *BC200* RNA KO led to decreased myelin basic protein mRNA levels compared to wild-type cells upon cellular differentiation, indicating that the mild Pol III transcriptome alterations may be sufficient to alter oligodendrocyte differentiation and myelin basic protein expression (Choquet et al., 2019).

Moreover, in leukodystrophies and childhood ataxia with CNS hypomyelination/vanishing white matter, a correlation between mutations in the mitochondrial or cytoplasmic aminoacyl tRNA synthetases (ARS) and abnormal RNA regulation has also been also reported (Nowacki et al., 2022).

These hypotheses may explain the distinct phenotypes observed in *POLR3*-related disorders resulting from perturbation of different Pol III transcripts.

3.2 | Association between RNA editing dysfunction and leukodystrophies

The wide diversity between higher organisms largely depends on post-transcriptional regulatory mechanisms that create different RNA products (Hao et al., 2021). Indeed, after being transcribed by RNA polymerase, RNA frequently undergoes a series of processes, including maturation (e.g. 5′ capping, 3′ processing, and polyadenylation) and splicing. These enzyme-catalyzed transformations are usually referred to as RNA editing and allow changes in genetic information encoded by genome sequences (Zipeto et al., 2015).

RNA editing was first discovered more than 20 years ago in kinetoplastid protozoa where many uridine nucleotides were found to be inserted or deleted to generate functional proteins (Benne et al., 1986). Since then, many other types of RNA editing mechanisms have been identified. In the animal kingdom, the main type of RNA editing that alters one nucleotide into another is mediated by Adenosine Deaminase Acting on RNA (ADAR) enzymes (Eisenberg & Levanon, 2018). Specifically, ADAR enzymes convert adenosines to inosines (A→I editing) in double-stranded RNA (dsRNA) substrates through hydrolytic deamination of the adenine base (Walkley & Li, 2017). A→I RNA editing can lead to modifications in splice sites, changes RNA secondary structure, and consequent alterations of protein-coding sequences of selected genes (Picardi et al., 2015). Since inosine is interpreted as guanosine during translation, A→I in protein-coding sequences may result in codon changes. Indeed, a single amino acid difference often plays an important role in regulating protein function (Maas, 2010). In the brain, the ion-permeability, kinetic properties, trafficking of glutamate receptor channels, as well as the signaling properties of the 5HT-2c receptor, constitute prominent examples where highly conserved protein residues are altered through editing in a programmed and cell-type specific manner (Werry et al., 2008). For example, a relationship between polymorphisms in genes encoding the serotonin transporters and susceptibility to metachromatic leukodystrophy has been investigated (Kumperscak et al., 2008). However, most A→I RNA editing sites are in non-coding sequences, such as 5′ and 3′ UTRs and intronic retrotransposon elements (Nishikura, 2016; Yang et al., 2013). This aspect highlights the importance of ADAR enzymes not only in the synthesis of correct three-dimensional structured proteins, but also in overall regulation of both coding and non-coding sequences. There are three ADARs in humans; ADAR1, ADAR2, and ADAR3 (Goodman et al., 2012; Savva et al., 2012). Interestingly, while ADAR1 and ADAR2 are both catalytically active and expressed in almost all tissues, ADAR3 is expressed mainly in the brain and has no detectable catalytic activity (Chen et al., 2000). A→I editing is

critical for normal cellular function and dysregulated ADAR activity can result in a variety of neurological disorders such as epilepsy and Prader Willi Syndrome, depression, schizophrenia, Amyotrophic Lateral Sclerosis, as well as cancer (Maas et al., 2006; Morabito et al., 2010; Silberberg et al., 2012). To further support the role of A→I RNA editing in organismal health, it has been demonstrated that both genetic knockouts of *ADAR1* or *ADAR2* in mice result in embryonic and neonatal death respectively (Hartner et al., 2004; Higuchi et al., 2000; Wang et al., 2004).

While many diseases mentioned above are associated with dysregulated ADAR activity, Dyschromatosis Symmetrica Hereditaria (DSH) and AGS can be attributed to specific mutations mapped to the *ADAR1* gene. Moreover, most of the mutations of these disorders map to the catalytic domain of ADAR1 (Al Wardat et al., 2024; Hou et al., 2007; Rice et al., 2012), indicating the important role that this domain has on identifying RNA targets and efficiently editing dsRNA sites. Patients with DSH, commonly found in East Asian countries, display a rare pigmentary genodermatosis, but otherwise healthy asymptomatic individuals also exist (Hayashi & Suzuki, 2013). Further research is needed to better dissect the link between mutant *ADAR1* and different DSH phenotype. On the other hand, AGS is caused by mutations in multiple genes whose protein products, including *ADAR1*, are all involved in nucleic acid metabolism or sensing, suggesting a variety of nucleic acid ligands that trigger the AGS-associated IFN response (Livingston & Crow, 2016). Sensing of viral nucleic acids and distinguishing them from host nucleic acids is a key aspect of the human immune response. A→I editing of RNA by ADAR1 differentiates "self" RNA from "non-self" RNA (Liddicoat et al., 2016). Retinoic acid-inducible gene I (*RIG-I*)-like receptors, including melanoma differentiation-associated protein 5 and RIG-I, are cytosolic RNA surveillance machineries that screen for "non-self" RNAs generated following ADAR mutations (Hartmann, 2017). Both these RLRs interact with the mitochondrial activation signaling protein, ultimately activating transcription factors that initiate the expression of immune response genes, ranging from interferon to antiviral genes (Grochowska et al., 2021). Recent studies suggest that defects in ADAR1 activity lead to the production of dsRNA which are considered recognized as "non-self" from RLRs causing interferon induction and canonical AGS symptoms (Mannion et al., 2014). A correct surveillance system for RNA editing and maturation is thus fundamental to avoid insurgence of this peculiar leukodystrophy.

3.3 | Association between RNA translation dysfunction and leukodystrophies

Translation of DNA into functional proteins is one of the cornerstones of cellular biology. Indeed, proper cell metabolism depends on tightly controlled processes of conversion of DNA into mRNA followed by proper translation of mRNA into proteins (Hershey et al., 2019). Little is currently known about the impact of translational aberrations on the development of neurological disorders (Chen et al., 2019). Protein synthesis is one of the most complex processes in the cell because it requires the action of ribosomes, tRNAs and numerous translation factors which decode the information contained in mRNA into a polypeptide chain. Specifically, during canonical protein synthesis, the cytosolic ribosome is recruited to the mRNA and scans its 5′ UTR (Yan et al., 2016). Several key signaling pathways, including mTOR, MAPKs and integrated stress response pathways, converge on the initiation step to control the rate of protein synthesis in response to a variety of external and internal cues (Proud, 2019). The intricate nature of this process makes it susceptible to deregulation at multiple levels, leading to a wide spectrum of human diseases, including immunodeficiency, neurological disorders and cancer (Buffington et al., 2014; Piccirillo et al., 2014). Emerging evidence revealed that neurons have a slower protein turnover than the rest of the cells, leading to extended protein half-lives in the brain (about 3 times longer than rest of the tissues). As a consequence, alterations in mRNA translation will have specific long-lasting effects in neurons (Jishi et al., 2021). Translation of synaptic proteins in neurons occurs continuously in both neuronal dendrites and in the synapse with dendritic-localized mRNA, with nascent proteins then transported to synaptic sites (Hafner et al., 2019; Jung et al., 2012). In either case, inducing production of nascent synaptic proteins in a timely manner seems to be essential to respond to neuronal activity in the synapse.

Dysregulation of RNA translation during brain development has been reported in POLR3-related leukodystrophy, as transcribed targets of Pol III include multiple tRNAs and rRNAs (Dorboz et al., 2018; Dumay-Odelot et al., 2010). A recent study demonstrated the correlation between POLR3-related leukodystrophy caused by biallelic pathogenic variants in *POLR3D gene* and overall decrease in both tRNAs expression and protein expression (Macintosh et al., 2023). Multiple proteins of the CNS seem to be affected by the previous described mechanism, including myelin. Therefore, hypomyelination takes place and contributes to the pathogenicity of POLR3-related leukodystrophy as consequence of impaired protein synthesis (Dorboz et al., 2018). Moreover, mutations in Aminoacyl-tRNA synthetases (ARSs) were also linked to multiple neurological diseases, including hypomyelinating leukodystrophies (HLDs) (Yoon et al., 2023),

TABLE 1 Summary of proposed epigenetic and RNA metabolism mechanisms reported as involved in leukodystrophies.

Name of disorder	Mim	Gene	Inherit.	Reported epigen mechan	RNA Metab
Pol-III Related Disorders (4H Syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism))	607,694	(HLD7) *POLR3A*	AR	H3K9ac; H3K27ac; BC200; 7SL; AIMP1 splice variant	RPC4/RPC5 dimerization; RPC4 Sumoylation; tRNA levels; snRNA expression
	614,381	(HLD8) *POLR3B*	AR		
	n.a.	*POLR3D*	n.a.		
	616,494	(HLD11) *POLR1C*	AR		
	619,310	(HLD21) *POLR3K*	AR		
18q Minus Syndrome	601,808	18q	AD	/	/
X Linked Adrenoleukodystrophy (X-ALD)	300,100	*ABCD1*	XLR	Histone modifications (HDACs); DNA methylation	/
Adult Onset Leukodystrophy with Neuroaxonal Spheroids and Pigmented Glia (Including Hereditary Diffuse Leukoencephalopathy with Spheroids, HDLS, and Pigmentary Type of Orthochromatic Leukodystrophy with Pigmented Glia, POLD)	619,661	*AARS1*	AD	/	Altered expression of ARS mRNA
	221,820	*CSF1R*	AD	/	/
Aicardi–Goutières Syndrome (AGS)	225,750	(AGS1) *TREX1*	AD/AR	miR-219; let-7e;	/
	610,181	(AGS2) *RNASEH2B*	AR	miR-16-1; miR-27a;	/
	610,329	(AGS3) *RNASEH2C*	AR	miR-95; miR-134; miR-181a;	/
	610,333	(AGS4) *RNASEH2A*	AR	miR-185; miR-302e;	/
	612,952	(AGS5) *SAMHD1*	AR	miR-371; miR-375;	/
	615,010	(AGS6) *ADAR1*	AD/AR	miR-425; miR-509; miR-557;	mRNAs degradation
	615,846	(AGS7) *IFIH1*	AD	miR-636; miR-637;	/
	619,486	(AGS8) *LSM11*	AR	miR-1226; miR-1247;	/
	619,487	(AGS9) *RNU7-1*	AR	[miR-3614-5p, miR-320c miR-181a-2-3p A→I editing 218 altered lncRNas]*	/
Alexander Disease (AxD)	203,450	*GFAP*	AD	Histone acetylation (HATs) and deacetylation (HDAC6); DNA methylation	/
Autosomal Dominant Leukodystrophy with Autonomic Disease (ADLD)*	169,500	*LMNB1*	AD	miR-23	/
Canavan Disease	271,900	*ASPA*	AR	/	/
Cerebrotendinous Xanthomatosis (CTX)	213,700	*CYP27A1*	AR	/	/
Chloride Ion Channel 2 (CIC-2) Related Leukoencephalopathy with Intramyelinic Oedema	615,651	*CLCN2*	AR	/	/

(Continues)

TABLE 1 (Continued)

Name of disorder	Mim	Gene	Inherit.	Reported epigen mechan	RNA Metab
eIF2B Related Disorder (Vanishing White Matter Disease or Childhood Ataxia with Central Nervous System Hypomyelination (CACH))	(VWM1) 603,896	*EIF2B1*	AR	/	/
	(VWM2) 620,312	*EIF2B2*	AR	/	/
	(VWM3) 620,313	*EIF2B3*	AR	/	/
	(VWM4) 620,314	*EIF2B4*	AR	/	/
	(VWM5) 620,315	*EIF2B5*	AR	/	/
Fucosidosis	230,000	*FUCA1*	AR	/	/
Globoid Cell Leukodystrophy (Krabbe)	245,200	*GALC*	AR	/	/
Hypomyelination With Atrophy of The Basal Ganglia and Cerebellum (H-ABC)	612,438	*TUBB4A*	AD	/	/
Hypomyelination With Brainstem and Spinal Cord Involvement and Leg Spasticity (HBSL)*	615,281	*DARS1*	AR	/	Altered expression of DARS mRNA
Hypomyelination With Congenital Cataract (HCC)	610,532	*HYCC1*	AR	/	/
Leukoencephalopathy With Brainstem and Spinal Cord Involvement and Lactate Elevation (LBSL)	611,105	*DARS2*	AR	/	Altered expression of DARS mRNA
Leukoencephalopathy with Thalamus and Brainstem Involvement and High Lactate (LTBL)	614,924	*EARS2*	AR	/	Altered expression of EARS mRNA
Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC)	604,004	*MLC1*	AR	/	/
Metachromatic Leukodystrophy and Its Biochemical Variants (MLD)	250,100	*ARSA*	AR	/	/
Oculodentodigital Dysplasia	164,200	*GJA1*	AD	/	/
Pelizaeus Merzbacher Disease (PMD)	312,080	*PLP1*	XLR	/	/
Peroxisomal Biogenesis Disorders (Including Zelleweger, Neonatal Adrenoleukodystrophy and Infantile Refsum)	601,498	*PEX6*	AR	/	/
	601,758	*PEX12*	AR	/	/
	608,666	*PEX26*	AR	/	/
	602,859	*PEX10*	AR	/	/
	170,993	*PEX2*	AR	/	/
	600,414	*PEX5*	AR	/	/
	601,789	*PEX13*	AR	/	/
	603,360	*PEX16*	AR	/	/
	603,164	*PEX3*	AR	/	/
	600,279	*PEX19*	AR	/	/
	601,791	*PEX14*	AR	/	/
	603,867	*PEX11B*	AR	/	/
	601,757	*PEX7*	AR	/	/

TABLE 1 (Continued)

Name of disorder	Mim	Gene	Inherit.	Reported epigen mechan	RNA Metab
Polyglucosan Body Disease (PGBD)	263570	*GBE1*	AR	/	/
RNAse T2 Deficient Leukoencephalopathy	612,944	*RNASET2*	AR	/	RNA processing and degradation
Sialic Acid Storage Disorders (Salla Disease, Infantile Sialic Acid Storage Disease and Intermediate Form)	604,322	*SLC17A5*	AR	/	/
Single Enzyme Deficiencies of Peroxisomal Fatty Acid Beta Oxidation (Including Only D-Bifunctional Protein Deficiency; Sterol Carrier Protein X (SCPx) Deficiency; Peroxisomal Acyl-Coa-Oxidase Deficiency)	261,515	*HSD17B4*	AR	/	/
	613,724	*SCP2*	AR	/	/
	264,470	*ACOX1*	AR	/	/
Sjögren–Larsson Syndrome	270200	*ALDH3A2*	AR	/	/
SOX10-Associated PCWH: Peripheral Demyelinating Neuropathy, Central Dysmyelinating Leukodystrophy, Waardenburg Syndrome, And Hirschsprung Disease	609136	*SOX10*	AD	/	/

Note: Leukodystrophies are listed according to the consensus classification published by Vanderver et al., 2015. "INHERIT." stays for inheritance; "REPORTED EPIGEN MECHAN" stays for reported epigenetic mechanisms; "RNA METAB" stays for RNA metabolism. "/" means that no evidence regarding epigenetics has been found in the state of the art. "*" Specific to ADAR1 mutation. "n.a." stays for not available OMIM related to the pathology and not available inheritance reported.

leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) and leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) (Yoon et al., 2023). ARSs are enzymes that catalyze the ligation of amino acids to tRNAs for translation, and mutations in these enzymes were linked to multiple neurological diseases, including hypomyelinating leukodystrophies (HLDs) (Yoon et al., 2023). A different classification is present depending on the cellular localization and type of ARS, and cytoplasmic ARS are associated with hypomyelinating forms, whereas mitochondrial ARS are associated with demyelinating forms of the pathology (Sissler et al., 2017; Turvey et al., 2022; Yoon et al., 2023). Moreover, a novel homozygous splice site variant in aminoacyl tRNA synthetase complex interacting multifunctional protein 1 (AIMP1), whose precursor protein is identical to the p43 subunit, associated with the multi-tRNA synthetase complex, was found to be linked to HLD (Quental et al., 2023).

4 | CONCLUSION

In conclusion, leukodystrophies are rare genetic disorders that primarily affect the white matter of the CNS, leading to progressive and often debilitating neurological symptoms. While our understanding of leukodystrophies has grown significantly, there is still much to learn about their underlying mechanisms. Epigenetic alterations at the DNA level have emerged as an important area of research in leukodystrophies. DNA methylation and histone modifications can influence gene transcription and contribute to the development of these disorders. The dynamic nature of epigenetic changes suggests their potential role in disease pathogenesis and progression. Furthermore, non-coding RNAs, including miRNAs and lncRNAs, have been implicated in the regulation of gene expression and may play a crucial role in leukodystrophies. These molecules are involved in various cellular processes, and their dysregulation could contribute to the heterogeneity of leukodystrophies. Additionally, disruptions in RNA metabolism, including transcription, editing, and translation, have been associated with leukodystrophies. Mutations in genes encoding components of RNA polymerases and RNA editing enzymes have been linked to these diseases, highlighting the importance of proper RNA processing in maintaining neurological health. In summary, leukodystrophies represent a complex group of disorders with diverse underlying mechanisms, including epigenetic and RNA-related processes (Table 1). Ongoing research in these areas holds promise for improving our understanding of leukodystrophies and developing potential therapeutic strategies to alleviate the symptoms and enhance the quality of life for affected individuals (Ashrafi et al., 2020;

Bradbury & Ream, 2021). Indeed, several approaches can be explored in the context of epigenetic therapy, such as DNA methylation inhibitors, HDACs inhibitors and gene editing technologies (Aerts-Kaya & van Til, 2023; Bradbury & Ream, 2021; Lanciotti et al., 2021). Even so, some limitations still exist, and further research is needed before moving toward therapy. Epigenetic approaches may not exclusively target the intended genomic regions, leading to off-target effects that could result in unintended consequences. Moreover, achieving precise control over specific epigenetic modifications at the desired genomic loci remains a challenge. Exploring more precise delivery systems, such as nanoparticles or viral vectors, and improving the specificity of drugs or gene-editing tools to target specific regions could prove of value in this case. Getting therapeutic agents to the target cells in the CNS is also challenging, and researchers are investigating innovative delivery methods, such as intrathecal administration or developing nanoparticles that can cross the blood–brain barrier. Lastly, leukodystrophies are a diverse group of disorders with different genetic mutations; thus, tailoring therapies to the specific genetic and molecular characteristics of each subtype is a significant challenge, especially considering that a comprehensive understanding of these pathologies is still lacking. Precision medicine approaches that consider the individual genetic profile of patients will offer a more personalized and effective treatment strategy.

AUTHOR CONTRIBUTIONS

Federica Rey: Conceptualization (lead); investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Letizia Esposito:** Formal analysis (equal); investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Erika Maghraby:** Investigation (equal); writing – original draft (equal). **Alessia Mauri:** Investigation (equal); writing – review and editing (equal). **Clarissa Berardo:** Investigation (equal); writing – review and editing (equal). **Eleonora Bonaventura:** Investigation (equal); writing – review and editing (equal). **Davide Tonduti:** Funding acquisition (equal); investigation (equal); writing – original draft (equal). **Stephana Carelli:** Conceptualization (lead); methodology (equal); project administration (equal); supervision (equal); writing – original draft (lead); writing – review and editing (lead). **Cristina Cereda:** Conceptualization (supporting); funding acquisition (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

OPEN RESEARCH BADGES

This article has earned an Open Data badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available at wrna.wiley.com.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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