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Alexander Disease (AxD) Is a Progressive, Usually Fatal Neurodegenerative Disease[1]

AxD is a rare type of astrocytic leukodystrophy caused by *GFAP* mutations and characterized by the formation of Rosenthal fibers that generally affect the CNS.[1-3]

AxD Can Lead to the Progressive Development of Severe Disabilities and Death[3-5]

AxD generally affects the white matter of the CNS, which can lead to a range of symptoms (eg, macrocephaly, seizures, difficulty speaking and/or swallowing).[1,3]
In addition, AxD has been observed across all ages and typically progresses in severity, which may eventually lead to death.[3-5]

Pathogenic variants in *GFAP* can cause AxD, which results in the formation of Rosenthal fibers[a] that can alter astrocytic function.[1,6,7]

Figure 1: Percentage of Patients With AxD by Age Group[3,b]

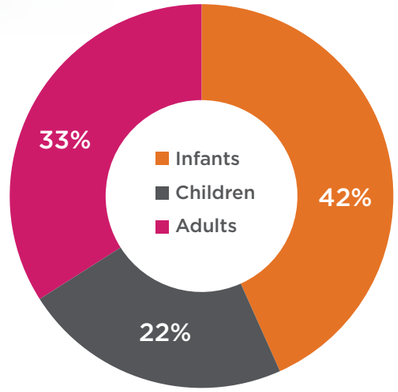
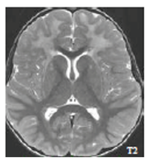


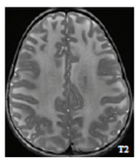
Figure 2: AxD Can Manifest With a Range of Radiologic Features[8,c]

AxD With Predominant White Matter Abnormalities

Frontally predominant

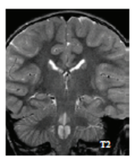


Diffuse

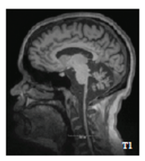


AxD With Absent to Mild White Matter Abnormalities

Brainstem lesion



Medullary atrophy



MRI pattern recognition in AxD is critical for timely diagnosis.
In an MRI study, patients with AxD typically had white matter abnormalities (54/73), which were frontally predominant and diffuse. However, patients with absent to mild white matter abnormalities presented with brainstem lesions and atrophy in the medulla, cerebellum, and/or spinal cord (19/73).[8]

Adapted from Waldman 2019.

Systems that classify AxD into subtypes based on age of onset or symptoms do not sufficiently capture the range of clinical manifestations and radiologic features of this disease.[3,8,9]

[a]Cytoplasmic protein aggregates resulting from the overexpression and accumulation of GFAP.[6] [b]3% of patients were asymptomatic.[3] [c]Results are based on a single natural history study of 73 patients with AxD at the Children's Hospital of Philadelphia. MRI images for each of the patients were reviewed by a blinded neuroradiologist and yielded case reports that included 23 variables capturing signal or tissue abnormality in distinct regions of interest.[8]
CNS, central nervous system; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging.

1. Messing A. *Handb Clin Neurol.* 2018;148:693-700. 2. Sosunov AA, et al. *Acta Neuropathol Commun.* 2017;5(1):27. 3. Srivastava S, et al. Alexander disease. In: Adam MP, Ardinger HH, Pagon RA, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2024. November 15, 2002. Updated November 12, 2020. Accessed January 22, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1172/ 4. Li R, et al. *Ann Neurol.* 2005;57(3):310-326. 5. Yoshida T, et al. *J Hum Genet.* 2013;58(9):635-638. 6. Kuhn J, Cascella M. Alexander disease. In: *StatPearls.* January 2024. Updated September 4, 2023. Accessed January 30, 2024. https://www.ncbi.nlm.nih.gov/books/NBK562242/ 7. Jung S, et al. *BMC Med Inform Decis Mak.* 2015;15(suppl 1):S6. 8. Waldman A, et al. Presented at: 2019 Annual Meeting of the American Academy of Neurology; May 4-10, 2019; Philadelphia, PA. 9. Messing A. *Alexander Disease: A Guide for Patients and Families.* Morgan & Claypool Life Sciences; 2018. Revised with Appendix 2021.

AxD Is a Progressive, Usually Fatal Neurodegenerative Disease[1]

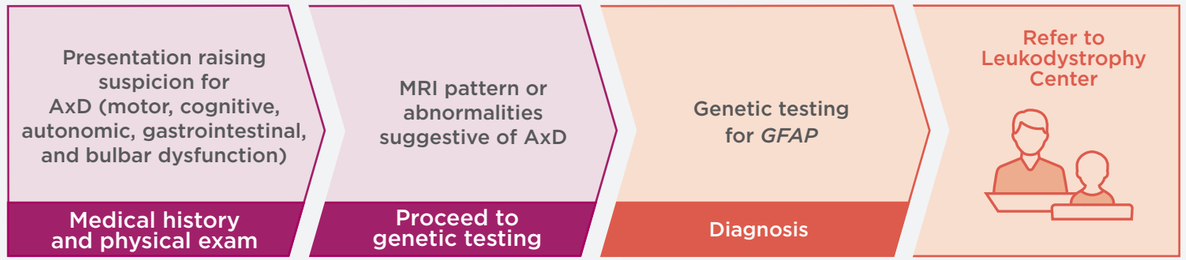
Clinical manifestations associated with AxD may overlap with more prevalent neurodegenerative disorders, which can lead to a misdiagnosis or delayed diagnosis and impact care.[1-3]

Table: Differential Diagnoses for AxD[2-7,a]

Pediatric-Onset Diseases		Adult-Onset Diseases	
Adrenoleukodystrophy	Tumors	Parkinson's disease	Multiple sclerosis
Canavan disease	Pelizaeus-Merzbacher disease	Multisystem atrophy	Tumors
Krabbe leukodystrophy	Metachromatic leukodystrophy	Ataxias	Adrenoleukodystrophy
	Zellweger spectrum disorder		

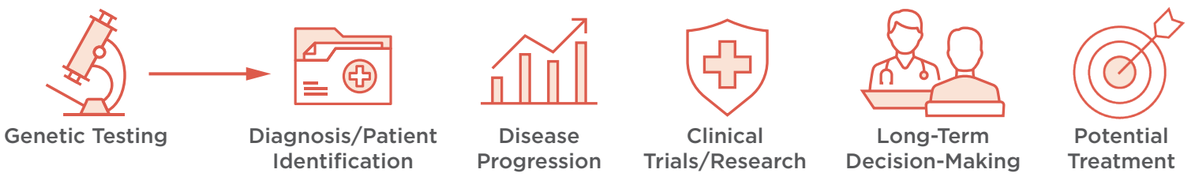
Patients with AxD should ideally be managed with a collaborative multidisciplinary team of HCPs due to the range of clinical symptoms and treatment considerations.[6]

Figure 3: Genetic testing for variant *GFAP* confirms a diagnosis for AxD, which is generally preceded by suspicion based on clinical and radiographic features[3,6,8,9,b]



Genetic testing should be considered to identify a patient with AxD due to the heterogeneity of clinical features associated with the disease.[6,7]

Genetic testing may shorten the time it takes to identify patients, inform treatment choices, and provide opportunities for research or clinical trials.[10-12]



[a]Not a comprehensive list. [b]Approximately 95% of AxD patients have a confirmed mutation in *GFAP*.[7]
AxD, Alexander disease; *GFAP*, glial fibrillary acidic protein; HCP, healthcare professional; MRI, magnetic resonance imaging.

1. Alexander disease. National Organization for Rare Disorders. Accessed January 30, 2024. https://rarediseases.org/rare-diseases/alexander-disease/ 2. Pareyson D, et al. *Brain.* 2008;131(Pt 9):2321-2331. 3. Srivastava S, et al. Alexander disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2024. November 15, 2002. Updated November 12, 2020. Accessed February 11, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1172/ 4. Messing A. *Handb Clin Neurol*. 2018;148:693-700. 5. van der Knaap MS, et al. *AJNR Am J Neuroradiol.* 2001;22(3):541-552. 6. Kuhn J, Cascella M. Alexander disease. In: *StatPearls.* January 2024. Updated September 4, 2023. Accessed January 22, 2024. https://www.ncbi.nlm.nih.gov/books/NBK562242/ 7. Messing A. *Alexander Disease: A Guide for Patients and Families*. Morgan & Claypool Life Sciences; 2018. Revised with Appendix 2021. 8. Adang LA, et al. *Mol Genet Metab*. 2017;122(1-2):18-32. 9. Prust M, et al. *Neurology*. 2011;77(13):1287-1294. 10. Zhang L, Hong H. *Pharmaceutics*. 2015;7(4):542-553. 11. Roggenbuck J, et al. *Genet Med*. 2017;19(3):267-274. 12. Klein CJ, Foroud TM. *Mayo Clin Proc*. 2017;92(2):292-305.

MECP2 Duplication Syndrome (MDS) Is a Rare, X-Linked, Neurodevelopmental Disorder[1]

MDS is a rare, severe, neurodevelopmental disorder caused by duplication of the chromosomal region containing the *MECP2* gene (Xq28). Overproduction of the MeCP2 protein leads to neurotoxicity.[1,2]

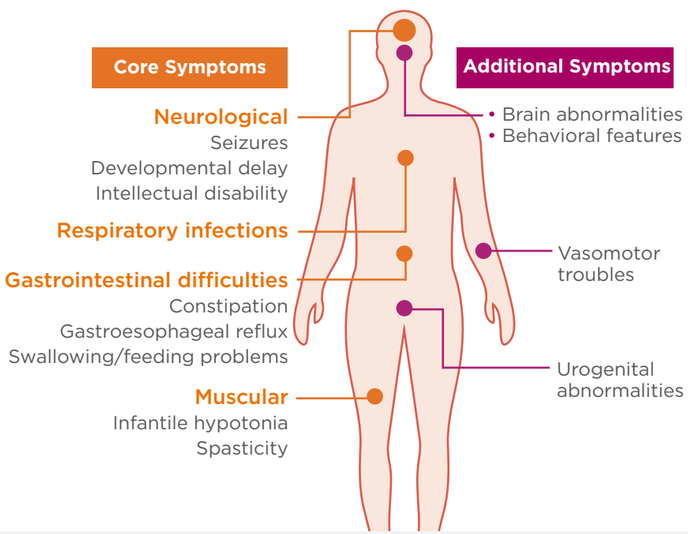
MDS predominantly affects males (~90%).[3] Females with MDS are typically carriers but may show neuropsychiatric symptoms such as depression, anxiety, and autistic features.[1]

MDS is not to be confused with Rett syndrome, which is caused by loss-of-function mutations in *MECP2* and primarily affects females.[4]

MDS Is Characterized by a Range of Symptoms, Including Neurological, Muscular, Respiratory, and Gastrointestinal Manifestations[1]

Symptoms of MDS begin neonatally, with infantile hypotonia. MDS is also characterized by global developmental delay, severe intellectual disability, poor speech development, seizures, gastrointestinal problems, and recurrent respiratory infections (**Figure 1**).[1]

Figure 1: Symptoms Associated With MDS[1,2,5,a]

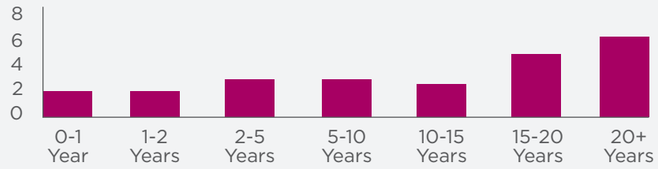


Up to 90% of people with MDS will develop seizures by adolescence. Epilepsy tends to occur later in childhood and then progress, becoming treatment refractory. It may develop into symptoms consistent with Lennox-Gastaut syndrome. Developmental regression often follows the onset of epilepsy.[6]

~50% of people with MDS will not survive past the age of 25 years, mainly due to recurrent infections.[7,8]

The severity of functional disability and frequency of hospitalizations due to respiratory infections (**Figure 2**) both increase with disease progression.[3,9]

Figure 2: Median Number of Estimated Hospitalizations per Hospitalized Individual due to Respiratory Infections[3]



[a]Not a complete list of symptoms.
MECP2, methyl CpG binding protein-2.
1. Ta D, et al. *Orphanet J Rare Dis*. 2022;17(1):131. 2. John Cherian D, et al. *Children (Basel)*. 2023;10(7):1202. 3. Ta D, et al. *Children (Basel)*. 2022;9(5):633. 4. D'Mello SR 3rd. *J Neurochem*. 2021;159(1):29-60. 5. National Organization for Rare Disorders. MECP2 Duplication Syndrome. 2013. Updated March 22, 2017. Accessed January 10, 2024. https://rarediseases.org/rare-diseases/mecp2-duplication-syndrome/ 6. Marafi D, et al. *Neurology*. 2019;92(2):e108-e114. 7. Van Esch H. *MECP2* duplication syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2023. January 18, 2008. Updated May 21, 2020. Accessed January 12, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1284/ 8. Van Esch H. *Mol Syndromol*. 2012;2(3-5):128-136. 9. Peters SU, et al. *Am J Med Genet A*. 2021;185(2):362-369.

Earlier Diagnosis and Treatments Targeting the Underlying Pathophysiology Are Critical Unmet Needs for Patients With *MECP2* Duplication Syndrome (MDS)[1-3]

Prevalence of MDS is unknown because patients may be misdiagnosed or undiagnosed.[1]

1% to 2% of males with moderate to severe intellectual disability are estimated to have MDS.[4]

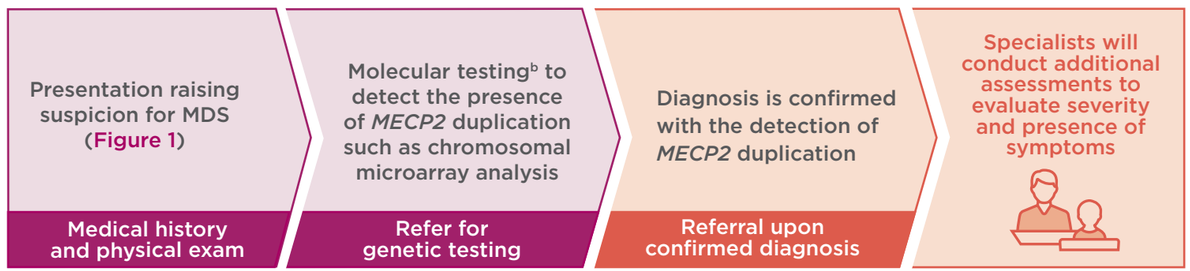
Understanding which disorders have overlapping symptomology with MDS (**Table 1**) and how they differ may be useful for a differential diagnosis.[1]

Table: Disorders With Overlapping Symptomology[1,5,a]

Autism spectrum disorder	Alpha thalassemia X-linked intellectual disability	Coffin-Lowry syndrome	*MCT8*-specific thyroid hormone cell transporter deficiency
Rett syndrome	L1 syndrome	Lowe syndrome	Renpenning syndrome

MDS is distinguished from Rett syndrome by a higher incidence in males, early-onset hypotonia, and recurrent respiratory infections[2]

Figure 3: Molecular Genetic Testing for Duplication of *MECP2* Confirms MDS[1,6-8]



Treatment and Management Approaches Focus on Minimizing Symptoms and Maintaining Quality of Life[1,6]

Currently, there is no cure or treatment for patients with MDS that can stop, reverse, or address the underlying pathogenic cause of disease.[1]

Management is complex and may require coordination with multiple specialists. Current management strategies include pharmacological and nonpharmacological interventions, such as surgical procedures, dietary regimens, physical therapy, and social activities.[1]

[a]Not a complete list. [b]Tests include intellectual disability multigene panel, comprehensive genomic testing, exome array, array comparative genomic hybridization, polymerase chain reaction, fluorescent in situ hybridization analysis, chromosome microarray SNP analysis, and multiplex ligation-dependent probe amplification.[1,6]
L1, L1 cell adhesion molecule protein; *MCT8*, monocarboxylate transporter 8; *MECP2*, methyl CpG binding protein-2; SNP, single nucleotide polymorphism.
1. National Organization for Rare Disorders. MECP2 Duplication Syndrome. 2013. Updated March 22, 2017. Accessed February 10, 2024. https://rarediseases.org/rare-diseases/mecp2-duplication-syndrome/ 2. Collins BE, Neul JL. *Neuropsychiatr Dis Treat*. 2022;18:2813-2835 3. D'Mello SR 3rd. *J Neurochem*. 2021;159(1):29-60. 4. Lugtenberg D, et al. *Eur J Hum Genet*. 2009;17(4):444-453. 5. Ta D, et al. *Children (Basel)*. 2022;9(5):633. 6. Van Esch H. *MECP2* duplication syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2023. January 18, 2008. Updated May 21, 2020. Accessed January 12, 2024. https://www.ncbi.nlm. nih.gov/books/NBK1284/ 7. Van Esch H. *Mol Syndromol*. 2012;2(3-5):128-136. 8. Ramocki MB, et al. *Ann Neurol*. 2009;66(6):771-782.

Pelizaeus-Merzbacher Disease (PMD) Is a Spectrum of Rare, X-Linked Recessive Hypomyelinating Leukodystrophies[1-3]

PMD is caused by genetic variants to proteolipid protein 1 (*PLP1*) and is associated with a wide spectrum of clinical symptoms depending on the variant form (**Table**). PMD typically presents in males and is broadly classified into three categories of disease ranging from least to most severe (**Figure 1 and Table**).[2-4]

PMD is associated with impairments in patient quality of life, including ambulatory, cognitive, developmental, ocular, and dietary impairments.[4,5] Cognitive and motor impairments, hypotonia, and nystagmus are seen in the majority of patients.[6]

Figure 1: Percentage of Patients With PMD by Category[4]

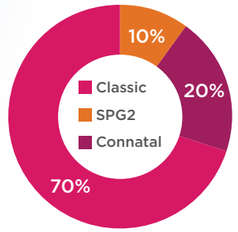


Table: Clinical Spectrum of PMD[4,5,7]

	Spastic Paraplegia 2 (SPG2)[a]	Classic	Connatal
	Least Severe	Moderately Severe	Most Severe
Typical Etiology	Inactivation of *PLP1*	Gene duplication[b]	Intragenic sequence variants[c]
Molecular Mechanism	Absence of PLP1	PLP1 overexpression	PLP1 misfolding
Disease Pathology	Decreased myelin synthesis and axonal injury	Absent or decreased myelination and oligodendrocyte dysfunction	Decreased myelination, oligodendrocyte apoptosis and axonal injury
Age of Onset	1st-5th year	1st-5th year	Neonatal
Life Span	4th decade-normal lifespan	3rd-7th decade	Infancy to 3rd decade
Type-Specific Symptoms[d]	Mild spasticity, ataxia, mild to absent developmental impairments	Impaired ambulation, spasticity, motor and cognitive developmental delay, ataxia	Severe motor and cognitive developmental delay, severe spasticity, ataxia, lack of ambulation and verbal skills

PMD Is Associated With Imaging Abnormalities and Hypomyelination[7,8]

Figure 2: Decreased Myelination Is Seen Across Brain Regions in PMD Patients[8,9]

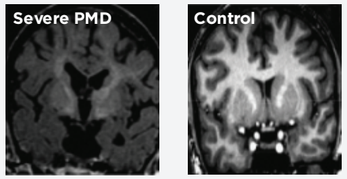


Figure adapted from Laukka JJ, et al. *J Neurol Sci*. 2013;335(1-2):75-81.

PMD is associated with developmental hypomyelination.[2,4,8] The degree of white matter atrophy is correlated with functional disability.[9] Lack of myelin is the imaging hallmark in all cases of PMD.[8]

In a patient with *PLP1* duplication with severe functional disability, brain imaging shows reduced signal in the subcortical white matter, internal capsule and temporal lobes (**Figure 2**).[9]

[a]This category includes patients with *PLP1* null syndrome.[5] [b]Duplications commonly present as classic PMD.[8] [c]Missense variants may cause other forms of PMD.[8] [d]Not a complete list.

1. Bonkowsky JL, et al. *Neurology*. 2010;75(8):718-725. 2. Grossi S, et al. *Orphanet J Rare Dis*. 2011;6:40. 3. Singh R, Samanta D. Pelizaeus-Merzbacher disease. In: *StatPearls*. Updated July 4, 2023. Accessed October 16, 2023. https://www.ncbi.nlm.nih.gov/books/NBK560522/ 4. Khalaf G, et al. *Biomedicines*. 2022;10(7):1709. 5. Wolf NI, et al. *PLP1* disorders. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2023. Updated December 19, 2019. Accessed October 16, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1182/ 6. Trepanier AM, et al. *Clin Case Rep*. 2023;11(9):e7814. 7. Osório JM, Goldman SA. *Handb Clin Neurol*. 2018;148:701-722. 8. Harting I, et al. *Eur J Paediatr Neurol*. 2022;41:71-79. 9. Laukka JJ, et al. *J Neurol Sci*. 2013;335 (1-2):75-81.

Earlier Diagnosis and Treatments Targeting the Genetic Cause of Pelizaeus-Merzbacher Disease (PMD) Are Critical Unmet Needs for Patients[1-3]

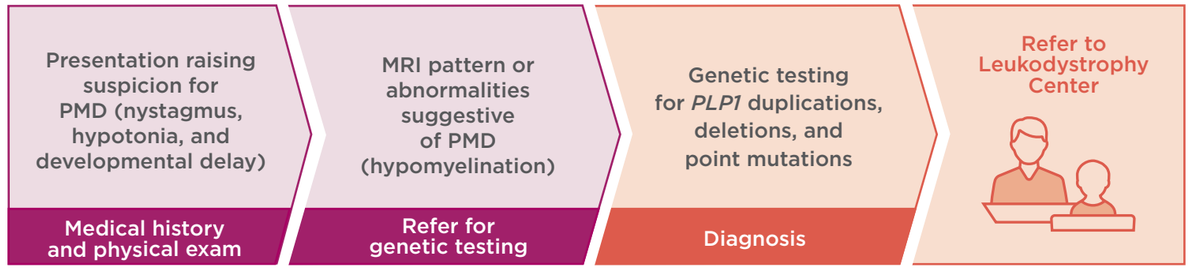
Clinical Features That Should Prompt Suspicion of PMD[3,4]

PMD is the most common hypomyelinating leukodystrophy seen in males, and screening for PMD should be considered in all males presenting with a leukodystrophy.[3]

PMD should be suspected in male patients with hypomyelination, clinical nystagmus, hypotonia, and developmental delay.[4]

Nystagmus, either isolated or associated with other symptoms, is the symptom that initially presents in almost all patients with PMD.[1,5,6]

Figure 3: Pediatric Genetic Testing for Variants in *PLP1* Confirms PMD, Which Is Generally Preceded by Suspicion Based on Clinical and Radiographic Features[2-8]



Effective Therapeutics and Early Patient Identification Are Needed[1-3]

Early neurophysiological diagnosis and physical rehabilitation have been shown to help improve the quality of life of patients with PMD.[1]

Patients receive palliative treatments to ease pain, therapies to prevent secondary complications, and careful monitoring for additional PMD-related disease complications.[1,4]

To date, no effective cure is established, and patients are limited to palliative treatments.[1,7]

PLP1, proteolipid protein 1.

1. Khalaf G, et al. *Biomedicines*. 2022;10(7):1709. 2. Osório JM, Goldman SA. *Handb Clin Neurol*. 2018;148:701-722. 3. Bonkowsky JL, et al. *Neurology*. 2010;75(8): 718-725. 4. Wolf NI, et al. *PLP1* disorders. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2023. Updated December 19, 2019. Accessed October 16, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1182/ 5. Grossi S, et al. *Orphanet J Rare Dis*. 2011;6:40. 6. Trepanier AM, et al. *Clin Case Rep*. 2023;11(9):e7814. 7. National Organization for Rare Disorders. Pelizaeus-Merzbacher disease. Accessed December 28, 2023. https://rarediseases.org/rare-diseases/pelizaeus-merzbacher-disease/ 8. Adang LA, et al. *Mol Genet Metab*. 2017;122(1-2):18-32.