IONIS' COMMITMENT TO NEUROLOGY

LEADING THE WAY IN RNA-TARGETED THERAPEUTICS

for neurologic diseases

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Angelman Syndrome (AS) Is a Rare and Severe Neurodevelopmental Disorder[1-4]

AS is a rare, monogenic, neurodevelopmental disorder that is caused by a loss of function in the maternally inherited ***UBE3A* gene**.[1-4] The majority of AS cases (~70%-75%) are caused by **deletions in the *UBE3A* gene**, leading to the **most severe symptoms**. Truncations or missense mutations, imprinting center defects, and paternal uniparental disomy can also cause AS.[3-7]

The diagnosed prevalence of AS is approximately 1 in 21,000 people worldwide.[3,6,8,9] AS symptoms and impairments present early in life and persist throughout a normal lifespan, resulting in medical challenges that require lifelong care.[3,5,10-13]

The lack of FDA-approved disease-modifying therapies, combined with the severity of the condition, results in **high unmet clinical needs** for individuals with AS and their families.[14,15]

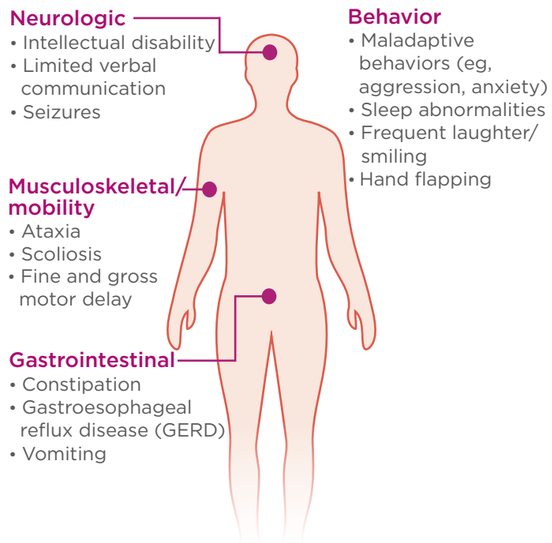
AS Is Characterized by a Range of Impairments, Including Communication, Cognitive, Motor, and Behavioral Manifestations[3,5,13]

AS is characterized by intellectual disability, seizures, communication difficulty, a very happy demeanor with frequent laughter, sleep disturbances, delays in fine and gross motor milestones, and movement issues (Figure 1).[3,5,13]

Individuals with AS may be asymptomatic at birth, but often have feeding problems in the first months of life, developmental delays between 6 and 12 months, and seizures beginning around 2 to 3 years of age.[3,5,13,16]

Clinical signs and symptoms of AS may vary based on genetic subtype. Expressive communication and cognitive impairment are universal features of AS, with the most severe disability seen in those with deletion subtype. Epilepsy is also common in all subtypes, with higher rates in those with deletion subtype and later onset in the nondeletion subtype (>5 years of age). Microcephaly is often seen in those with deletion subtype but not as frequently noted in other subtypes, while hyperphagia is more common in those with uniparental disomy or imprinting defects.[10,17]

Figure 1: Primary Symptoms Associated With AS[3,5,13]



In adulthood, individuals with AS continue to experience AS-related impairments, including cognitive disability, communication difficulties, anxiety, issues with self-care, and further decline in mobility. Sleep, seizures, and hyperactivity often become less significant impairments as individuals with AS age.[3,5,10,11]

Individuals with AS have a near-normal life expectancy but require lifelong care[3,10]

FDA, US Food and Drug Administration; *UBE3A*, ubiquitin protein ligase E3A gene.

1. Kishino T, et al. *Nat Genet*. 1997;15(1):70-73. 2. Matsuura T, et al. *Nat Genet*. 1997;15(1):74-77. 3. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 4. Larson AM, et al. *Am J Med Genet A*. 2015;167A(2):331-344. 5. Prasad A, et al. *Am J Med Genet A*. 2018;176(6):1327-1334. 6. Mertz LGB, et al. *Am J Med Genet A*. 2013;161A(9):2197-2203. 7. Hagenaar DA, et al. *J Intellect Disabil Res*. 2024;68(3):248-263. 8. Yakoreva M, et al. *Eur J Hum Genet*. 2019;27(11):1649-1658. 9. Luk HM, et al. *Eur J Med Genet*. 2016;59(6-7):315-319. 10. Duis J, et al. *Mol Genet Genomics Med*. 2022;10:e1843. 11. Khan N, et al. *Qual Life Res*. 2023;32(7):2059-2067. 12. Willgoss T, et al. *Child Psychiatry Hum Dev*. 2021;52(4):654-668. 13. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 14. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 15. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed December 16, 2025. https://rarediseases.org/rare-diseases/angelman-syndrome/ 16. Williams CA, et al. *Am J Med Genet*. 1995;56:237-238. 17. Keute M, et al. *Mol Psychiatry*. 2021;26(7):3625-3633.

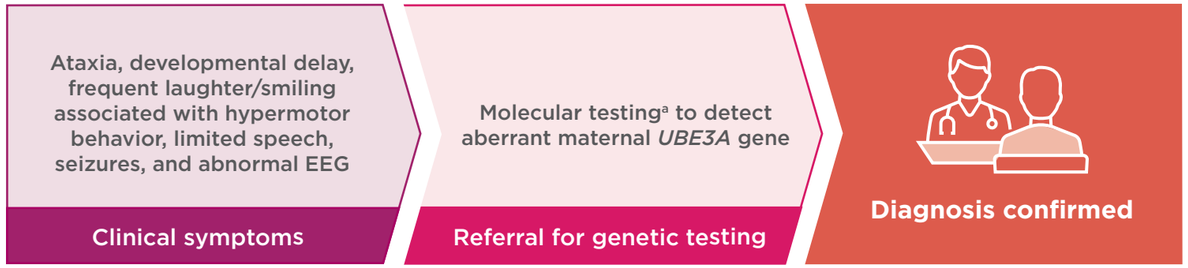
Prompt Diagnosis and Interventions Targeting the Underlying Pathophysiology of Angelman Syndrome (AS) Are Critical Unmet Needs[1-3]

Patients may experience a delay in diagnosis of up to ~3 years after symptom onset[5,6]

Disorders with overlapping symptomology[4]

- Alpha-thalassemia
- Lennox-Gastaut syndrome
- Infant autism spectrum disorder
- Mowat-Wilson syndrome
- Rett syndrome
- X-linked intellectual disability

Figure 2: Diagnosis Is Made by Clinical Observation Followed by Confirmatory *UBE3A* Genetic Testing[1-4,7]



Further diagnostic and screening efforts are needed to identify individuals with AS early in life, as they often experience developmental delays in early childhood[6]

There Are No Disease-Modifying Treatment Options Available for Individuals With AS[2,3,5]

Current treatments provide only symptomatic relief

Expressive communication[1,2,8]
- Speech therapy
- Augmentative and Alternative Communication
- Individualized education plan

Sleep[1,2,8]
- Treatment of contributing problems (eg, GERD, epilepsy, anxiety, obstructive sleep apnea)
- Sleep hygiene
- Sleep aid medications

Behavior[1,2,8]
- Physical and occupational therapy
- Hydrotherapy

Seizures[8]
- Antiseizure medications
- Low carbohydrate diet

[a]Tests include methylation studies, chromosome microarray, uniparental disomy studies, imprinting center studies, and gene sequencing.[3,4,9]

EEG, electroencephalogram; GERD, gastroesophageal reflux disease; *UBE3A*, ubiquitin protein ligase E3A gene.

1. Wheeler AC, et al. *Orphanet J Rare Dis*. 2017;12(1):164. 2. Angelman syndrome. National Organization for Rare Disorders. Updated February 14, 2018. Accessed December 16, 2025. https://rarediseases.org/rare-diseases/angelman-syndrome/ 3. Madaan M, Mendez MD. Angelman Syndrome. *StatPearls*. Treasure Island (FL): StatPearls Publishing; January 2025. Accessed December 16, 2025. https://www.ncbi.nlm.nih.gov/books/NBK560870/ 4. Maranga C, et al. *FEBS J*. 2020;287(11):2154-2175. 5. Wheeler AC, et al. *J Neurodev Disord*. 2023;15(1):37. 6. Williams CA, et al. *Am J Med Genet A*. 2006;140(5):413-418. 7. Clayton-Smith J, et al. *J Med Genet*. 2003;40(2):87-95. 8. Duis J, et al. *Mol Genet Genomic Med*. 2022;10(3):e1843. 9. Diagnosis & tests. Angelman Syndrome Foundation. Accessed December 16, 2025. https://www.angelman.org/what-is-as/testing-and-diagnosis/

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

AxD is a rare type of astrocytic leukodystrophy caused by pathological variants in *GFAP* 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]

Pathologic 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]

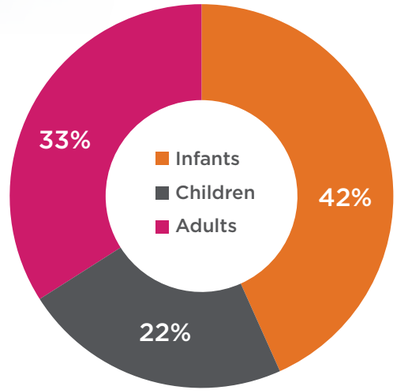
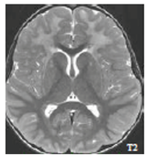


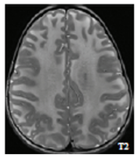
Figure 2: AxD Can Manifest With a Range of Radiologic Features[8,c]

AxD With Predominant White Matter Abnormalities

Frontally predominant

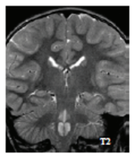


Diffuse

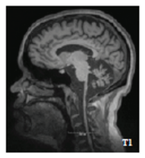


AxD With Absent to Mild White Matter Abnormalities

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]

Figures 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; *GFAP*, glial fibrillary acidic protein gene; 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 December 16, 2025. 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 December 16, 2025. 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]

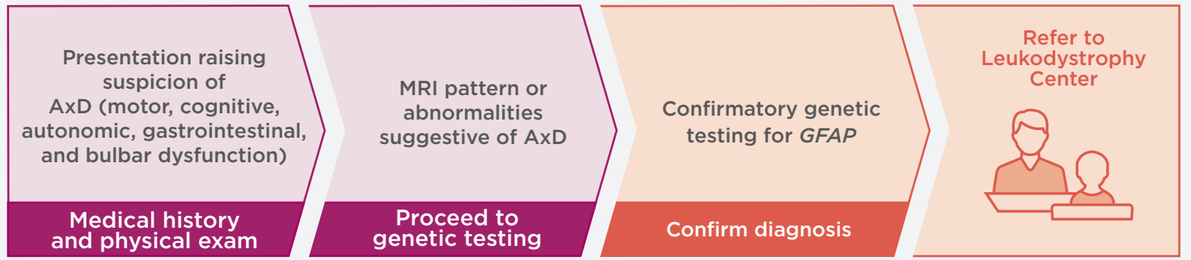
Clinical manifestations associated with AxD may overlap with more prevalent neurodegenerative disorders, which can lead to a misdiagnosis or delayed diagnosis and impact care.[1-3]

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		

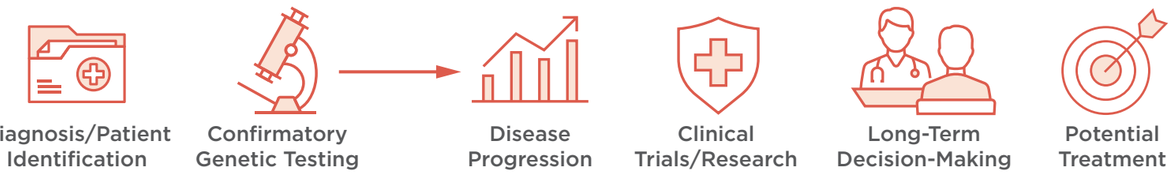
Patients with AxD should ideally be managed with a collaborative multidisciplinary team of HCPs due to the range of clinical symptoms and treatment considerations.[6]

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,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]

Confirmatory genetic testing can help inform treatment choices and provide opportunities for research or clinical trials.[9-11]



[a]Not a comprehensive list. [b]Approximately 95% of AxD patients have a confirmed variant in *GFAP*.[4]
AxD, Alexander disease; *GFAP*, glial fibrillary acidic protein gene; HCP, healthcare professional; MRI, magnetic resonance imaging.
1. Alexander disease. National Organization for Rare Disorders. Accessed December 16, 2025. 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 December 16, 2025. 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 December 16, 2025. 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. Zhang L, Hong H. *Pharmaceutics*. 2015;7(4):542-553. 10. Roggenbuck J, et al. *Genet Med*. 2017;19(3):267-274. 11. Klein CJ, Foroud TM. *Mayo Clin Proc*. 2017;92(2):292-305.

Dravet Syndrome (DS) Is a Rare, Severe, Developmental, and Epileptic Encephalopathy[1,2]

Approximately 80% to 90% of individuals with DS have a loss of function in one copy of the ***SCN1A* gene**, which encodes the sodium voltage-gated channel alpha subunit 1, $Na_V1.1$.[3-6] The presence of only one functional copy of the *SCN1A* gene results in haploinsufficiency of the sodium channel, which is primarily expressed in inhibitory interneurons. This loss of function reduces inhibitory signaling, which may contribute to disinhibition and brain hyperexcitability, that clinically manifests as treatment-resistant seizures and lifelong developmental delays.[6,7]

The prevalence of DS is estimated to be 1 in 30,000 based on studies conducted in the US, Germany, and Sweden.[8-10]

DS carries a substantial mortality risk of ~15–20%, with sudden unexpected death in epilepsy (SUDEP) accounting for nearly 50% of reported deaths.[11,12] In addition, developmental disabilities in individuals with DS remain unaddressed.[13] There are currently no disease-modifying therapies approved.[3,7,13]

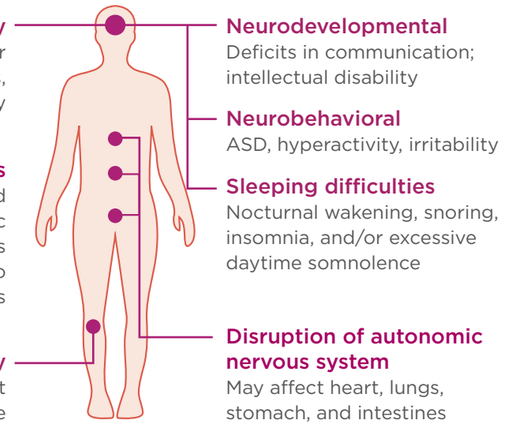
The Clinical Presentation of DS and Patient Impact[1,2]

In otherwise normally developing infants, DS is characterized by early onset seizures, which can be prolonged, **sometimes leading to status epilepticus.[1,2,7]**

By 2 years of age, **delays in language and speech, cognitive impairment, behavioral issues, as well as motor dysfunction (such as ataxia and for older children, a crouched gait)** may be present. Although seizures tend to be less severe in adulthood, developmental disabilities remain.[1,2,6,7,13]

The constant care and vigilance required for individuals with DS can **severely impact the quality of life of both patient and family.[1]**

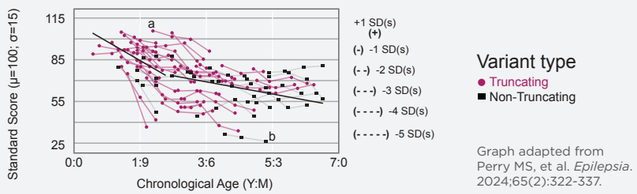
Figure 1: Primary Symptoms of DS[1-3,7,13-15]



Children With DS Experienced Comparative Progressive Worsening in Communication Impairments[16]

This was a prospective, observational, multicenter study of children aged 6 months to 5 years with a clinical diagnosis of DS and a pathogenic or likely pathogenic *SCN1A* variant. Language/communication delays were observed early, and developmental stagnation occurred after 2 years of age.[16]

Figure 2: VABS-III Communication Domain Mean Standard Scores Decreased From Baseline With Age[16]



Graph adapted from Perry MS, et al. *Epilepsia*. 2024;65(2):322-337.

[a]The highest recorded score was 106 in a child at age 2:1 Y:M.[16] [b]The lowest score was 27 in a child at age 5:1 Y:M. Higher scores are better (+) and lower scores are worse (−).[16]
ASD, autism spectrum disorder; DS, Dravet syndrome; M, month; SD, standard deviation; *SCN1A*, sodium voltage-gated channel alpha subunit 1 gene; SUDEP, sudden unexpected death in epilepsy; US, United States; VABS-III, Vineland Adaptive Behavior Scales, Third Edition; Y, year.

1. Dravet Syndrome Foundation. What is Dravet syndrome? Accessed December 16, 2025. https://dravetfoundation.org/what-is-dravet-syndrome/ 2. Epilepsy Foundation. What is Dravet syndrome? Accessed December 16, 2025. https://www.epilepsy.com/what-is-epilepsy/syndromes/dravet-syndrome#What-is-Dravet-syndrome? 3. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-77 4. Carvill GL, et al. *Neurology*. 2014;82(14):1245-1253. 5. Bayat A, et al. *Epilepsia*. 2015;56(4):e36-e39. 6. Andrade DM, et al. *Epilepsy Behav*. 2025;171:110575. 7. Shao W, et al. *Transl Psychiatry*. 2025;15(1):84. 8. Bjurulf B, et al. *Epilepsy Res*. 2022;182:106922. 9. Schubert-Bast S, et al. *Epilepsy Behav*. 2022;126:108442. 10. Hollenack K, et al. AMCP Managed Care & Specialty Pharmacy Annual Meeting 2019. *J Manag Care Spec Pharm*. 2019;25(3-a):S58. 11. Cardenal-Muñoz E, et al. *Epilepsia Open*. 2022;7(1):11-26. 12. Shmuely S, et al. *Epilepsy Behav*. 2016;64(Pt A):69-74. 13. Juandó-Prats C, et al. *Epilepsy Behav*. 2021;122:108198. 14. He Z, et al. *Epilepsy Res*. 2022;188:107041. 15. Dravet Syndrome Foundation. Comorbidities in Dravet syndrome. Accessed December 16, 2025. https://dravetfoundation.org/what-is-dravet-syndrome/comorbidities/#:~:text=Behavior,Publications/Resources 16. Perry MS, et al. *Epilepsia*. 2024;65(2):322-337.

Treatments That Target the Genetic Root Cause of DS Remain a Critical Unmet Need[1,2]

DS presents differently in each patient and may be misdiagnosed as[2]:

1. Myoclonic-Astatic Epilepsy
2. Lennox-Gastaut Syndrome
3. Intractable Epilepsy

Early and accurate diagnosis through genetic testing can help tailor management with appropriate antiseizure medications and improve outcomes in individuals with DS.[2-4]

Genetic Testing Is Recommended for Patients With Unexplained Epilepsy per AES and NSGC Guidelines[5,6]

- This includes an epilepsy gene panel or broader sequencing[2]

There Are No Disease-Modifying Treatments Approved[1,2,4]

Although disease-modifying therapies are in development, standard-of-care (SOC) treatments provide only symptomatic relief for seizures. Despite the use of multiple antiseizure medications, many patients do not achieve seizure freedom. Prolonged exposure to contraindicated medications during early life is associated with adverse developmental outcomes.[1,2,4,7,a] A natural history study showed that despite the use of SOC treatments, cognitive and behavioral development in individuals with DS plateaus at ~2 years of age, with delays increasing over time compared with neurotypical individuals.[8]

Figure 3: Current Therapeutic Algorithm for Managing Seizures in DS[4,b]:

Several areas of care in individuals with DS remain unaddressed, highlighting a significant treatment gap[1,9]:

Developmental disabilities
- Communication
- Cognition

Behavior

Movement

Sleep

SUDEP

The devastating impact of DS on patients and caregivers[1,2,10]:

- Intractable, sometimes catastrophic seizures
- Developmental disabilities
- High mortality rates (15%-20%)
- Medications lack/lose efficacy over time
- Medication side effects
- Loss of independence requiring constant supervision
- Lifelong care

[a]Sodium channel blockers, such as lamotrigine, are contraindicated for individuals with DS.[4] [b]Based on Delphi Consensus Guidelines.[4] AES, American Epilepsy Society; DS, Dravet syndrome; NSGC, National Society of Genetic Counselors; SUDEP, sudden unexpected death in epilepsy.

1. Dravet Syndrome Foundation. Voice of the patient report. Accessed December 16, 2025. https://dravetfoundation.org/wp-content/uploads/2022/05/Voice-of-the-Patient-report-5.31.22_compressed.pdf 2. Dravet Syndrome Foundation. What is Dravet syndrome? Accessed December 16, 2025. https://dravetfoundation.org/what-is-dravet-syndrome/ 3. Epilepsy Foundation. What is Dravet syndrome? Accessed December 16, 2025. https://www.epilepsy.com/what-is-epilepsy/syndromes/dravet-syndrome#What-is-Dravet-syndrome? 4. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-1777. 5. Smith L, et al. *J Genet Couns*. 2023;32(2):266-280. 6. Melendez-Zaidi A, et al. Genetic testing in the epilepsy clinic. American Epilepsy Society. June 2025. Accessed December 16, 2025. https://aesnet.org/docs/default-source/pdfs-clinical/genetic-testing-in-the-epilepsy-clinic-final.pdf?sfvrsn=45fe619c_1 7. Lagae L, et al. *Dev Med Child Neurol*. 2018;60(1):63-72. 8. Sullivan J, et al. *Neurology*. 2025;105(11):e214388. 9. Juandó-Prats C, et al. *Epilepsy Behav*. 2021;122:108198. 10. Genton P, et al. *Epilepsia*. 2011;52(suppl 2):44-49.

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.[1-3]

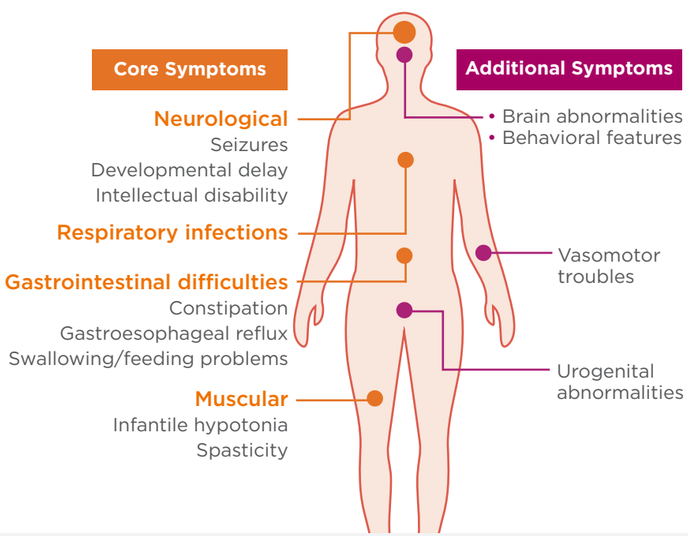
MDS predominantly affects males (~90%).[4] Females with MDS are typically carriers but may show neuropsychiatric symptoms such as depression, anxiety, and autistic features.[1]

MDS is not to be confused with Rett syndrome, which is caused by loss-of-function mutations in *MECP2* and primarily affects females.[5]

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[1,2,6,a]

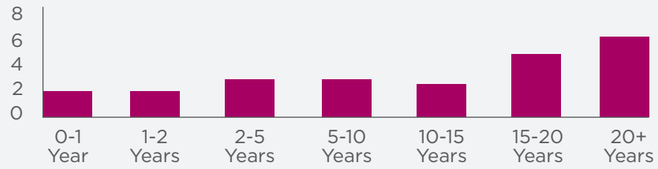


Up to 90% of people with MDS will develop seizures by adolescence. Epilepsy tends to occur later in childhood and then progress, becoming treatment refractory. It may develop into symptoms consistent with Lennox-Gastaut syndrome. Developmental regression often follows the onset of epilepsy.[7]

~50% of people with MDS will not survive past the age of 25 years, mainly due to recurrent infections.[8,9]

The severity of functional disability and frequency of hospitalizations due to respiratory infections (**Figure 2**) both increase with disease progression.[4,10]

Figure 2: Median Number of Estimated Hospitalizations per Hospitalized Individual due to Respiratory Infections[4]



[a]Not a complete list of symptoms.
MeCP2, methyl-CpG-binding protein 2; *MECP2*, methyl-CpG-binding protein 2 gene.
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. Pehlivan D, et al. *Genome Med*. 2024;16(1):146. 4. Ta D, et al. *Children (Basel)*. 2022;9(5):633. 5. D'Mello SR 3rd. *J Neurochem*. 2021;159(1):29-60. 6. National Organization for Rare Disorders. MECP2 Duplication Syndrome. 2013. Updated March 22, 2017. Accessed December 16, 2025. https://rarediseases.org/rare-diseases/mecp2-duplication-syndrome/ 7. Marafi D, et al. *Neurology*. 2019;92(2):e108-e114. 8. 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 December 16, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1284/ 9. Van Esch H. *Mol Syndromol*. 2012;2(3-5):128-136. 10. 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]

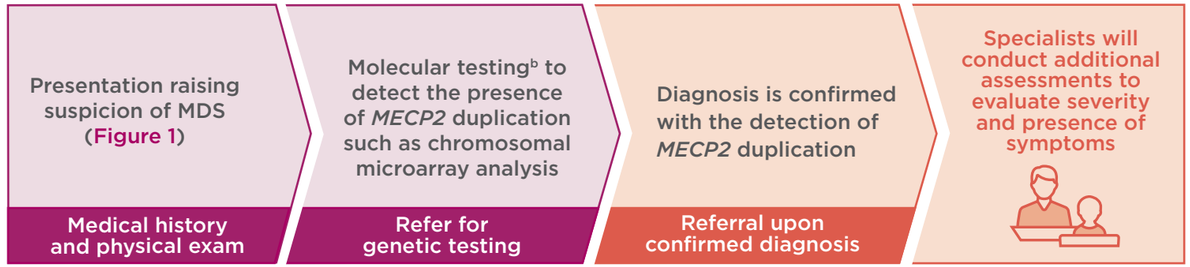
Understanding which disorders have overlapping symptomology with MDS (**Table**) and how they differ may be useful for a differential diagnosis.[1]

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 gene; SNP, single nucleotide polymorphism.
1. National Organization for Rare Disorders. MECP2 Duplication Syndrome. 2013. Updated March 22, 2017. Accessed December 16, 2025. 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 December 16, 2025. 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 in the proteolipid protein 1 gene (*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]

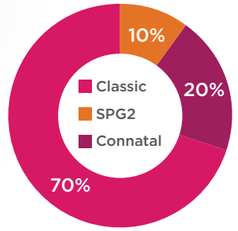
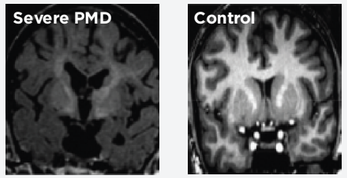


Table: Clinical Spectrum of PMD[4,5,7]

	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 life span	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]



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PMD is associated with developmental hypomyelination.[2,4,8] The degree of myelination achieved is correlated with functional ability.[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.
PLP1, proteolipid protein 1.
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 December 16, 2025. https://www.ncbi.nlm.nih.gov/books/NBK560522/ 4. Khalaf G, et al. *Biomedicines*. 2022;10(7):1709. 5. Wolf NI, et al. *PLP1*-related disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2025. Updated June 12, 2025. Accessed December 16, 2025. 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]

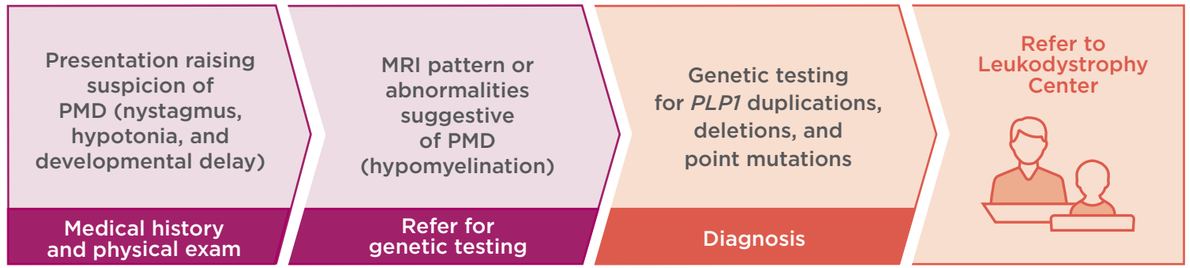
Clinical Features That Should Prompt Suspicion of PMD[3,4]

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



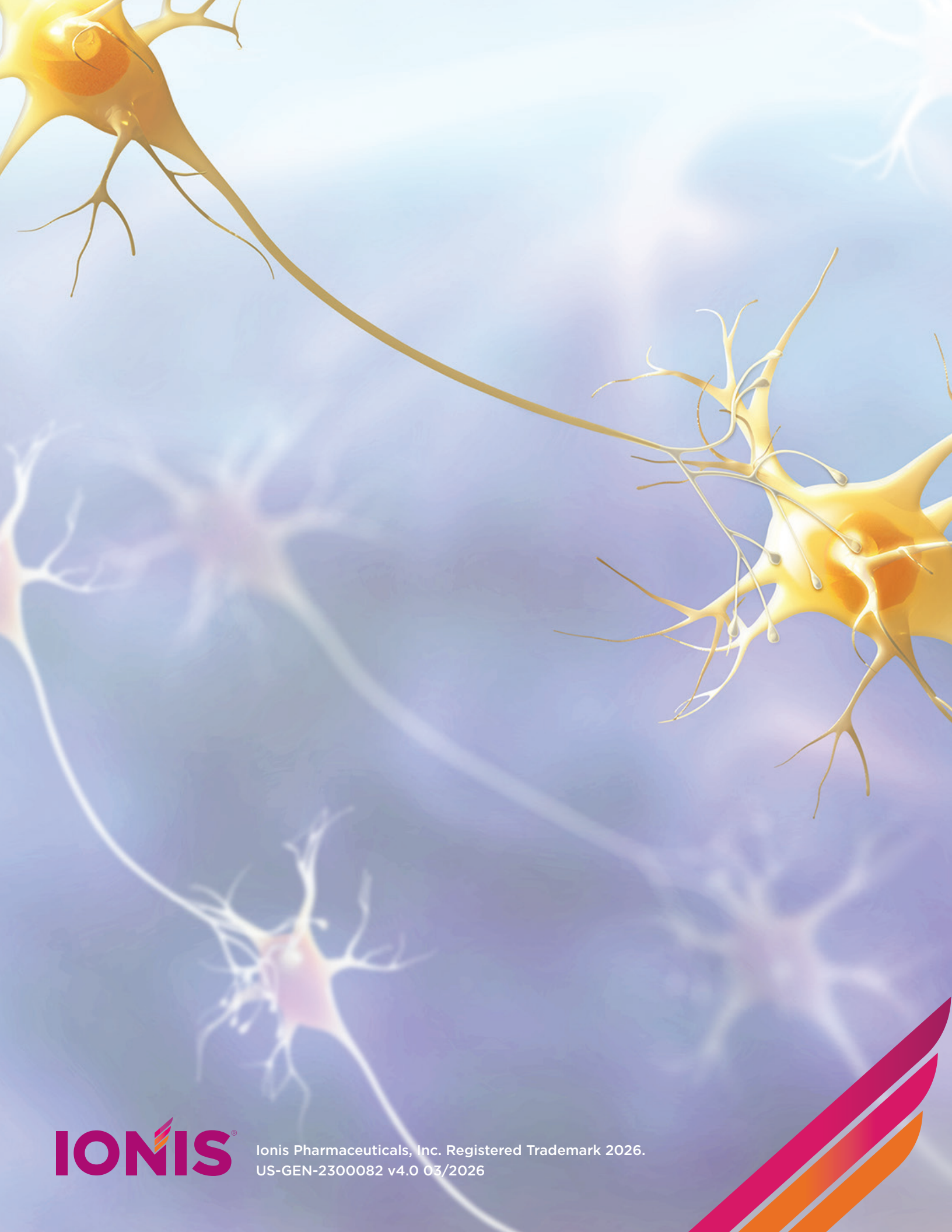
Effective Therapeutics and Early Patient Identification Are Needed[1-3]

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]

MRI, magnetic resonance imaging; *PLP1*, proteolipid protein 1 gene.
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*-related disorders. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2025. Updated June 12, 2025. Accessed December 16, 2025. 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 16, 2025. https://rarediseases.org/rare-diseases/pelizaeus-merzbacher-disease/ 8. Adang LA, et al. *Mol Genet Metab*. 2017;122(1-2):18-32.



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