



PLP1 Disorders

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Summary

Clinical characteristics

PLP1 disorders of central nervous system myelin formation include a range of phenotypes from Pelizaeus-Merzbacher disease (PMD) to spastic paraplegia 2 (SPG2). PMD typically manifests in infancy or early childhood with nystagmus, hypotonia, and cognitive impairment; the findings progress to severe spasticity and ataxia. Life span is shortened. SPG2 manifests as spastic paraparesis with or without CNS involvement and usually normal life span. Intrafamilial variation of phenotypes can be observed, but the signs are usually fairly consistent within families. Heterozygous females may manifest mild-to-moderate signs of the disease.

Diagnosis/testing

The diagnosis of a *PLP1* disorder is established in a male proband by identification of a hemizygous pathogenic variant involving *PLP1*. The diagnosis of a *PLP1* disorder is usually established in a female with neurologic signs, a family history of a *PLP1* disorder, and a heterozygous pathogenic variant in *PLP1* identified by molecular genetic testing.

Management

Treatment of manifestations: A multidisciplinary team comprising specialists in neurology, physical medicine, orthopedics, pulmonary medicine, and gastroenterology is optimal for care. Treatment may include gastrostomy for individuals with severe dysphagia; anti-seizure medication for seizures; and routine management of spasticity including physical therapy, exercise, medications (baclofen, diazepam, tizanidine), orthotics, and surgery for joint contractures. Individuals with scoliosis benefit from proper wheelchair seating and physical therapy; surgery may be required for severe scoliosis. Specialized education and assessments are generally necessary, and assistive communication devices may be helpful.

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Prevention of secondary complications: Proper wheelchair seating and physical therapy may help prevent scoliosis; speech and swallowing evaluations can identify individuals who may need a feeding tube for safer and/or adequate nutrition and hydration.

Surveillance: Semiannual to annual neurologic and physical medicine evaluations during childhood to monitor developmental progress, spasticity, and orthopedic complications.

Genetic counseling

PLP1 disorders are inherited in an X-linked manner. *De novo* pathogenic variants have been reported.

- If the mother has a *PLP1* pathogenic variant, the chance of transmitting the variant in each pregnancy is 50%. Males who inherit the variant will be affected; females who inherit the variant may manifest mild-to-moderate signs of the disorder. (*PLP1* alleles that cause relatively mild neurologic signs in affected males are more likely to be associated with neurologic manifestations in heterozygous females.)
- Males with the PMD phenotype do not reproduce; males with SPG2 phenotype transmit the *PLP1* pathogenic variant to all of their daughters and none of their sons.

Prenatal testing for a pregnancy at increased risk is possible if the *PLP1* pathogenic variant in the family is known.

GeneReview Scope

<i>PLP1</i> Disorders: Included Phenotypes ¹
<ul style="list-style-type: none"> • Pelizaeus-Merzbacher disease (PMD) • <i>PLP1</i> null syndrome • Hypomyelination of early myelinating structures (HEMS) • Spastic paraplegia 2 (SPG2)

For synonyms and outdated names see Nomenclature.

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

A *PLP1* disorder **should be suspected** in an individual with the following clinical and imaging features.

Clinical features

- Infantile or early childhood onset of nystagmus, hypotonia, and cognitive impairment
- Progression to severe spasticity and ataxia
- Spastic paraparesis with or without CNS involvement
- Spastic urinary bladder

Imaging features

Magnetic resonance imaging (MRI) (T₂-weighted or fluid-attenuated inversion recovery [FLAIR] scans):

- Diffusely increased T₂ signal intensity in the white matter of the cerebral hemispheres, cerebellum, and brain stem, consistent with hypomyelination [Steenweg et al 2010].
- Slowly progressive volume loss in older children [Sarret et al 2016].

Note: Because the bulk of myelination normally occurs during the first two years of life, the T₂-weighted MRI images may not show definitive abnormalities until a child is at least age one or two years. However, a normal newborn should have myelination-related T₁ and T₂ signal changes in the pons and cerebellum, and a normal three-month-old infant should have evidence of myelination in the posterior limb of the internal capsule, in the splenium of the corpus callosum, and in optic radiations [Barkovich 2005]. Absence of these early changes should raise the consideration for PMD or other hypomyelinating disorders.

- **Hypomyelination of early myelinating structures (HEMS).** Individuals with HEMS show hypomyelinated structures which normally myelinate early in development, such as optic radiation and brain stem, whereas other white matter structures are better myelinated [Kevelam et al 2015].
- **Spastic paraplegia 2 (SPG2).** People with the SPG2 phenotype show less severe abnormalities on MRI scanning; they may have patchy abnormalities on T₂-weighted scans or more diffuse leukoencephalopathy [Hodes et al 1999].

Magnetic resonance spectroscopy (MRS) may show reduced white matter N-acetyl aspartate (NAA) levels, especially in individuals with the *PLP1* null syndrome [Bonavita et al 2001, Garbern & Hobson 2002, Plecko et al 2003]. In contrast, individuals with *PLP1* duplications may have increased white matter NAA levels.

Establishing the Diagnosis

The diagnosis of a *PLP1* disorder:

- **Is established in a male proband** by identification of a hemizygous pathogenic (or likely pathogenic) variant in *PLP1* by molecular genetic testing (see Table 1);
- **Is usually established in a female** with neurologic signs, a family history of *PLP1* disorder, and a heterozygous pathogenic (or likely pathogenic) variant in *PLP1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *PLP1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (targeted deletion/duplication analysis, single-gene testing, multigene panel), and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing), depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *PLP1* disorders is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with hypotonia, cognitive impairment, and/or spastic paraparesis are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of a *PLP1* disorder, molecular genetic testing approaches can include **targeted deletion/duplication analysis, single-gene testing,** or use of a **multigene panel**:

- **Targeted deletion/duplication analysis.** Multiplex ligation-dependent probe amplification (MLPA), targeted microarray, quantitative PCR (qPCR), or FISH analysis should be considered first to identify a *PLP1* deletion/duplication.
- **Single-gene testing.** If a deletion/duplication is not identified, *PLP1* sequence analysis should be considered. Sequence analysis of *PLP1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions.

Note: In individuals with HEMS, sequence analysis of intron 3 should be performed if no pathogenic variant is identified in exon 3B.

- **A multigene panel** that includes *PLP1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by motor and cognitive impairment, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 1. Molecular Genetic Testing Used in *PLP1* Disorders

Gene ¹	Method	Proportion of Probands with a Pathogenic Variant ² Detectable by Method
<i>PLP1</i>	Gene-targeted deletion/duplication analysis ³	60%-70% ^{4, 5, 6}
	Sequence analysis ⁷	30%-40%
	See footnote 8.	<1%

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as multiplex ligation-dependent probe amplification (MLPA), a gene-targeted microarray, quantitative PCR, and long-range PCR designed to detect single-exon deletions or duplications.

4. The majority of gene dosage changes are tandem duplications occurring in Xq22, which include all of *PLP1*. In rare instances, the duplicated region can be inserted at some distance from Xq22; four insertions have been reported: at Xp22, Xq28 [Woodward et al 1998, Hodes et al 2000], and 19qtel [Inoue et al 2002]; and in the Y chromosome [Woodward et al 2005]. Triplication, partial triplication, and quintuplication of *PLP1* also occur [Boespflug-Tanguy et al 1994, Woodward et al 1998, Wolf et al 2005, Combes et al 2006]. In simplex females, *PLP1* duplication often occurs with complex chromosomal rearrangements.

5. Whole-gene deletions of *PLP1* occur in fewer than 2% of those with the Pelizaeus-Merzbacher disease phenotype [Raskind et al 1991; Boespflug-Tanguy et al 1994; Inoue et al 2002; Shaffer, unpublished observations]. Inoue et al [2002] determined that the individual originally described with a *PLP1* deletion has a complex rearrangement with both a deletion of *PLP1* and an inverted insertion of a more distal portion of the X chromosome at the deletion junction. In addition, this individual has duplication of a region distal of *PLP1* [Hobson et al 2002, Lee et al 2007]. Partial *PLP1* deletion has also been reported [Combes et al 2006].

6. Depending on the method used, larger deletion or duplication events may be detected. Position effect of a duplication identified by FISH that was near but did not include *PLP1* has been invoked as the cause of the neurologic syndrome in a man with spastic paraplegia [Lee et al 2006].

7. Sequence analysis which should include analysis of intron 3B detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

8. An inversion of the X chromosome with a breakpoint 70 kbp upstream of *PLP1*, identified by chromosome analysis, was proposed to disrupt *PLP1* expression through position effect in a child with PMD-like syndrome [Muncke et al 2004].

Clinical Characteristics

Clinical Description

Males

Pelizaeus-Merzbacher disease (PMD) and X-linked spastic paraplegia 2 (SPG2) are at opposite ends of a clinical spectrum of disease caused by pathogenic variants in *PLP1*, which results in defective central nervous system (CNS) myelination. PMD and SPG2 have been observed in different males within the same family [Hodes et al 1993, Sisternans et al 1998].

Boulloche & Aicardi [1986], Hodes et al [1993], and Cailloux et al [2000] have summarized the clinical features of their series of individuals with PMD. The phenotypes in this spectrum cannot be neatly categorized into distinct syndromes but are summarized using designations frequently encountered in the medical literature (Table 2).

Table 2. Spectrum of *PLP1* Disorders

Phenotype	Age of Onset	Neurologic Findings	Ambulation	Speech	Age at Death
Severe "connatal" PMD	Neonatal period	Nystagmus at birth; pharyngeal weakness; stridor; hypotonia; severe spasticity; ± seizures; cognitive impairment	Never achieved	Absent, but nonverbal communication & speech comprehension possible	Infancy to 3rd decade
Classic PMD	1st 5 yrs	Nystagmus in 1st 2 mos; initial hypotonia; spastic quadriparesis; ataxia titubation; ± dystonia, athetosis; cognitive impairment	W/assistance if achieved; lost in childhood/adolescence	Usually present	3rd-7th decade
<i>PLP1</i> null syndrome	1st 5 yrs	No nystagmus; mild spastic quadriparesis; ataxia; peripheral neuropathy; mild-to-moderate cognitive impairment	Present	Present; usually worsens after adolescence	5th-7th decade
Complicated SPG (SPG2) & HEMS	1st 5 yrs	Nystagmus; ataxia; autonomic dysfunction ¹ ; spastic gait; little or no cognitive impairment	Present	Present	4th-7th decade
Uncomplicated SPG (SPG2)	Usually 1st 5 yrs; may be 3rd-4th decade	Autonomic dysfunction ¹ ; spastic gait; normal cognition	Present	Present	Normal

HEMS = hypomyelination of early myelinating structures; PMD = Pelizaeus-Merzbacher disease; SPG = spastic paraplegia
1. Spastic urinary bladder

Severe or "connatal" PMD is apparent at birth or in the first few weeks of life. Findings include pendular nystagmus, hypotonia, and stridor. Seizures may develop in affected infants, and motor deficits are severe (e.g., infants do not gain head control).

Later, children with severe PMD may have short stature and poor weight gain. Hypotonia later evolves into spasticity of the extremities that is usually quite severe. Children do not walk or develop effective use of the upper limbs. Verbal expression is severely limited, but comprehension may be significant. Swallowing difficulties may require feeding tube placement.

Affected children may die during infancy or childhood, usually of aspiration; with attentive care, they may live into the third decade or longer.

Classic PMD. Males with classic PMD usually develop nystagmus, which may not be recognized until several months of age; in rare cases, nystagmus does not develop. Affected children have hypotonia and develop titubation (tremor of the head and neck), ataxia, and spastic quadriparesis beginning in the first five years; they usually have some purposeful voluntary control of the arms. If acquired, ambulation usually requires assistive devices such as crutches or a walker; ambulation is generally lost as spasticity increases during later childhood or adolescence.

Cognitive abilities are impaired, but exceed those of the more severely affected children; language and speech usually develop. Extrapyramidal abnormalities, such as dystonic posturing and athetosis, may occur.

Survival into the sixth or seventh decade has been observed.

A transitional form, intermediate in onset and severity to the congenital and classic forms of PMD, has also been defined.

PLP1 null syndrome is distinguished by the absence of nystagmus and the presence of relatively mild spastic quadriparesis that mostly affects the legs, with ataxia and mild multifocal demyelinating peripheral neuropathy. Those with the *PLP1* null syndrome generally ambulate better than those with classic PMD but may progress more rapidly because of degeneration of axons, inferred on the basis of magnetic resonance spectroscopy, which demonstrates reduced levels of white matter N-acetyl aspartate [Garbern et al 2002].

Complicated spastic paraparesis (SPG2) and hypomyelination of early myelinating structures (HEMS) often include autonomic dysfunction (e.g., spastic urinary bladder), ataxia, and nystagmus. A clear distinction cannot be drawn on objective criteria between complicated spastic paraplegia and relatively mild PMD (e.g., *PLP1* null syndrome).

Pure spastic paraparesis (SPG2) does not, by definition, include other significant CNS signs, although autonomic dysfunction, such as spastic urinary bladder, may also occur. Life span is normal.

Males with SPG2 have reproduced; males with the PMD phenotype have not.

Neurophysiologic Studies

Visual, auditory, and somatosensory evoked potential testing show normal-to-near-normal latencies of the peripheral component of the respective sensory modality, but severely prolonged or absent central latencies.

Except in families with *PLP1* null alleles or pathogenic variants affecting the *PLP1*-specific region or some splice site variants [Shy et al 2003, Vaur-Barrière et al 2003], peripheral nerve conduction studies are normal. When peripheral neuropathy is present, it is mild in comparison to the CNS disorder, and is characterized by mild slowing of conduction velocities that may be more pronounced across those regions of a limb susceptible to compression, such as the wrist and elbow.

Heterozygous Females

Women with a *PLP1* pathogenic variant may or may not have symptoms. Several investigators have observed that in families with severely affected males, the heterozygous women are unlikely to have clinical manifestations of a *PLP1* disorder, whereas in families with mildly affected males, the heterozygous women are more likely to have symptoms [Keogh et al 2017]. Thus, an inverse relationship exists between the severity of manifestations in males and the likelihood of heterozygous females having neurologic signs.

The risk to heterozygous females of developing neurologic signs is greatest in families in which affected males have a *PLP1* null syndrome, followed by those in which affected males have an SPG2 syndrome or HEMS [Hurst et al 2006]. The risk of developing neurologic signs is lowest in heterozygous females with a *PLP1* duplication, who usually have favorably skewed X-chromosome inactivation [Woodward et al 2000].

The following explanation is offered:

- Alleles associated with a severe phenotype cause apoptosis (cell death) of oligodendrocytes (the cells that make myelin in the CNS) during early childhood. In heterozygous females, the oligodendrocytes that express the mutated *PLP1* allele on the active X chromosome undergo apoptosis early in life but are replaced over time by oligodendrocytes that express the normal *PLP1* allele on the active X chromosome. Thus, females who carry a severe *PLP1* pathogenic variant may develop neurologic signs because of skewed inactivation of the X chromosome with the normal *PLP1* allele (as with other X-linked recessive disorders) or may have transient signs (while the oligodendrocytes expressing the mutated *PLP1* are still present) that abate as the degenerating oligodendrocytes are replaced by those expressing the normal *PLP1* allele [Inoue et al 2001].

- Alleles associated with a mild phenotype in males do not cause apoptosis of oligodendrocytes. In heterozygous females, abnormal oligodendrocytes persist and can cause neurologic signs [Sivakumar et al 1999].

Hurst et al [2006] analyzed families with SPG2 or PMD and provided statistical support for the inverse correlation between the severity of phenotypes in affected males and their heterozygous relatives. These observations have important implications for genetic counseling and are discussed in Risk to Family Members, **Sibs of a male proband**.

Manifesting heterozygotes are usually not index cases, but rather are identified in the course of evaluating the relatives of an affected male.

Females with PMD have been described. This is thought to be due to unfavorable X inactivation in the brain [Scala et al 2019]. In some, there was considerable improvement of signs and symptoms after infancy. One female with classic PMD had an insertion of an extra copy of *PLP1* at chromosome 1p36 [Masliah-Planchon et al 2015]. Additional complex chromosome rearrangements in females with PMD have been described [Ida et al 2003, Yiu et al 2009].

Genotype-Phenotype Correlations

Some genotype-phenotype correlations exist.

Most individuals with *PLP1* duplications have classic PMD; however, some are classified as having congenital PMD and may have three or more copies of the *PLP1* locus [Wolf et al 2005]. Variation in the extent of duplication or location(s) of the breakpoints or reinsertion sites may account for clinical variability.

The most severe clinical syndromes are typically caused by missense variants (especially nonconservative amino acid substitutions) and other *PLP1* single-nucleotide variants or indels.

The milder spastic paraplegia syndrome is most often caused by conservative amino acid substitutions in presumably less critical regions of the protein. The locations of these pathogenic variants do not provide a clear correlation between amino acid position and clinical phenotype. However, pathogenic variants in the *PLP1*-specific domain encoded by amino acid residues 117-151 and in intron 3 tend to cause less severe syndromes [Cailloux et al 2000, Taube et al 2014, Kevelam et al 2015] (see Molecular Genetics).

Although PMD has classically been regarded as a strictly CNS disorder, those with null *PLP1* variants, including deletion of *PLP1* [Raskind et al 1991], a frameshift variant, and a missense variant affecting the initiation codon do develop a relatively mild demyelinating peripheral neuropathy, demonstrating that myelin proteolipid protein (PLP1) and/or DM20 (an alternatively spliced transcript; see following paragraph and Molecular Genetics) does indeed function in the peripheral nervous system as well as in the CNS. Furthermore, the null phenotype has less severe CNS signs than those seen with the more typical forms of PMD. The null phenotype is associated with length-dependent degeneration of major central motor and sensory tracts and reduced levels of N-acetyl aspartate in cerebral white matter.

Peripheral neuropathy as well as a relatively mild CNS syndrome results from pathogenic variants that affect only the *PLP1*-specific region [Shy et al 2003] (see Molecular Genetics). The CNS syndrome can be milder than that observed in individuals with the null phenotype.

Penetrance

PLP1 pathogenic variants are believed to be completely penetrant in males.

Nomenclature

Pelizaeus-Merzbacher disease is also known as sudanophilic or orthochromatic leukodystrophy.

Proteolipid protein 1 was previously called proteolipid protein. After discovery of a similar gene that is predominantly expressed in gut, numerical designation was added.

Note also that the older literature usually begins numbering of the amino acids with the glycine encoded by codon 2, since the initiation methionine is cleaved post-translationally.

Prevalence

In the US, the prevalence of PMD in the population is estimated at 1:200,000 to 1:500,000.

In a survey of leukodystrophies in Germany, the incidence of PMD was approximately 0.13:100,000 live births [Heim et al 1997].

Seeman et al [2003] reported that in the Czech Republic *PLP1* pathogenic variants were detected in 1:90,000 births. While this may reflect a situation particular to the Czech Republic, it suggests that the prevalence of PMD may be higher than is generally recognized.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *PLP1*.

Differential Diagnosis

Individuals with *PLP1* disorders are often initially diagnosed with cerebral palsy or static encephalopathy.

Pelizaeus-Merzbacher Disease (PMD)

The combination of nystagmus within the first two years of life, initial hypotonia, and abnormal white matter changes on the brain MRI (e.g., abnormal signal in the posterior limbs of the internal capsule, the middle, and superior cerebellar peduncles and the medial and lateral lemnisci, all of which should be myelinated in a normal newborn) should suggest the diagnosis of PMD, especially if the family history is consistent with an X-linked disorder. In a recent survey of children with inherited diseases of white matter identified by neuroimaging, 7.4% had PMD, the second most common cause of leukodystrophy [Bonkowsky et al 2010], suggesting that the disease is relatively common.

Approximately 20% of males with clinical findings consistent with a *PLP1* disorder do not have identifiable pathogenic variants in *PLP1*. Pathogenic variants in additional genes have been identified in individuals with a PMD-like phenotype and hypomyelination on brain MRI (see Table 3).

Hypomyelination occurs in several disorders with clinical phenotypes distinct from PMD. [4H leukodystrophy](#) is the most frequent hypomyelinating disorder after PMD, individuals with 4H leukodystrophy usually do not have nystagmus, ataxia is prominent, and spasticity is mild or not present [Wolf et al 2014]. Oculodentodigital dysplasia presents sometimes in adulthood, with a SPG-like phenotype; nystagmus is usually not present [Harting et al 2019]. (For MRI characteristics and differential diagnosis of hypomyelination see also Steenweg et al [2010] and van der Knaap et al [2019]).

Table 3. Genes of Interest in the Differential Diagnosis of Pelizaeus-Merzbacher Disease (PMD)

Gene(s) ¹	Disorder ²	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/PMD	Distinguishing from PMD
<i>AIFM1</i>	Hypomyelination w/ spondyloepiphyseal dysplasia ³	XL	Hypomyelination	Spondyloepiphyseal dysplasia
<i>DARS1</i>	Hypomyelination w/brain stem & spinal cord involvement & severe leg spasticity (OMIM 615281)	AR	Spasticity/ataxia; nystagmus; hypomyelination	Characteristic involvement of brain stem & spinal cord structures on MRI
<i>EPRS1</i>	Hypomyelinating leukodystrophy 15 (OMIM 617951)	AR	Spasticity/ataxia; nystagmus; hypomyelination	Posterior columns may be affected on MRI
<i>GJA1</i>	Oculodentodigital dysplasia (OMIM 164200)	AD	Hypomyelination	Mild symptoms, sometimes diagnosis only in adulthood; syndactyly; ocular abnormalities; dysmorphic signs; prominent spastic bladder
<i>GJC2</i>	Pelizaeus-Merzbacher-like disease 1	AR	Spasticity/ataxia; nystagmus; hypomyelination	Epilepsy is frequent. More pronounced hypomyelination in subcortical white matter; prominent brain stem involvement
<i>HSPD1</i>	Hypomyelinating leukodystrophy 4 (OMIM 612233)	AR	Resembles severe PMD ⁴ ; hypomyelination	Acquired microcephaly; severe epilepsy
<i>HYCC1</i> (FAM126A)	Hypomyelination & congenital cataract	AR	Spasticity/ataxia; nystagmus; demyelinating peripheral neuropathy; hypomyelination	Congenital cataract; areas w/both T ₂ -weighted hyperintensity & T ₁ -weighted hypointensity
<i>NKX6-2</i>	NKX6-2 disorder	AR	Spasticity/ataxia; nystagmus; hypotonia; hypomyelination	Severe early dystonia, early-onset (transitory) respiratory failure
<i>POLR3A</i> <i>POLR3B</i> <i>POLR3K</i> <i>POLR1C</i>	4H leukodystrophy (hypomyelination, hypodontia, & hypogonadotropic hypogonadism)	AR	Ataxia; hypomyelination	Myopia (no nystagmus); hypodontia; hypogonadotropic hypogonadism; early cerebellar atrophy; better myelination of posterior limb of the internal capsule, ventrolateral thalamus & optic radiation
<i>RARS1</i>	Hypomyelinating leukodystrophy 9 (OMIM 616140)	AR	Spasticity/ataxia; nystagmus; hypomyelination	No specific distinguishing features; in severe cases, microcephaly & early epileptic encephalopathy
<i>SLC16A2</i>	Allan-Hernon-Dudley syndrome (MCT8-specific thyroid hormone cell-membrane transporter deficiency)	XL	Neonatal hypotonia, nystagmus, severe DD	High serum T3 concentration; low serum reverse T3 concentration; MRI shows (severely) delayed myelination, but not hypomyelination
<i>SLC17A5</i>	Salla disease (See Free Sialic Acid Storage Disorders.)	AR	± hypotonia, nystagmus, DD; in severely affected children, diffusely abnormal myelination w/uniformly hyperintense white matter on T ₂ -weighted images; in less severely affected children, delayed myelination, occurring mainly in periventricular regions	Seizures are more common than in PMD, but children w/Salla disease are more likely to show improvement; MRI shows thin corpus callosum early on.

Table 3. continued from previous page.

Gene(s) ¹	Disorder ²	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/PMD	Distinguishing from PMD
<i>SOX10</i>	PCWH syndrome (OMIM 609136)	AD	Hypomyelination	Peripheral congenital hypomyelinating neuropathy; Waardenburg-Hirschsprung syndrome
<i>TMEM106B</i>	Hypomyelinating leukodystrophy 16 (OMIM 617964)	AD	Nystagmus; hypomyelination	Mild clinical presentation (mild ataxia, mild cognitive impairment)
<i>TMEM63A</i>	Transient hypomyelination ⁵	AD	Initially indistinguishable from PMD (congenital nystagmus, hypotonia, hypomyelination)	Positive evolution w/normalization of development & MRI findings
<i>TUBB4A</i>	Hypomyelination w/atrophy of basal ganglia & cerebellum (See TUBB4A-Related Leukodystrophy .)	AD	Spasticity, nystagmus (not invariable); hypomyelination	Usually atrophy of basal ganglia & cerebellum

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; MOI = mode of inheritance; PCWH = peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease; XL = X-linked

1. Genes are listed alphabetically.

2. Other leukodystrophies should also be considered.

3. Miyake et al [2017]

4. Described in an Israeli Bedouin family

5. Yan et al [2019]

Spastic Paraplegia 2 (SPG2)

To date, more than 80 genetic types of hereditary spastic paraplegia have been defined. See the [Hereditary Spastic Paraplegia Overview](#) for clinical characteristics of other hereditary spastic paraplegias.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a *PLP1* disorder, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Physical examination to determine extent and severity of respiratory and feeding difficulties, weakness, hypotonia, spasticity, scoliosis, ataxia, visual impairment, cognitive impairment, contractures, joint dislocations, and ambulation
- In infants and children, developmental assessment to determine capabilities and needs for cognitive, physical, and other symptomatic therapies
- Brain MRI (more helpful age ≥ 9 months) to determine severity of myelination abnormalities; in older children and adults, magnetic resonance spectroscopy to ascertain axonal dysfunction
- Assessment of peripheral nerve function using NCV to presumptively identify individuals with the *PLP1* null syndrome (probably reliable only after age 4 years)
- Family history to identify other affected or at-risk individuals
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

A multidisciplinary team comprising specialists in neurology, physical medicine, orthopedics, pulmonary medicine, and gastroenterology is optimal for care [Van Haren et al 2015].

Early attention to swallowing difficulties and airway protection, especially in the most severely affected individuals, is important. Those with severe dysphagia may require feeding by gastrostomy.

Seizures are usually restricted to individuals with the most severe (connatal) syndrome and although they may not always be associated with electroencephalographic evidence for epileptiform waveforms, they generally respond to anti-seizure medication such as carbamazepine.

Spasticity management may include physical therapy and exercises, including regular stretching exercises. Anti-spasticity medications such as baclofen (including intrathecal administration), diazepam, and tizanidine may be helpful, especially in combination with physical therapy, exercise, orthotics, and other assistive devices. In advanced cases, surgery to release joint contractures may be required.

Severe scoliosis may result in pulmonary compromise as well as discomfort, especially with position changes, and necessitate corrective surgery to preserve pulmonary function. Proper seating (especially wheelchair) and physical therapy may reduce or prevent the need for surgery.

Specialized schooling arrangements are typically necessary for children with *PLP1* disorders. Developmental assessments can accurately assess a child's capabilities, which may be greater than is apparent because of severe motor deficits. Electronic or other communication devices may facilitate communication especially in children with visual and auditory impairment.

Prevention of Secondary Complications

Proper wheelchair seating and physical therapy may help prevent scoliosis. Speech and swallowing evaluations can help prevent or reduce aspiration and identify individuals who may need a feeding tube for safer and/or adequate nutrition and hydration.

Surveillance

Semiannual to annual neurologic and physical medicine evaluation is indicated to monitor developmental progress during childhood and to monitor and treat spasticity and orthopedic complications as needed.

Agents/Circumstances to Avoid

Elevated body temperature, as with fever, may cause neurologic signs and symptoms to transiently worsen.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

CNS stem cells were transplanted into brains of individuals with PMD in a US FDA-approved Phase I trial [Gupta et al 2012]. The procedure was well tolerated, however minimal evidence of myelination was thought to be present in the transplanted regions. Several years later, the situation was unchanged [Gupta et al 2019].

Pharmacologic agents that lower expression of *PLP1* should be of theoretic benefit in individuals with extra copies of *PLP1*, as well as those with pathogenic variants associated with protein overexpression. Gene therapy

using inhibitory RNA may be efficient; care should be taken to ascertain the right amount of *PLP1* expression, as abolishing *PLP1* expression altogether would lead to the *PLP1* null syndrome.

Several interventions had positive effects in mouse models (e.g., ketogenic diet, cholesterol supplementation) and/or cell models of PMD (e.g., deferiprone) [Saher et al 2012, Nobuta et al 2019, Stumpf et al 2019].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The *PLP1* disorders are inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *PLP1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote and may manifest mild-to-moderate signs of the disease. Note: If a woman has more than one affected child and no other affected relatives and if the *PLP1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- In most families, the mother of a proband is heterozygous for a *PLP1* pathogenic variant regardless of family history.
- If a male is the only affected family member (i.e., he represents a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* *PLP1* pathogenic variant, in which case the mother is not heterozygous [Hodes et al 1998, Grossi et al 2011].

Sibs of a male proband. The risk to the sibs depends on the genetic status of the mother:

- If the mother of the proband has a *PLP1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
 - Males who inherit the pathogenic variant will be affected. Significant intrafamilial clinical variability is uncommon in *PLP1* disorders; still, families in which males have had a milder phenotype are at risk of having affected offspring who may display a more severe phenotype.
 - Females who inherit the pathogenic variant will be heterozygotes and may manifest mild-to-moderate signs of the disorder. Female sibs are more likely to develop neurologic signs if the phenotype in affected males is relatively mild (complicated or pure spastic paraparesis) [Hurst et al 2006]. The risk to a heterozygous female of being clinically affected is highest when the brother has the *PLP1* null syndrome, and lowest when he has a *PLP1* duplication. Heterozygous females with *PLP1* duplication have been reported to have favorably skewed X inactivation [Woodward et al 2000].

- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *PLP1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism [Woodward et al 2003].

Offspring of a male proband

- Males with typical PMD do not reproduce.
- Males with SPG2 may be able to father children. Affected males transmit the *PLP1* pathogenic variant to:
 - All of their daughters, who may manifest mild-to-moderate signs of the disease;
Note: *PLP1* alleles that cause relatively mild neurologic signs in affected males are more likely to be associated with neurologic manifestations in heterozygous females.
 - None of their sons.

Other family members of a male proband

- The proband's maternal aunts and their offspring may be at risk of being heterozygous, and manifesting mild-to-moderate signs of the disease, or of being hemizygous and affected (depending on their sex, family relationship, and the genetic status of the proband's mother).
- Females who are heterozygous are more likely to have neurologic signs (usually adult-onset spastic paraparesis) if affected males in their family have a less severe syndrome.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for this X-linked disorder are usually neurologically normal but may manifest mild-to-moderate signs of the disease. (2) Identification of female heterozygotes requires either (a) prior identification of the *PLP1* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Related Genetic Counseling Issues

Phenotypic variability. It is important for couples at risk to be aware that varying phenotypes can coexist in the same kindred or sibship; thus, families in which males have had a milder phenotype are at risk of having affected offspring who may display a more severe phenotype.

Distantly inserted duplications. While distantly inserted duplications are a rare cause of *PLP1* disorders, they may raise potentially difficult genetic counseling issues because the inheritance pattern may not be X-linked [Hodes et al 2000, Inoue et al 2002].

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, heterozygous, or at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PLP1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing (PGT) are possible. However; the prenatal or PGT finding of a familial *PLP1* pathogenic variant cannot be used to accurately predict clinical outcome, as varying phenotypes may coexist in the same kindred or sibship; families in which males have had a milder phenotype are at risk of having affected offspring with a more severe phenotype and females may be neurologically normal or manifest mild-to-moderate signs of the disease.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **National Institute of Neurological Disorders and Stroke (NINDS)**
PO Box 5801
Bethesda MD 20824
Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
[Pelizaeus-Merzbacher Disease Information Page](#)
- **PMD Foundation**
1307 White Horse Road
Suite 603
Voorhees NJ 08043
Phone: 302-383-7748; 609-443-9623
Email: donhobson@pmdfoundation.org; jeffleonard@pmdfoundation.org
www.pmdfoundation.org
- **European Leukodystrophy Association (ELA)**
Phone: 03 83 30 93 34
www.ela-asso.com
- **Leukodystrophy Australia**
Australia
Phone: 1800-141-400
Email: info@leuko.org.au
www.leuko.org.au
- **United Leukodystrophy Foundation**
Phone: 800-SAV-LIVE; 815-748-3211
Email: office@ulf.org
www.ulf.org
- **Myelin Disorders Bioregistry Project**

Phone: 215-590-1719

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Myelin Disorders Bioregistry Project

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PLP1 Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>PLP1</i>	Xq22.2	Myelin proteolipid protein	PLP1 @ LOVD	PLP1	PLP1

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for PLP1 Disorders ([View All in OMIM](#))

300401	PROTEOLIPID PROTEIN 1; PLP1
312080	PELIZAEUS-MERZBACHER DISEASE; PMD
312920	SPASTIC PARAPLEGIA 2, X-LINKED; SPG2

Molecular Pathogenesis

Introduction. *PLP1* encodes myelin proteolipid protein 1 (PLP1), which is the predominant protein constituent of central nervous system (CNS) myelin, constituting approximately 50% of the myelin protein mass. An additional gene product, the isoform DM20, which lacks the *PLP1*-specific domain encoded by amino acids 117-151, is also encoded by *PLP1*. PLP1 and DM20 are both transmembrane proteins that span the lipid bilayer four times and are anchored to cell membranes through covalent acyl linkages to fatty acids. There is evidence that PLP1 cements adjacent leaflets of myelin; however, additional or alternative functions are also possible [Griffiths et al 1998, Aggarwal et al 2011].

PLP1, but not DM20, has been shown to form dimers at an intracellular cysteine residue [Daffu et al 2012]. This dimerization may contribute to the molecular pathogenesis of PMD, both in affected individuals with indels and those with duplications.

Mechanism of disease causation. Duplication of *PLP1* results in overexpression of PLP1, leading to dysfunction and death of oligodendrocytes, the myelin-forming cells in the CNS [Griffiths et al 1998, Yool et al 2000]. Increased PLP1 expression results in mislocalization of PLP1 along with cholesterol and lipids to the late endosomal/lysosomal compartment [Simons et al 2000]. The association of hypomyelination and subsequent axonal injury in PMD and other leukodystrophies is reviewed by Mar & Noetzel [2010].

Pathogenic missense variants cause misfolding of PLP1 or DM20. These misfolded proteins are retained in the endoplasmic reticulum (ER), failing to be incorporated into the cell membrane where they activate the unfolded protein response [Southwood et al 2002, Inoue 2017]. In a severe mouse model, the jimpy mouse, there is ER stress and subsequent cell death when oligodendrocyte progenitors mature [Elitt et al 2018].

Deletion of *PLP1*, and probably other loss-of-function variants, results in mild myelin defects but subsequent more severe axonal degeneration [Garbern et al 2002].

Variants in the *PLP1* specific part of the gene (described as exon 3B) and the adjacent intron 3 lead to hypomyelination of early myelinating structures, through decreased PLP1 expression in relation to DM20 [Taube et al 2014, Kevelam et al 2015].

PLP1-specific laboratory considerations. Some deep intronic variants outside of the immediate splice junction regions have been associated with *PLP1* disorders [Taube et al 2014, Kevelam et al 2015]. Of note, the complete conservation of amino acid sequence between rodent and human *PLP1* suggests little tolerance for sequence variation.

Table 4. Notable *PLP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000533.4	c.453+159G>A	--	Deep intronic variants assoc w/HEMS [Kevelam et al 2015]
	c.453+164G>A	--	
	c.454-312C>G	--	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

Chapter Notes

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