# Pelizaeus-Merzbacher Disease, Pelizaeus-Merzbacher-Like Disease 1, and Related Hypomyelinating Disorders

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**Abstract**

The purpose of this article is to present contemporary information on the clinical and molecular diagnosis and the treatment of Pelizaeus-Merzbacher's disease (PMD) and related leukodystrophies. Various types of mutations of the X-linked proteolipid protein 1 gene (*PLP1*) that include copy number changes, point mutations, and insertions or deletions of a few bases lead to a clinical spectrum from the most severe connatal PMD, to the least severe spastic paraplegia 2 (SPG2). Signs of PMD include nystagmus, hypotonia, tremors, titubation, ataxia, spasticity, athetotic movements and cognitive impairment; the major findings in SPG2 are leg weakness and spasticity. A diffuse pattern of hypomyelination is seen on magnetic resonance imaging (MRI) of PMD/SPG2 patients. A similar constellation of signs and pattern of hypomyelination lead to the autosomal recessive disease called Pelizaeus-Merzbacher-like disease 1 (PMLD1) and the less-severe spastic paraplegia 44 (SPG44), caused by mutations of the gap junction protein, gamma-2 gene (*GJC2*), formerly known as the gap junction protein, α-12 gene (*GJA12*). Magnetic resonance spectroscopy (MRS) and brainstem auditory evoked potentials (BAEP) may assist with differential clinical diagnosis of PMD and PMLD1. Supportive therapy for patients with PMD/SPG2 and PMLD1/SPG44 includes medications for seizures and spasticity; physical therapy, exercise, and orthotics for spasticity management; surgery for contractures and scoliosis; gastrostomy for severe dysphagia; proper wheelchair seating, physical therapy, and orthotics to prevent or ameliorate the effects of scoliosis; special education; and assistive communication devices.

**Keywords**

► Pelizaeus-Merzbacher disease
► spastic paraplegia 2
► Pelizaeus-Merzbacher-like disease
► spastic paraplegia 44

## Background

**Pelizaeus-Merzbacher Disease and Spastic Paraplegia 2**

Pelizaeus-Merzbacher disease (PMD; MIM #312080), also called leukodystrophy hypomyelinating 1 (HDL1), and the less severe spastic paraplegia 2, X-linked (SPG2; MIM #312920) are inherited allelic leukodystrophies caused by mutations of the proteolipid protein 1 gene (*PLP1*; MIM #300401). *PLP1* encodes the major protein of the myelin sheath, proteolipid protein (PLP), a 4-pass transmembrane protein with two extracellular and three intracellular domains. The *PLP1* gene also encodes the DM20 isoform by alternative splicing at exon 3. PMD/SPG2 is inherited as an X-linked recessive trait. Males with *PLP1* mutations have the disease; females are usually unaffected carriers. PMD/SPG2 is caused by various types of mutations of the *PLP1* gene. When strict clinical criteria for PMD are applied, more than 50% of cases are caused by duplication of a genomic region, including the entire *PLP1* gene.[1] Duplications can range in size from less than 100 kilobases to 9 or more megabases.[2–5] They are usually tandem direct repeats at Xq22.2 where the *PLP1* gene is located, but duplicated segments have been reported at Xq26, Xp, 19pter, and Y.[2, 6, 7] The duplications include other

genes in addition to *PLP1*, but it is not known whether these other genes affect the disease phenotype. Size of the duplication does not correlate with clinical severity of the disease.[4, 5] Point mutations and indels (insertion or deletion of one to a few bases) of *PLP1* account for ~25% of PMD/SPG2 cases.[1]

Point mutations that result in amino acid substitutions (missense mutations) have been reported throughout coding regions. Frameshift mutations that result in truncated protein or are null, and mutations that result in aberrant splicing are less common than missense mutations but have also been reported.[8–11] Genomic triplication and higher copy numbers of *PLP1*, partial triplication, and complete and partial deletion are rare, but also result in PMD.[7, 12, 13] Reported mutations of the *PLP1* gene are cataloged at http://www.ncbi.nlm.nih.gov/books/NBK1182/.[14] PMD is a rare disease that is not limited to nationality or race. Incidence was reported to be 0.13 in 100,000 live births in Germany and 1 in 90,000 in the Czech Republic.[15, 16] The reason for the discrepant incidence numbers is unknown.

### Pelizaeus-Merzbacher-Like Disease 1 and Spastic Paraplegia 44

When patients have symptoms of PMD but do not have mutations of *PLP1*, their disease is called Pelizaeus-Merzbacher-like disease (PMLD).[17] Only 8% of PMLD cases are caused by mutations of the gap junction protein, gamma-2 gene (*GJC2*, MIM #608803), formerly known as the gap junction protein, α-12 gene (GJA12). *GJC2* encodes a member of a large family of connexin proteins. Like PLP, the gap junction protein gamma-2, also called connexin 47 (Cx47) or connexin 46.6 (Cx46.6), encoded by the *GJC2* gene is a 4-pass transmembrane protein with two extracellular and three intracellular domains. PMLD caused by *GJC2* mutations is called PMLD1 (MIM #608804), or leukodystrophy hypomyelinating 2 (HDL2). Molecular etiology of the remaining cases of PMLD is unknown. PMLD1 is inherited as an autosomal recessive trait, affecting males and females with equal frequency. Patients with PMLD1 have homozygous or compound heterozygous mutations.[18–23] Missense, nonsense, frameshift, and indel mutations have been reported. A mutation in the promoter of *GJC2* was also reported to cause PMLD1.[24] Five patients with PMLD were reported to have only one mutation of the *GJC2* gene, leaving their disease not fully explained at the molecular level.[22] A milder disease, spastic paraplegia 44 (SPG44), was reported in one family with individuals who have a homozygous mutation of *GJC2*.[25] Incidence of PMLD1 and SPG44 has not been reported. It should be noted that mutations of the *GJC2* gene have also been reported to cause autosomal dominant lymphedema.[26]

## Clinical and magnetic resonance imaging (MRI) Features

### Clinical Features of Pelizaeus-Merzbacher Disease and Spastic Paraplegia 2

Early signs suggestive of PMD that are present at birth or in the first few months of life include nystagmus and hypotonia, and in the more severe cases there may be stridor, sometimes with vocal cord paralysis, feeding difficulty, and seizures. Subsequently, developmental milestones are delayed. By around 6 months or later, ataxia of the limbs becomes apparent and over several years, the limb hypotonia is replaced by spasticity of the limbs. Dystonic posturing and athetotic movements may be present, and cognitive impairment is present in most children. The cognitive delay often leads to difficulty in clinical educational assessment. When sufficient time is given for children to respond to questions or instructions, they are often found to be more capable than they initially appear. Clinical phenotypes reported range from the severe so-called connatal form of PMD to the milder complicated and pure SPG2.[27–29]

*Connatal PMD* is observed at birth or in the first 2 weeks of life. Stridor and seizures are common in this form. Hypotonia in infancy evolves into severe spasticity during childhood. Patients do not develop the ability to walk, gain use of their upper extremities, or talk, although there may be comprehension of verbal language. Patients may have short stature and have poor weight gain. They often require gastrostomy feeding tubes for nutritional support. Dystonia may occur. Most children with connatal disease die in the first one to two decades of life.

*Classic PMD* is the phenotype originally described by Pelizaeus and Merzbacher. It is the most common phenotype because patients with duplication most frequently have classic PMD. Patients develop nystagmus, usually noticed within the first 2 months of life, but occasionally, patients do not develop nystagmus. It typically resolves within 2 to 5 years of age. Patients develop head titubation that may resolve. Hypotonia in infancy begins to evolve to spastic quadriplegia in the first 5 years. Patients usually develop purposeful use of the upper extremities and dysarthric language. At the milder end of the classic PMD range, patients may begin to walk in childhood, usually with an assistive device, but as spasticity becomes greater, they lose the ability to walk. Dystonia and athetosis may occur at the severe end of the classic PMD range. Seizures are rare. Lifespan may be shortened, but patients with classic PMD have lived to the seventh decade.

*The PLP null phenotype* occurs when no PLP protein is present and is typically a complicated SPG phenotype that develops in the first 1 to 5 years of life. It is characterized by mild to moderate developmental delay, spastic gait, and mild demyelinating peripheral neuropathy.[30] Over time, progression of signs after puberty is typical and ultimately leads to severe spastic quadriplegia, with loss of communication abilities.

*Complicated SPG2* begins in the first 5 years of life with nystagmus, ataxia, and autonomic dysfunction, such as spastic urinary bladder. Patients are able to walk with a spastic gait. Patients are able to talk, but speech may be slow. Lifespan may be normal.

*Pure SPG2* is usually apparent in the first 5 years, but onset may be delayed until the third or fourth decade. Patients are able to walk with a spastic gait. Patients are able to talk, but speech may be slow. Lifespan is normal.

The wide clinical spectrum in PMD/SPG2 is a reflection of the diverse molecular etiology. Disease severity increases

with increasing copy number of *PLP1* and is not affected by the size of the duplicated region.[4, 5, 12] Duplications of the *PLP1* gene usually result in classic PMD, while triplications are reported to cause a more severe phenotype. Complete deletion of the *PLP1* gene and point mutations that disrupt the methionine codon or that cause truncation of the protein near the amino-terminus result in the milder null phenotype.[30] Other point mutations (missense, frameshift, nonsense) and indels are reported to result in severity across the entire spectrum of PMD/SPG2 phenotypes.[11, 29] Mutations that affect the PLP-specific region and not the DM20 isoform result in disease toward the mild end of the spectrum, including spastic paraplegia phenotypes.[29] There can be some intrafamilial phenotypic heterogeneity.[28, 31, 32] Females can exhibit mild or moderate disease signs, especially in families in which the males are mildly affected.[33, 34]

### MRI and MRS Features of Pelizaeus-Merzbacher Disease and Spastic Paraplegia 2

Patients with PMD have a diffuse pattern of hypomyelination on MRI.[35–37] This is seen best as increased signal intensity on T2-weighted or fluid-attenuated inversion recovery (FLAIR) scans. Affected white matter regions include the cerebral hemispheres, cerebellum, and brainstem. Thinning of the corpus callosum is sometimes noted.[36] Atrophy of the cerebral hemispheres may be seen in severe PMD cases. Sparing of the corticospinal tracts can occur in classical PMD. Patients with the PLP null phenotype have milder diffuse abnormalities of the white matter on MRI scans.[30] Patients with the milder SPG2 phenotype may have patchy areas of hypomyelination on MRI. Children with PMD may not have definitively abnormal MRI scans until the age of 1 or 2 when rapid myelination is completed. However, absence of normal myelin-related changes in the pons and cerebellum of a newborn or absence of normal myelin-related changes in the posterior limb of the internal capsule, the splenium of the corpus callosum, and the optic radiations of a 3-month-old child could suggest PMD or other leukodystrophies.[38] It should be noted that T1-weighted images may be more sensitive to these early changes than T2-weighted images.[38]

Metabolite levels on magnetic resonance spectroscopy (MRS) are not necessarily consistent across the forms of PMD. Patients with duplications have increased levels of *N*-acetyl aspartate (NAA),[39] whereas patients with other mutations, especially those that lack PLP protein, have reduced NAA levels.[36, 40, 41] Most patients with point mutations or duplications have low levels of choline consistent with hypomyelination of *PLP1*, but increased levels of choline are seen in some cases, suggesting ongoing demyelination.[41] In PMD duplication patients, increased levels of glutamine, inositol, and creatine are seen on MRS in addition to increased NAA.[42] This pattern is distinctive and may assist with distinguishing PMD from other leukodystrophies.[42]

### Clinical Features of Pelizaeus-Merzbacher-Like Disease 1 and Spastic Paraplegia 44

PMLD1 has only recently been reported, so the full phenotypic spectrum may not yet be known. The clinical phenotype of most PMLD1 patients reported to date is not appreciably different from that of the classic phenotype of PMD. The phenotypic spectrum of *GJC2* mutations was recently extended to include a milder complicated spastic paraplegia phenotype, SPG44 (MIM #613206), with the description of a homozygous mutation in three members of one mildly affected family.[25]

### MRI/MRS Features of Pelizaeus-Merzbacher-Like Disease 1 and Spastic Paraplegia 44

The MRI of PMLD1 patients shows a diffuse pattern of hypomyelination, quite similar or indistinguishable from those of true PMD patients (see above).[17–21, 37] Sparing of the corticospinal tracts, as can occur in classical PMD, has been reported. However, unlike PMD patients, two PMLD1 patients had normal or almost normal levels of choline, NAA and creatine on MRS, suggesting that MRS might be useful in distinguishing PMD and PMLD1.[21]

## Diagnosis and Testing of PMD/SPG2 and PMLD1/SPG44

Diagnosis of PMD/SPG2 is made based on clinical presentation, MRI indicative of diffusely abnormal myelin, X-linked inheritance pattern, and molecular testing indicating duplication or other mutation of the *PLP1* gene.[27] Diagnosis of PMLD1/SPG44 is made based on clinical presentation, MRI indicative of diffusely abnormal myelin, autosomal recessive inheritance pattern, and molecular testing indicating mutations of the *GJC2* gene.[22]

Brainstem auditory evoked potentials (BAEP) may be a helpful tool to distinguish between classic PMD and PMLD1.[43] In one study, waves III, IV, and V generated in the pons and midbrain, were absent in 10 patients with PMD, but were present in 11 of 13 investigations in 8 patients with PMLD1.

### Molecular Testing of Male Patients

When PMD is suspected clinically in male patients, *PLP1* gene duplication testing is a reasonable first step because duplications are the most common *PLP1* gene defect occurring in over 50% of the patients who fit strict clinical criteria for PMD.[1] The tests for duplication will also detect less common deletions. Several methods are currently in use by clinical diagnostic laboratories for duplication/deletion testing: quantitative multiplex polymerase chain reaction (PCR), multiple ligation probe analysis (MLPA), real time PCR, array comparative genomic hybridization (aCGH), and fluorescent in situ hybridization (FISH). Considerations and limitations for these methods are as follows:

- Quantitative multiplex PCR, MLPA, real time PCR, aCGH, and interphase FISH can detect copy number changes. These methods cannot be used to determine whether the duplication is tandem or inserted elsewhere in the genome. Tandem duplications that are smaller than 100 kilobases may not be resolved by interphase FISH.
- Most PMD duplications are too small to resolve by metaphase FISH. However, metaphase FISH can be used to

determine location of duplicated segments that are inserted in a region of the genome that is distant from the *PLP1* gene.

- Quantitative multiplex PCR, MLPA, and real-time PCR are generally designed to detect only copy number changes in the *PLP1* gene itself. They do not give information about the extent of the region that is duplicated unless they are designed to do so.
- aCGH can give information about the extent of the region that is duplicated. Size and spacing of the probes on the array should be taken into consideration. When aCGH is performed with closely spaced oligonucleotide probes, it is more sensitive than when performed with larger probes such as BACs or cosmids. If probes are spaced too far apart on aCGH, false-negatives may result.

If duplication or deletion of the *PLP1* gene is not detected in male patients, sequence analysis of the *PLP1* gene is the next step. Mutations of *PLP1* that can be detected by sequence analysis account for ~25% of cases that fit strict clinical criteria for PMD.[1] Male patients who are negative for *PLP1* mutations should next be tested for *GJC2* mutations. Approximately 8% of PMLD patients (those who test negative for *PLP1* duplications or other mutations) have mutations in the *GJC2* gene.[22] However, the percentage of *GJC2* mutations in consanguineous PMLD cases was 30%, suggesting that sequence analysis for *GJC2* mutations prior to sequence analysis for *PLP1* mutations might be justified in these cases.

When a mild spastic paraplegia phenotype is determined clinically in male patients, it is reasonable to undertake DNA sequence analysis of the *PLP1* gene prior to duplication analysis.

### Molecular Testing of Female Patients

A reasonable approach for testing females who have clinical symptoms of PMD/PMLD in families with no affected male family members is to begin with sequence analysis for mutations of the *GJC2* gene. Approximately 16% of females with PMLD had mutations of *GJC2*.[22] If an affected female tests negative for *GJC2* mutations, then duplication analysis and sequence analysis of the *PLP1* gene might be justified, especially if the phenotype is mild because carrier females in families with *PLP1* duplications and mutations can be mildly affected.

### Carrier Testing, Prenatal Testing, and Preimplantation Genetic Diagnosis for Family Members

Carrier testing for at-risk females and prenatal testing for at-risk pregnancies in PMD families require prior identification of the disease-causing mutation in a male family member. Preimplantation genetic diagnosis has been reported for point mutation of *PLP1*.[44]

Carrier testing for at-risk individuals and prenatal testing in PMLD1 families require prior identification of the disease-causing alleles. Carrier testing for parents of patients with PMLD1 may help determine whether heterozygous individuals are compound heterozygotes (two mutations are on different alleles) and whether individuals with one mutation are homozygous or have a deletion of one allele. Preimplantation genetic diagnosis should be possible for PMLD1 families.

### Other Considerations

When only one heterozygous *GJC2* mutation is identified in a PMLD patient, the following may be considered: (1) the mutation may be unrelated to the disease in the patient; (2) the patient may have a second mutation in a region of the other *GJC2* allele that was not sequenced, such as a transcriptional or splicing regulatory region; (3) the mutation in the patient may be causing autosomal dominant disease; and (4) the mutation detected may combine with mutation of a different gene to produce the disease phenotype (digenic inheritance). Both options 3 and 4 have been reported for gap junction protein genes that cause congenital deafness.[45]

Other diseases that may be considered when PMD/SPG2 and PMLD1/SPG44 mutations are not identified:

- Hypomyelinating leukodystrophy 3 (HDL3; MIM #260600)—autosomal recessive, caused by mutations of the aminoacyl-tRNA synthetase complex-interacting multifunctional protein 1 gene (*AIMP1*; MIM #603605)[46]
- Hypomyelinating leukodystrophy 4 (HLD4; MIM#612233), also called mitochondrial HSP60 chaperonopathy and mitchap 60 disease – autosomal recessive, caused by mutations of the heat-shock 60-kd protein 1 gene (*HSPD1*, MIM#118190)[47]
- Hypomyelinating leukodystrophy 5 (HLD5; MIM#610532), also called hypomyelination and congenital cataract (HCC)—autosomal recessive, caused by mutations of the family with sequence similarity 126, member A gene (*FAM126A*, MIM# 610531)[48]
- Allan-Herndon-Dudley's syndrome (AHDS; MIM#300523), also called Allan-Herndon's syndrome, monocarboxylate transporter 8 deficiency, triiodothyronine resistance, T3 resistance, X-linked mental retardation with hypotonia, and mental retardation and muscular atrophy—X-linked, caused by mutations of the solute carrier family 16 (monocarboxylic acid transporter) member 2 gene (*SLC16A2*, MIM#300095), also known as MCT8[49]
- Leukodystrophy, demyelinating, adult-onset, autosomal dominant (ADLD; MIM# 169500), also known as Pelizaeus-Merzbacher disease, autosomal dominant or late-onset type, multiple sclerosis-like disorder—autosomal dominant, caused by duplications of the lamin B1 gene (*LMNB1*; MIM# 150340)[50]
- Sialuria, Finnish type (MIM# 604369), also known as Salla's disease (SD) and the allelic infantile sialic acid storage disorder (ISSD; MIM# 269920), also known as sialuria, infantile form, *N*-acetylneuraminic acid storage disease, and nana storage disease (NSD)—autosomal recessive, caused by mutations of the solute carrier family 17 (sodium phosphate cotransporter), member 5 gene (*SLC17A5*; MIM# 604322)[51]
- Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg's syndrome, and Hirschsprung's

disease (PCWH; MIM# 609136), also known as Waardenburg-Shah's syndrome, neurological variant—autosomal dominant, caused by mutations of the sry-box 10 gene (*SOX10*; MIM# 602229), also known as sry-related HMG-box gene 10 and dominant megacolon, mouse, homolog of (DOM)[52]

- Mental retardation, aphasia, shuffling gait, and adducted thumbs (MASA syndrome; MIM# 303350), also known as spastic paraplegia 1, X-linked (SPG1); L1 syndrome; clasped thumb and mental retardation; thumb, congenital clasped, with mental retardation; adducted thumb with mental retardation, Gareis-Mason's syndrome, CRASH syndrome—X-linked recessive, caused by mutations of the L1 cell adhesion molecule gene (*L1CAM*; MIM# 308840), also known as MIC5 and neural cell adhesion molecule L1 (CAML1)[53]

- Several forms of spastic paraplegia need to be considered in the differential diagnosis of SPG2 and SPG44, reviewed at http://www.ncbi.nlm.nih.gov/books/NBK1182/ [54]

## Treatment for PMD/SPG2 and PMLD1/SPG44

Supportive therapy from a team that includes specialists in neurology, physical medicine, orthopedics, pulmonary medicine, and gastroenterology is recommended for patients with PMD/SPG2 and PMLD1/SPG44.[14] Medications may include antiepileptic drugs, such as carbamazepine for seizures and medications to reduce spasticity (baclofen, diazepam, tizanidine, botulinum toxin). Spasticity management may also include physical therapy, exercise, and orthotics. Surgery may be indicated for contractures and scoliosis. Gastrostomy may be indicated for individuals who have severe dysphagia. Proper wheelchair seating, physical therapy, and orthotics may help to prevent scoliosis or may ameliorate its effects. Special education is usually necessary except in the mildest forms. Assistive communication devices may be helpful.

## References

1 Mimault C, Giraud G, Courtois V, et al; The Clinical European Network on Brain Dysmyelinating Disease. Proteolipoprotein gene analysis in 82 patients with sporadic Pelizaeus-Merzbacher disease: duplications, the major cause of the disease, originate more frequently in male germ cells, but point mutations do not. Am J Hum Genet 1999;65(2):360–369

2 Woodward KJ, Cundall M, Sperle K, et al. Heterogeneous duplications in patients with Pelizaeus-Merzbacher disease suggest a mechanism of coupled homologous and nonhomologous recombination. Am J Hum Genet 2005;77(6):966–987

3 Lee JA, Inoue K, Cheung SW, Shaw CA, Stankiewicz P, Lupski JR. Role of genomic architecture in PLP1 duplication causing Pelizaeus-Merzbacher disease. Hum Mol Genet 2006;15(14):2250–2265

4 Regis S, Biancheri R, Bertini E, et al. Genotype-phenotype correlation in five Pelizaeus-Merzbacher disease patients with PLP1 gene duplications. Clin Genet 2008;73(3):279–287

5 Shimojima K, Inoue T, Hoshino A, et al. Comprehensive genetic analyses of PLP1 in patients with Pelizaeus-Merzbacher disease applied by array-CGH and fiber-FISH analyses identified new mutations and variable sizes of duplications. Brain Dev 2010;32 (3):171–179

6 Hodes ME, Woodward K, Spinner NB, et al. Additional copies of the proteolipid protein gene causing Pelizaeus-Merzbacher disease arise by separate integration into the X chromosome. Am J Hum Genet 2000;67(1):14–22

7 Inoue K, Osaka H, Thurston VC, et al. Genomic rearrangements resulting in PLP1 deletion occur by nonhomologous end joining and cause different dysmyelinating phenotypes in males and females. Am J Hum Genet 2002;71(4):838–853

8 Shy ME, Hobson G, Jain M, et al. Schwann cell expression of PLP1 but not DM20 is necessary to prevent neuropathy. Ann Neurol 2003;53(3):354–365

9 Hobson GM, Huang Z, Sperle K, et al. Splice-site contribution in alternative splicing of PLP1 and DM20: molecular studies in oligodendrocytes. Hum Mutat 2006;27(1):69–77

10 Bonnet-Dupeyron MN, Combes P, Santander P, Cailloux F, Boespflug-Tanguy O, Vaurs-Barrière C. PLP1 splicing abnormalities identified in Pelizaeus-Merzbacher disease and SPG2 fibroblasts are associated with different types of mutations. Hum Mutat 2008;29(8):1028–1036

11 Grossi S, Regis S, Biancheri R, et al. Molecular genetic analysis of the PLP1 gene in 38 families with PLP1-related disorders: identification and functional characterization of 11 novel PLP1 mutations. Orphanet J Rare Dis 2011;6:40

12 Wolf NI, Sistermans EA, Cundall M, et al. Three or more copies of the proteolipid protein gene PLP1 cause severe Pelizaeus-Merzbacher disease. Brain 2005;128(Pt 4):743–751

13 Combes P, Bonnet-Dupeyron MN, Gauthier-Barichard F, et al. PLP1 and GPM6B intragenic copy number analysis by MAPH in 262 patients with hypomyelinating leukodystrophies: Identification of one partial triplication and two partial deletions of PLP1. Neurogenetics 2006;7(1):31–37

14 Garbern J, Krajewski K. Hobson G, PLP1-related disorders. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle University of Washington1993. Accessed September 29, 2011

15 Heim P, Claussen M, Hoffmann B, et al. Leukodystrophy incidence in Germany. Am J Med Genet 1997;71(4):475–478

16 Seeman P, Krsck P, Namestkova K, et al. Pelizaeus-Merzbacher's disease (PMD) - Detection of the most frequent mutation of the proteolipid protein gene in Czech patients and families with the classical form of PMD. Ceska Slovenska Neurol Neurochir 2003;66:95–104

17 Abrams CK, Scherer SS. Gap junctions in inherited human disorders of the central nervous system. Biochim Biophys Acta 2011

18 Uhlenberg B, Schuelke M, Rüschendorf F, et al. Mutations in the gene encoding gap junction protein alpha 12 (connexin 46.6) cause Pelizaeus-Merzbacher-like disease. Am J Hum Genet 2004;75(2):251–260

19 Salviati L, Trevisson E, Baldoin MC, et al. A novel deletion in the GJA12 gene causes Pelizaeus-Merzbacher-like disease. Neurogenetics 2007;8(1):57–60

20 Wolf NI, Cundall M, Rutland P, et al. Frameshift mutation in GJA12 leading to nystagmus, spastic ataxia and CNS dys-/demyelination. Neurogenetics 2007;8(1):39–44

21 Bugiani M, Al Shahwan S, Lamantea E, et al. GJA12 mutations in children with recessive hypomyelinating leukoencephalopathy. Neurology 2006;67(2):273–279

22 Henneke M, Combes P, Diekmann S, et al. GJA12 mutations are a rare cause of Pelizaeus-Merzbacher-like disease. Neurology 2008;70(10):748–754

23 Wang J, Wang H, Wang Y, Chen T, Wu X, Jiang Y. Two novel gap junction protein alpha 12 gene mutations in two Chinese patients with Pelizaeus-Merzbacher-like disease. Brain Dev 2010;32 (3):236–243

24 Combes P, Kammoun N, Monnier A, et al. Relevance of GJC2 promoter mutation in Pelizaeus-Merzbacher-like disease. Ann Neurol 2010;71(1):146–148

25 Orthmann-Murphy JL, Salsano E, Abrams CK, et al. Hereditary spastic paraplegia is a novel phenotype for GJA12/GJC2 mutations. Brain 2009;132(Pt 2):426–438

26 Ferrell RE, Baty CJ, Kimak MA, et al. GJC2 missense mutations cause human lymphedema. Am J Hum Genet 2010;86(6):943–948

27 Boulloche J, Aicardi J. Pelizaeus-Merzbacher disease: clinical and nosological study. J Child Neurol 1986;1(3):233–239

28 Hodes ME, Pratt VM, Dlouhy SR. Genetics of Pelizaeus-Merzbacher disease. Dev Neurosci 1993;15(6):383–394

29 Cailloux F, Gauthier-Barichard F, Mimault C, et al; Clinical European Network on Brain Dysmyelinating Disease. Genotype-phenotype correlation in inherited brain myelination defects due to proteolipid protein gene mutations. Eur J Hum Genet 2000;8 (11):837–845

30 Garbern JY, Yool DA, Moore GJ, et al. Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. Brain 2002;125(Pt 3):551–561

31 Sistermans EA, de Coo RF, De Wijs IJ, Van Oost BA. Duplication of the proteolipid protein gene is the major cause of Pelizaeus-Merzbacher disease. Neurology 1998;50(6):1749–1754

32 Fattal-Valevski A, DiMaio MS, Hisama FM, et al. Variable expression of a novel PLP1 mutation in members of a family with Pelizaeus-Merzbacher disease. J Child Neurol 2009;24(5):618–624

33 Hurst S, Garbern J, Trepanier A, Gow A. Quantifying the carrier female phenotype in Pelizaeus-Merzbacher disease. Genet Med 2006;8(6):371–378

34 Carvalho C, Bartnik M, Pehlivan D, et al. Evidence for disease penetrance relating to CNV size: Pelizaeus-Merzbacher disease and manifesting carriers with a familial 11 Mb duplication at Xq22. Clin Genet, in press

35 Nezu A, Kimura S, Takeshita S, Osaka H, Kimura K, Inoue K. An MRI and MRS study of Pelizaeus-Merzbacher disease. Pediatr Neurol 1998;18(4):334–337

36 Plecko B, Stöckler-Ipsiroglu S, Gruber S, et al. Degree of hypomyelination and magnetic resonance spectroscopy findings in patients with Pelizaeus Merzbacher phenotype. Neuropediatrics 2003;34 (3):127–136

37 Steenweg ME, Vanderver A, Blaser S, et al. Magnetic resonance imaging pattern recognition in hypomyelinating disorders. Brain 2010;133(10):2971–2982

38 Barkovich AJ. Magnetic resonance techniques in the assessment of myelin and myelination. J Inherit Metab Dis 2005;28(3):311–343

39 Takanashi J, Inoue K, Tomita M, et al. Brain N-acetylaspartate is elevated in Pelizaeus-Merzbacher disease with PLP1 duplication. Neurology 2002;58(2):237–241

40 Bonavita S, Schiffmann R, Moore DF, et al. Evidence for neuro-axonal injury in patients with proteolipid protein gene mutations. Neurology 2001;56(6):785–788

41 Hobson GM, Huang Z, Sperle K, Stabley DL, Marks HG, Cambi F. A PLP splicing abnormality is associated with an unusual presentation of PMD. Ann Neurol 2002;52(4):477–488

42 Hanefeld FA, Brockmann K, Pouwels PJ, Wilken B, Frahm J, Dechent P. Quantitative proton MRS of Pelizaeus-Merzbacher disease: evidence of dys- and hypomyelination. Neurology 2005;65(5): 701–706

43 Henneke M, Gegner S, Hahn A, et al. Clinical neurophysiology in GJA12-related hypomyelination vs Pelizaeus-Merzbacher disease. Neurology 2010;74(22):1785–1789

44 Verlinsky Y, Rechitsky S, Laziuk K, Librach C, Genovese R, Kuliev A. Preimplantation genetic diagnosis for Pelizaeus-Merzbacher disease with testing for age-related aneuploidies. Reprod Biomed Online 2006;12(1):83–88

45 Welch KO, Marin RS, Pandya A, Arnos KS. Compound heterozygosity for dominant and recessive GJB2 mutations: effect on phenotype and review of the literature. Am J Med Genet A 2007;143A (14):1567–1573

46 Feinstein M, Markus B, Noyman I, et al. Pelizaeus-Merzbacher-like disease caused by AIMP1/p43 homozygous mutation. Am J Hum Genet 2010;87(6):820–828

47 Magen D, Georgopoulos C, Bross P, et al. Mitochondrial hsp60 chaperonopathy causes an autosomal-recessive neurodegenerative disorder linked to brain hypomyelination and leukodystrophy. Am J Hum Genet 2008;83(1):30–42

48 Biancheri R, Zara F, Bruno C, et al. Hypomyelination and congenital cataract. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle: University of Washington; 1993. Accessed September 29, 2011

49 Dempsey MA, Dumitrescu AM. Refetoff S, MCT8 (SLC16A2)-specific thyroid hormone cell transporter deficiency. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle: University of Washington; 1993. Accessed September 29, 2011

50 Padiath QS, Saigoh K, Schiffmann R, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat Genet 2006;38 (10):1114–1123

51 Adams D, Gahl WA. Free sialic acid storage disorders. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle: University of Washington; 1993. Accessed September 29, 2011

52 Inoue K, Khajavi M, Ohyama T, et al. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. Nat Genet 2004;36(4):361–369

53 Schrander-Stumpel C, Vos YJ. L1 Syndrome. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle: University of Washington; 1993. Accessed September 29, 2011

54 Fink JK. Hereditary spastic paraplegia overview. In: Pagon R, Bird T, Dolan C, Stephens K, eds. GeneReviews. Seattle: University of Washington; 1993. Accessed September 29, 2011