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Pelizaeus-Merzbacher-Like Disease 1

Synonyms: Hypomyelinating Leukodystrophy 2 (HLD2), PMLD1

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Summary

Clinical characteristics

Pelizaeus-Merzbacher-like disease 1 (PMLD1) is a slowly progressive leukodystrophy that typically presents during the neonatal or early-infantile period with nystagmus, commonly associated with hypotonia, delayed acquisition of motor milestones, speech delay, and dysarthria. Over time the hypotonia typically evolves into spasticity that affects the ability to walk and communicate. Cerebellar signs (gait ataxia, dysmetria, intention tremor, head titubation, and dysdiadochokinesia) frequently manifest during childhood. Some individuals develop extrapyramidal movement abnormalities (choreoathetosis and dystonia). Hearing loss and optic atrophy are observed in rare cases. Motor impairments can lead to swallowing difficulty and orthopedic complications, including hip dislocation and scoliosis. Most individuals have normal cognitive skills or mild intellectual disability – which, however, can be difficult to evaluate in the context of profound motor impairment.

Diagnosis/testing

The diagnosis of PMLD1 is established in a proband with suggestive clinical and neuroimaging findings and identification of biallelic pathogenic variants in *GJC2* on molecular genetic testing.

Management

Treatment of manifestations: To date no definite treatment is available; treatment is mainly supportive and includes assuring adequate nutrition and providing standard treatment for developmental delay/cognitive impairment, neurologic complications (spasticity, ataxia, epilepsy, extrapyramidal movement disorders), communication difficulties, hearing loss, and visual impairment.

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Surveillance: Routine assessment of growth, weight gain, vision, and hearing. Routine monitoring of disease progression, spine for evidence of scoliosis and hips for evidence of dislocation, and needs related to physical therapy, communication, and swallowing/feeding.

Genetic counseling

PMLD1 is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier (heterozygote), and a 25% chance of being unaffected and not a carrier. Once the *GJC2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Pelizaeus-Merzbacher-like disease 1 (PMLD1) **should be suspected** in individuals with the following classic clinical and neuroimaging findings:

Clinical findings

- Nystagmus that typically presents during the neonatal period or early infancy
- Mainly motor developmental delay and central hypotonia during infancy
- Signs of upper motor neuron dysfunction (including spasticity, brisk deep tendon reflexes, and Babinski sign) usually affecting the lower limbs more than the upper limbs
- Gait ataxia and other cerebellar signs
- Mild choreiform movements and dystonia of the extremities that can become severe and disabling
- Dysarthria and swallowing dysfunction

Neuroimaging findings. Findings on brain MRI include the following [Bugiani et al 2006, Steenweg et al 2010, Parikh et al 2015] (see Figure 1):

- Diffuse homogeneous hyperintense T_2-weighted signal that affects the white matter of the cerebrum and cerebellum
- Involvement of the corticospinal tracts with abnormal T_2-weighted signal extending into the brain stem resulting in extensive brain stem involvement not typically seen in Pelizaeus-Merzbacher disease (see Differential Diagnosis)
- Thin corpus callosum in older children
- Brain atrophy and ventricular dilatation as a consequence of white matter loss without specific cerebellar atrophy [Orthmann-Murphy et al 2009]
- Relative preservation of deep gray nuclei and the thalami

Establishing the Diagnosis

The diagnosis of PMLD1 **is established** in a proband with suggestive clinical and neuroimaging findings and identification of biallelic pathogenic variants in *GJC2* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel or single-gene testing) and **genomic testing** (comprehensive genomic sequencing) depending on the phenotype.

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Because the phenotype of PMLD1 is broad, children with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a

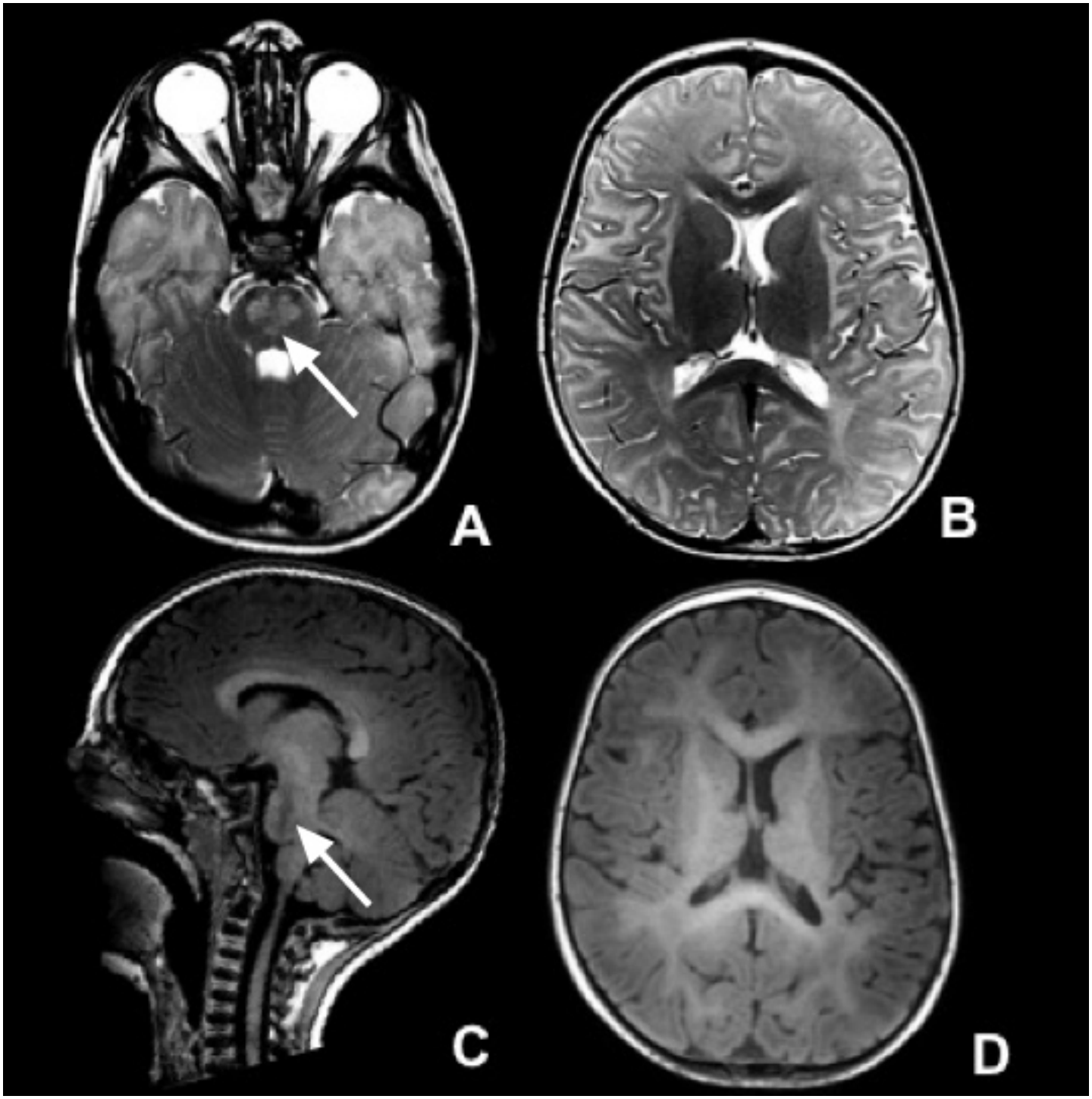

Figure 1. MRI in a male age 36 months with molecularly confirmed PMLD1. Note the diffuse T_2-weighted hyperintensity (A and B) and diffuseT_1 mild hyperintensity (C and D) consistent with hypomyelination. Involvement of pontine structures is seen in A (axial view) as T_2-weighted hyperintensity (arrow) and C (sagittal view) as T_1-weighted hypointensity (arrow). No cerebellar atrophy (A and C) and no abnormalities of the basal ganglia (B and D) – as may be observed in other hypomyelinating conditions – are seen.

mild phenotype indistinguishable from many other inherited leukodystrophies are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the clinical findings and brain MRI findings suggest the diagnosis of a PMLD1, molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *GJC2*, including the noncoding exon 1 (see Note), is performed first. If only one pathogenic variant is found, perform gene-targeted deletion/duplication analysis.

  Note: Two variants in the noncoding exon 1, c.-170A>G and c.-167A>G, have been frequently associated with disease and should be included in sequencing assays [Osaka et al 2010, Meyer et al 2011, Combes et al 2012, Kammoun Jellouli et al 2013, Gotoh et al 2014].

- **A multigene panel** that includes *GJC2* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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 leukodystrophies, molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) or **comprehensive genomic testing** (when available). Comprehensive genomic testing includes exome sequencing and genome sequencing.

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 Pelizaeus-Merzbacher-Like Disease 1

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
GJC2	Sequence analysis including promoter regions (first *GJC2* noncoding exon) [3]	53/79 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	26/79 [4, 5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Uhlenberg et al [2004], Bugiani et al [2006], Wolf et al [2007], Henneke et al [2008], Orthmann-Murphy et al [2009], Wang et al [2010], Zittel et al [2012], Al-Yahyaee et al [2013], Biancheri et al [2013], Shimojima et al [2013], Abrams et al [2014]
5. Twenty-two of 51 reported affected individuals had pathogenic variants in the noncoding exon 1 of *GJC2*: c.-170A>G in two individuals and c.-167A>G in 20 individuals [Osaka et al 2010, Meyer et al 2011, Combes et al 2012, Kammoun Jellouli et al 2013, Gotoh et al 2014]; thus, it is important that this noncoding exon be included in sequence analysis.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Pelizaeus-Merzbacher-like disease 1 (PMLD1) is a slowly progressive leukodystrophy that typically presents in the neonatal period or early infancy with nystagmus, often complicated by hypotonia and developmental delay. Over time the hypotonia may evolve into spasticity, and extrapyramidal movement abnormalities may emerge. Older children often manifest significant motor impairments that can also effect communication. Cognition is relatively preserved. The following detailed description of clinical manifestations is based on findings in individuals with a molecularly proven diagnosis [Uhlenberg et al 2004, Bugiani et al 2006, Wolf et al 2007, Henneke et al 2008, Orthmann-Murphy et al 2009, Wang et al 2010, Zittel et al 2012, Al-Yahyaee et al 2013, Biancheri et al 2013, Shimojima et al 2013, Abrams et al 2014].

Nystagmus (either rotatory or horizontal) appears in early infancy and is not present in all individuals.

During later infancy, signs of central hypotonia and delayed acquisition of motor milestones become more apparent, with most children having speech delay and dysarthria as well.

Over time, progressive pyramidal tract involvement (manifest as spasticity, brisk deep tendon reflexes, and bilateral Babinski signs) affects the ability to walk. The lower limbs are often more involved than in the upper limbs. Most affected children become wheelchair dependent in their first decade.

Cerebellar signs including gait ataxia, dysmetria, intention tremor, head titubation, and dysdiadochokinesia frequently manifest during childhood.

Some develop extrapyramidal movement disorders (choreoathetosis and dystonia), which may contribute to the functional disability.

Motor impairments can lead to swallowing difficulty and orthopedic complications, including hip dislocation and scoliosis.

Cognitive function is relatively preserved: Most individuals have normal cognitive skills or mild intellectual disability that may be difficult to evaluate in the context of profound motor impairment. Dysarthria may severely impair communication in adolescents and young adults.

Other less common findings:

- Seizures that are typically infrequent and responsive to antiepileptic drugs
- Sensorineural hearing loss [Orthmann-Murphy et al 2009]
- Optic atrophy [Bugiani et al 2006]

Onset is typically in infancy. Although connatal onset is thought to be very rare, one neonate with congenital nystagmus and severe neurologic impairment has been reported [Biancheri et al 2013]. Brain MRI revealed extensive white matter involvement and abnormal cervical spine white matter.

Neurophysiologic findings [Henneke et al 2010]

The following can be normal or delayed:

- Visual evoked potentials
- Brain stem auditory evoked potential
- Somatosensory evoked potential
- Nerve conduction studies [Uhlenberg et al 2004]

Electromyogram is usually normal.

Electroencephalography shows nonspecific findings or occasionally (multi)focal epileptiform activity.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been observed with recurrent pathogenic variants.

Prevalence

The disease prevalence is not known.

Genetically Related (Allelic) Disorders

Table 2. Allelic Disorders

Gene	Phenotype [1]	MOI
GJC2	Hereditary lymphedema type IC (OMIM 613480) [2]	AD
	Spastic paraplegia 44 (see Hereditary Spastic Paraplegia Overview) [3]	AR
	Subclinical leukodystrophy [Abrams et al 2014] [4]	AR

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. See hyperlinked *GeneReview*, OMIM phenotype entry, or cited reference for more information.

2. Heterozygous *GJC2* pathogenic variants cause hereditary lymphedema type IC [Ferrell et al 2010]. It is not yet clear how heterozygous pathogenic missense variants in *GJC2* may lead to disruption of lymphatic function.

3. Three individuals with adulthood-onset isolated spastic paraplegia [Orthmann-Murphy et al 2009]

4. One individual with subtle changes on brain MRI and subclinical leukodystrophy (episodes of loss of consciousness associated with loss of bowel and bladder control) [Abrams et al 2014]

Differential Diagnosis

Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder caused by a hemizygous pathogenic variant in *PLP1*. The clinical presentation and radiologic appearance are similar to PMLD1. Most individuals present with neonatal nystagmus, hypotonia, global developmental delay, spasticity, gait ataxia, and choreoathetosis. Diffuse hypomyelination on brain MRI is observed in most individuals. Note that MRI evidence of brain stem involvement is more characteristic of PMLD1 than PMD. Both PMD and PMLD1 can present as an isolated spastic paraparesis; see Genetically Related Disorders.

Hypomyelination with atrophy of the basal ganglia and cerebellum (see *TUBB4A*-Related Leukodystrophy) is caused by a heterozygous pathogenic variant in *TUBB4A*; affected individuals are typically simplex cases (i.e., a single occurrence in a family). Presentation is generally during infancy or early childhood with findings that overlap with PMLD1: psychomotor developmental delay, pyramidal signs, cerebellar signs, gait ataxia, extrapyramidal symptoms, and dysarthria. MRI demonstrates diffuse hypomyelination of the white matter typically associated with basal ganglia and cerebellar atrophy [Simons et al 2013].

4H syndrome (hypomyelination, hypodontia, and hypogonadotropic hypogonadism syndrome) (see POLR3-Related Leukodystrophy) is an autosomal recessive disorder caused by biallelic pathogenic variants in *POLR1C*, *POLR3A*, and *POLR3B*. 4H syndrome presents with a combination of motor findings (spasticity, gait ataxia and cerebellar tremor, extrapyramidal movement disorders, and generally mild spasticity) that are similar to those of PMLD1. Additional findings are abnormal dentition, severe myopia, and hypogonadotropic hypogonadism, which are not observed in PMLD1.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Pelizaeus-Merzbacher-like disease 1 (PMLD1), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of Pelizaeus-Merzbacher-Like Disease 1

Organ System	Evaluation	Comment
Eyes	Ophthalmology	Assessment for optic atrophy & nystagmus
ENT	Audiology	Assessment for sensorineural hearing loss
Gastrointestinal	Consultation w/gastroenterologist	Consideration of swallowing study to assess for swallowing dysfunction & mgmt of constipation & gastroesophageal reflux
Musculoskeletal	Referral to an orthopedic surgeon for tone mgmt or orthopedic complications as indicated	Exam to assess for evidence of hip dislocation, joint contractures, & scoliosis
Neurologic	Consultation w/pediatric neurologist	Eval of movement disorders, tone, & seizures
Miscellaneous/ Other	Consultation w/nutritionist	Assessment of nutritional status & needs
	Consultation w/developmental specialist	Assessment of developmental level & needs for supportive therapies
	Consultation w/clinical geneticist &/or genetic counselor	Eval of underlying diagnosis & familial recurrence risk
	Consultation w/rehab specialist	Assessment of functional disability & equipment needs/adjustments

Treatment of Manifestations

There is no curative treatment for PMLD1; measures that can be taken to improve the individual's quality of life are summarized in Table 4 [Van Haren et al 2015].

Table 4. Treatment of Manifestations in Individuals with Pelizaeus-Merzbacher-Like Disease 1

Manifestation	Treatment	Considerations/Other
Developmental delay & cognitive dysfunction	Accommodations in special classroom setting or w/aide	Recommendations from pediatric neurologist may be necessary to achieve maximum intellectual & functional abilities.
Spasticity	Oral GABA agonists (e.g., baclofen, diazepam)	For more focal spasticity, consider intramuscular injection of botulinum toxin.
	Physical therapy	
	Use of equipment such as walker & wheelchair	
Dystonia	When associated w/spasticity, mgmt of dystonia w/baclofen or intramuscular botulinum toxin; trihexyphenidyl or tetrabenazine potentially helpful	In many cases, dystonia is refractory to medical mgmt.
Scoliosis & joint dislocation	Mgmt or surgical intervention by orthopedist	
Swallowing dysfunction	Consider swallowing eval & feeding therapy	Affected individuals are at risk of aspiration.
	Nutrition plan & possible supportive feeding device to avoid malnutrition	
Dysarthria	Consider speech therapy to improve communication abilities	Augmentative communication approaches are often necessary.
Seizures	Standard antiepileptic drug therapy	
Hearing loss	Standard approaches to hearing loss incl augmentative communication approaches; no evidence exists for cochlear implants in this context	See Hereditary Hearing Loss and Deafness Overview.
Optic atrophy	Supportive approaches for the vision-impaired individual	

Prevention of Secondary Complications

Table 5. Prevention of Secondary Complications in Individuals with Pelizaeus-Merzbacher-Like Disease 1

Complication	Preventive Measure	Considerations/Other
Constipation	Dietary management, laxatives, stool softeners	
Bone health	Regular monitoring of serum vitamin D & calcium levels	If osteopenia is documented, consult w/bone health clinic to consider measures to avoid fracture.
Community-acquired pneumonia	Good hand hygiene; influenza & pneumococcal vaccines	Some affected individuals are reported to have deterioration of neurologic function w/febrile illness & infection. [1]
Psychosocial consequences in caregiver	Involvement of social worker	

1. Bugiani et al [2006], Meyer et al [2011]

Surveillance

Table 6. Recommended Surveillance for Individuals with Pelizaeus-Merzbacher-Like Disease 1

Organ System	Evaluation	Frequency/Comment
Constitutional	Monitoring of general health & growth; immunizations	Annually
Eyes	Ophthalmology	Biannually unless symptoms develop
Neurologic	Pediatric neurology assessment for disease progression, symptom control, & review of medications	Annually
Miscellaneous/ Other	Physiatrist & physical/occupational therapy assessments for functional capacity & equipment needs	Annually w/more frequent treatment visits once eval completed
	Assessment of communication abilities	Annually

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

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

Pelizaeus-Merzbacher-like disease 1 (PMLD1) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are typically obligate heterozygotes (carriers of one *GJC2* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with childhood-onset presentation of PMLD1 are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a heterozygote (carrier) of a *GJC2* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *GJC2* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier 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 carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GJC2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

No specific resources for Pelizaeus-Merzbacher-Like Disease 1 have been identified by *GeneReviews* staff.

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. Pelizaeus-Merzbacher-Like Disease 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GJC2	1q42.13	Gap junction gamma-2 protein	GJC2 database	GJC2	GJC2

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 Pelizaeus-Merzbacher-Like Disease 1 (View All in OMIM)

608803	GAP JUNCTION PROTEIN, GAMMA-2; GJC2
608804	LEUKODYSTROPHY, HYPOMYELINATING, 2; HLD2

Gene structure. *GJC2* (previously known as *GJA12*) comprises two exons. The first exon is noncoding and contains the binding site for transcriptional factors; the second contains part of the 5′ UTR, the coding sequence, and the 3′ UTR. See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. See Table 7.

Table 7. *GJC2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.-167A>G (-7899A>G relative to initiation codon) [2]	NA	NM_020435.3
c.-170A>G (-7902A>G relative to initiation codon) [3]	NA	

NA = not applicable
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.
1. Variant designation that does not conform to current naming conventions
2. Osaka et al [2010]
3. Gotoh et al [2014]

Normal gene product. *GJC2* encodes the gap junction gamma-2 protein, a 439-amino acid protein referred to as connexin 47 (Cx47), which is a member of the connexin family of highly conserved integral membrane proteins [Schlierf et al 2006, Wang et al 2010, Gotoh et al 2014]. Cx47 is highly expressed in the brain and spinal cord, specifically in oligodendrocytes [Odermatt et al 2003, Menichella et al 2006].

Connexins form complex intercellular channels called gap junctions between adjacent cell membranes [Willecke et al 2002]. Gap junction channels enable coupling between adjacent oligodendrocytes, as well as with astrocytes, forming a glial syncytium [Rash et al 2001, Maglione et al 2010, Wasseff & Scherer 2011]. Because astrocytes express connexin proteins (Cx43 and Cx30) that differ from those of oligodendrocytes (Cx47 and Cx32), the gap junction channels between astrocytes and oligodendrocytes are necessarily heterotypic (i.e., Cx47/Cx43 and Cx32/Cx30), whereas the gap junction channels between adjacent oligodendrocytes are likely homotypic (i.e., Cx47/Cx47 and Cx32/Cx32) [Orthmann-Murphy et al 2007].

Gap junctions enable the transfer of ions and small molecules between adjacent cells. The function of oligodendrocyte/astrocyte coupling in particular is unknown but appears to be critical for proper myelin formation and maintenance.

Mice that do not express Cx47 have a normal phenotype, but have evidence of disrupted myelin (vacuole formation) on pathology. Mice deficient for both oligodendrocyte connexins (Cx47 and Cx32) exhibit a severe phenotype, characterized by seizures, tremor, and development of widespread vacuolated myelin on pathology [Menichella et al 2006].

Abnormal gene product. Pelizaeus-Merzbacher-like disease 1 (PMLD1)-associated *GJC2* pathogenic variants result in loss of function of Cx47 [Uhlenberg et al 2004, Diekmann et al 2010, Kim et al 2013] which either fails to properly localize to the cell surface or mislocalizes to the endoplasmic reticulum [Orthmann-Murphy et al 2007]. The proteins of selected missense pathogenic variants had apparently normal location and distribution in gap-junction-deficient model cells, but showed no electric coupling in either the homopolymeric gap junction channel (Cx47/Cx47) or the heteropolymeric gap junction channel (Cx47/Cx43) [Kim et al 2013].

In a mouse model system, Tress et al [2011] showed that rather than dysfunctional Cx47, the critical outcome of PMLD1-associated *GJC2* pathogenic variants was a decreased number of cells coupled within glial networks.

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Chapter Notes

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