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Megalencephalic Leukoencephalopathy with Subcortical Cysts

Synonym: Van der Knaap Disease

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Summary

Clinical characteristics

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is characterized by two phenotypes: classic MLC and improving MLC.

- Individuals with **classic MLC** present with macrocephaly, often in association with seizures, gradual onset of ataxia, spasticity, and sometimes extrapyramidal findings, mild gross motor developmental delays, and late-onset cognitive deterioration. Macrocephaly, observed in most affected individuals, may be present at birth but more frequently develops during the first year of life. The degree of macrocephaly is variable, with head circumferences reaching four to six standard deviations greater than the mean. After the first year of life, head growth trajectory typically normalizes and growth follows a line parallel to, although several standard deviations above, the 98th centile. Initial mental and motor development is normal in most individuals. Walking is often unstable, followed by ataxia of the trunk and extremities, pyramidal dysfunction, and brisk deep tendon reflexes. Early-onset seizures are common, and approximately 60% of individuals have epilepsy that is typically well controlled with anti-seizure medication, but status epilepticus occurs relatively frequently. Cognitive deterioration occurs later in the course of the disease and is usually mild in severity. Overall disease severity varies, with some individuals being able to ambulate independently for only a few years from disease onset to other individuals continuing to independently walk in the fifth decade of life.
- Individuals with **improving MLC** have a similar initial presentation with delayed cognitive or motor development, followed by an improving clinical course: macrocephaly usually persists, but some children become normocephalic; motor function improves or normalizes; hypotonia and clumsiness may persist in some or neurologic examination may become normal. Some individuals have intellectual disability that is stable, with or without autism spectrum disorder. Epilepsy is much less frequent than in classic MLC.

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Diagnosis/testing

The diagnosis of classic MLC is established in individuals with suggestive clinical findings and characteristic abnormalities identified on brain MRI examination, including abnormal and swollen cerebral hemispheric white matter and subcortical cysts in the anterior temporal and often frontoparietal regions; and/or biallelic loss-of-function variants in *MLC1* or *HEPACAM* or a heterozygous pathogenic variant in *GPRC5B* identified by molecular genetic testing.

The diagnosis of improving MLC is established in individuals with suggestive clinical findings and a heterozygous gain-of-function variant in *HEPACAM* or biallelic pathogenic variants in *AQP4* identified by molecular genetic testing.

Management

Treatment of manifestations: Physical therapy to improve motor function; speech therapy as needed; special education; anti-seizure medication to control seizures.

Agents/circumstances to avoid: Contact sports and other activities associated with a high risk of head trauma should be avoided.

Genetic counseling

MLC is inherited in an autosomal recessive or an autosomal dominant manner.

- **Classic MLC** is most commonly caused by biallelic pathogenic variants in *MLC1* or *HEPACAM* and is inherited in an autosomal recessive manner. If both parents of a child with *MLC1*-related classic MLC or biallelic *HEPACAM*-related classic MLC are known to be heterozygous for an *MLC1* or *HEPACAM* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the autosomal recessive MLC-related pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives is possible. Rarely, classic MLC occurs as an autosomal dominant disorder caused by a heterozygous *GPRC5B* pathogenic variant. All individuals with *GPRC5B*-related classic MLC reported to date have had the disorder as a result of a *de novo* pathogenic variant.
- **Improving MLC** most commonly occurs as an autosomal dominant disorder caused by an inherited or *de novo* pathogenic variant in *HEPACAM*. Approximately 20% of individuals with heterozygous *HEPACAM*-related improving MLC have the disorder as a result of a *de novo* pathogenic variant. Each child of an individual with heterozygous *HEPACAM*-related improving MLC has a 50% chance of inheriting the pathogenic variant. Rarely, improving MLC is due to biallelic pathogenic variants in *AQP4* and is inherited in an autosomal recessive manner.

Once the MLC-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for MLC are possible.

GeneReview Scope

Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC): Included Phenotypes

Phenotype	Gene [1]	Locus Name	MOI	Clinical Characteristics
Classic MLC	*GPRC5B*	MLC3	AD (all *de novo* to date)	Macrocephaly, w/mild gross motor delays, seizures, delayed-onset progressive ataxia, spasticity, & late-onset cognitive deterioration
	HEPACAM	MLC2A	AR	
	MLC1	MLC1	AR	

Megalencephalic Leukoencephalopathy with continued from previous page.

Phenotype	Gene [1]	Locus Name	MOI	Clinical Characteristics
Improving MLC	*AQP4*	MLC4	AR	• Similar initial presentation followed by stabilization, sometimes improvement, & no secondary decline • Brain MRI changes typically improve or normalize; no delayed-onset neurologic decline
	HEPACAM	MLC2B	AD (*de novo* or inherited)	

AD = autosomal dominant; AR = autosomal recessive; MLC = megalencephalic leukoencephalopathy with subcortical cysts; MOI = mode of inheritance

For synonyms and outdated names, see Nomenclature.

1. Genes are listed in alphabetic order by phenotype.

Diagnosis

Suggestive Findings

Two phenotypes are observed in megalencephalic leukoencephalopathy with subcortical cysts (MLC): classic MLC and improving MLC.

Classic MLC

Classic MLC should be suspected in individuals with the following clinical and brain imaging findings and family history.

Clinical findings

- Macrocephaly with onset that is either congenital or within the first year of life
- Normal or mildly delayed early development
- Slow deterioration of motor functions with cerebellar ataxia and mild spasticity
- Seizures
- Dysarthria
- Decline in cognitive function (occurs later and is typically milder than motor decline)
- Behavioral problems in some individuals
- Temporary exacerbation of signs and symptoms after minor head trauma

Imaging findings. Brain MRI features include the following abnormalities (see Figure 1):

- Diffusely abnormal and mildly swollen cerebral hemispheric white matter
- Subcortical cysts are almost invariably present in the anterior temporal region and often in the frontoparietal regions.
- Over time, white matter swelling decreases and cerebral atrophy ensues. The subcortical cysts may increase in size and number. In some individuals, the cysts become very large, occupying a large part of the frontoparietal white matter. In others, the white matter abnormalities decrease over time, and signal intensities become less abnormal.
- Diffusion-weighted imaging reveals increased diffusivity of abnormal white matter [Itoh et al 2006, van der Voorn et al 2006].

Family history. Family history is most often consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Rarely, a proband has a *de novo* pathogenic variant and represents a simplex case. Absence of a known family history does not preclude the diagnosis.

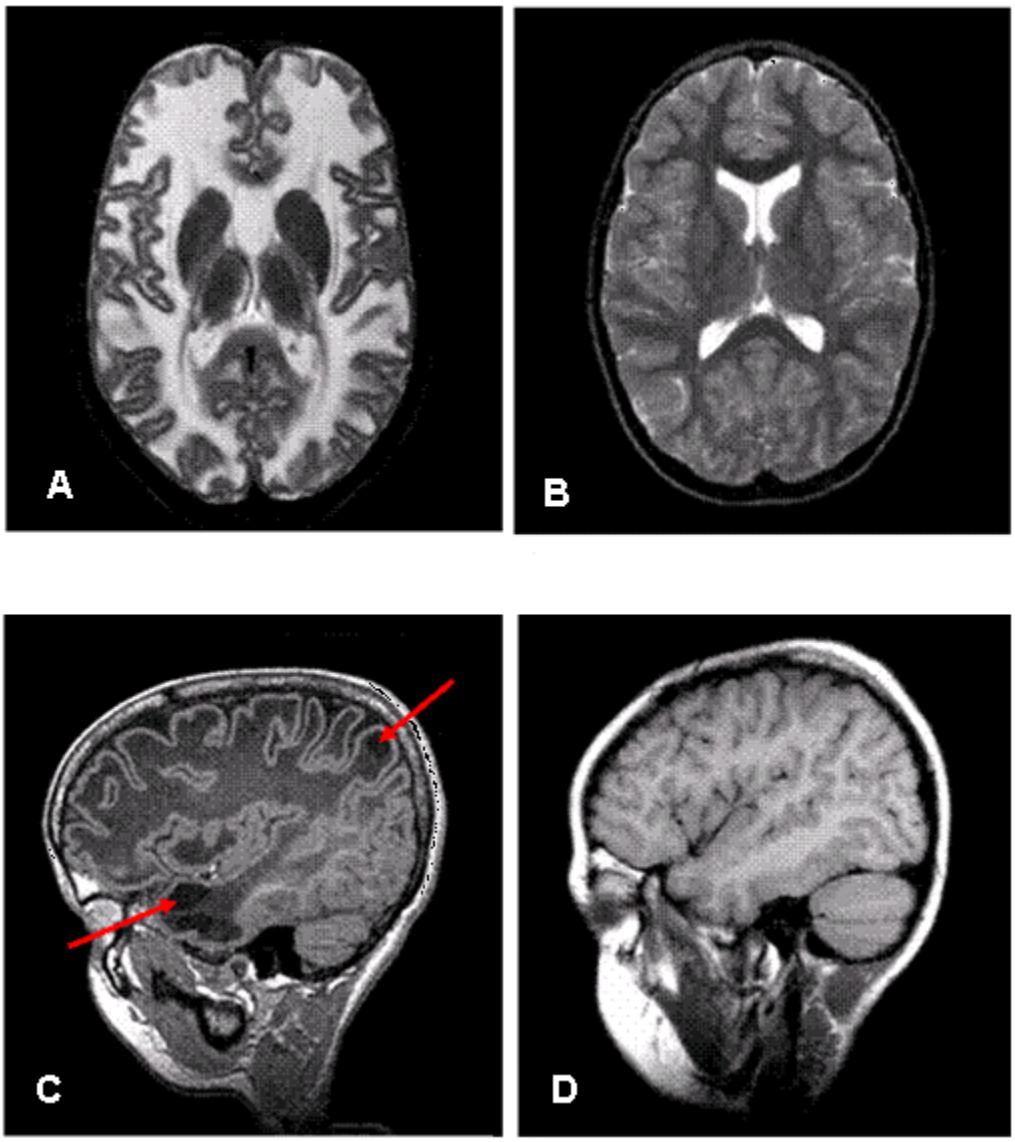

Figure 1. Brain images of an individual with MLC (A, C) and an unaffected individual (B, D)

A. Transverse T_2-weighted image of a child age nine years with MLC, showing diffusely abnormal and mildly swollen white matter

B. Transverse T_2-weighted image of an unaffected child

C. Sagittal T_1-weighted image of the same affected child, showing subcortical cysts in the anterior-temporal and parietal areas (arrows)

D. Sagittal T_1-weighted image of the unaffected child

Improving MLC

Improving MLC should be suspected in individuals with the following clinical and brain imaging findings and family history.

Clinical findings

- Macrocephaly with onset that is either congenital or within the first year of life; macrocephaly may persist or head size may be in the normal range in older individuals
- Normal or mildly delayed early development
- Motor function improves after the first year of life (clumsiness and hypotonia may persist)
- Seizures in some individuals

- Intellectual disability (with or without autism spectrum disorder) or normal cognitive function
- No regression of mental or motor functions

Imaging findings

- Brain MRI abnormalities within the first year of life are similar to those seen in the classic MLC phenotype, but cerebellar white matter is usually normal.
- Striking improvement occurs over time. Brain MRI may appear normal within a few years and no longer diagnostic of MLC. In some individuals, minor frontal and temporal subcortical white matter abnormalities and anterior temporal cysts persist.

Family history. Family history often suggests autosomal dominant inheritance (e.g., affected males and females in multiple generations) or, less commonly, a proband has a *de novo* pathogenic variant and represents a simplex case. Rarely, the family history may suggest autosomal recessive inheritance. Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of megalencephalic leukoencephalopathy with subcortical cysts (MLC) can be **established** in a proband based on the presence of clinical and imaging findings detailed in Suggestive Findings.

The molecular diagnosis of **classic MLC** is **established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *MLC1* or *HEPACAM* or a heterozygous pathogenic (or likely pathogenic) variant in *GPRC5B* identified by molecular genetic testing.

The molecular diagnosis of **improving MLC** is **established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *HEPACAM* or biallelic pathogenic (or likely pathogenic) variants in *AQP4* identified by molecular genetic testing.

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 section is understood to include likely pathogenic variants. (2) Identification of variant(s) of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

A multigene panel that includes some or all of the genes listed in Table 1 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.

Note: If no pathogenic variant(s) are identified in any of the genes listed in Table 1 in an individual with a clinical diagnosis of MLC, cDNA analysis of *MLC1* should be considered next to detect deep intronic variants (see Chapter Notes for research testing options).

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 similar to many other inherited disorders characterized by macrocephaly and white matter abnormalities, **comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Megalencephalic Leukoencephalopathy with Subcortical Cysts

Gene [1, 2]	Proportion of MLC Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [3] Detectable by Method	
			Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
AQP4	<1% [6, 7]	AR	100% [6]	None reported [6]
GPRC5B	<1% [6, 7]	AD	100% [6]	None reported [6]
HEPACAM	~22% [6]	AR AD	100% [6, 8]	None reported [6, 9]
MLC1	~76% [6]	AR	97% [6]	3% [6, 10]
Unknown [11]	<1%	NA	NA	NA

AD = autosomal dominant; AR = autosomal recessive; MLC = megalencephalic leukoencephalopathy with subcortical cysts; MOI = mode of inheritance; NA = not applicable

1. Genes are listed in alphabetic order.

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

3. See Molecular Genetics for information on variants detected in these genes.

4. 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.

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (as seen with *MLC1*) may not be detected by these methods. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

7. De novo heterozygous *GPRC5B* variants were identified in three unrelated individuals with classic MLC, and biallelic variants in *AQP4* were identified in one family with improving MLC [Passchier et al 2023].

8. A fraction of these variants are in a splice junction (most are within the canonical splice site, although deep intronic variants have also been reported).

9. No large intragenic deletions/duplications have been reported in individuals with *HEPACAM*-related MLC [Stenson et al 2020]. See Genetically Related Disorders for deletions involving *HEPACAM* and adjacent genes.

10. Including multiexon deletions [Leegwater et al 2002, Ilja Boor et al 2006].

11. In some individuals with clinical and brain MRI findings of MLC, pathogenic variants in *AQP4*, *GPRC5B*, *HEPACAM*, or *MLC1* have not been identified [Authors, personal observation].

Clinical Characteristics

Clinical Description

The two phenotypes observed in individuals with megalencephalic leukoencephalopathy with subcortical cysts (MLC) are classic MLC and improving MLC.

To date, approximately 500 individuals have been identified with biallelic pathogenic variants in *MLC1* or *HEPACAM*, or heterozygous pathogenic variants in *HEPACAM* [Hamilton et al 2018]. To date, three individuals with heterozygous pathogenic variants in *GPRC5B* and classic MLC as well as two individuals with a biallelic pathogenic variant in *AQP4* and improving MLC have been identified [Passchier et al 2023]. The following description of the phenotypic features associated with this spectrum is based on these reports.

Table 2. Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC): Comparison of Phenotypes by Select Features

Feature	Classic MLC	Improving MLC
Macrocephaly, typically persistent	~95%	~55%
Motor delays, initial	~30%	~15%
Ataxia	~80%	~20%
Pyramidal dysfunction	~20%	~5%
Cognitive delays	~70%	~30% (mild ID)
Autism spectrum disorder	~10%	~25%
Seizures	~65%	~10%
Brain MRI abnormalities	100%	Initially 100%, but typically followed by improvement or normalization

Data based on Hamilton et al [2018]
ID = intellectual disability; MLC = megalencephalic leukoencephalopathy with subcortical cysts

Classic MLC

Macrocephaly. Macrocephaly can be present at birth but more frequently develops during the first year of life. The degree of macrocephaly is variable; it may be as great as four to six standard deviations greater than the mean in some affected individuals. After the first year of life, head growth rate normalizes, and growth follows a line above and parallel to the 98th centile.

Motor development. Prior to age one year, motor development is normal in most infants and mildly delayed in some. Apart from progressive macrocephaly, the first clinical sign is usually delayed walking. Walking is often unstable, and the child falls frequently. However, most children can walk independently. Muscle tone tends to be low, apart from some ankle hypertonia.

Slow deterioration of motor function occurs over years with development of ataxia of the trunk and extremities. Signs of pyramidal dysfunction are late and minor and largely dominated by signs of cerebellar ataxia. Speech becomes increasingly dysarthric and dysphagia may develop. Deep tendon reflexes become brisk and Babinski signs become apparent. Some individuals display extrapyramidal movement abnormalities with dystonia and athetosis. Some individuals also develop tics [Sugiura et al 2006].

Gradually, the ability to walk independently is lost and many children become completely wheelchair dependent at the end of the first decade or in the second decade of life. Some children have a more severe clinical course and maintain their ability to walk independently for only a few years, or never achieve independent walking. Others maintain the ability to walk independently into the fifth decade of life.

Cognitive function. Initial cognitive development is normal in most children and mildly delayed in some. Intellectual deterioration is late and often mild, but in 15% of individuals the decline is severe. Decreasing school performance becomes evident during later years of primary school. Behavioral problems are reported in 25%-30% of individuals. Autism or autistic features are seen in 5%-10% of individuals [Sugiura et al 2006, Hamilton et al 2018].

Seizures. Approximately 75% of individuals with classic MLC experience at least one seizure before age 20 years [Dubey et al 2018, Hamilton et al 2018]. Seizure onset is typically early, often within a few years after birth. Approximately 60% of individuals develop epilepsy, which is usually easily controlled with anti-seizure medication [Dubey et al 2018]. Affected individuals (15%-20%) may experience one or more episodes of status epilepticus, the first of which typically occurs within a few years after seizure onset [Dubey et al 2018]. Seizures and status epilepticus are frequently precipitated by minor head trauma.

Minor head trauma may induce temporary deterioration in some individuals, most often observed as seizures or status epilepticus, prolonged unconsciousness, or acute motor deterioration with gradual improvement [Bugiani et al 2003, Dubey et al 2018].

Prognosis. Some children have a more benign clinical course and, even as teenagers, have macrocephaly only. Individuals who are ambulatory with or without support at age 15 years are most likely to remain ambulatory for decades [Authors, personal communication]. There are limited data regarding overall life span in this disorder. Some individuals have died in their teens or twenties; others are alive in their fifties.

Brain imaging findings. Brain MRI findings seen in affected individuals include diffusely abnormal and mildly swollen cerebral hemispheric white matter. Subcortical cysts are almost invariably present in the anterior temporal region and often the frontoparietal region. Over time, white matter swelling decreases and cerebral atrophy ensues. Subcortical cysts may increase in size and number. In some individuals, the cysts become very large, occupying a large part of the frontoparietal white matter. In others, white matter abnormalities decrease over time, and the signal intensity becomes less abnormal. Diffusion-weighted imaging reveals increased diffusivity of abnormal white matter [Itoh et al 2006, van der Voorn et al 2006]. Notably, central white matter structures, including the corpus callosum, internal capsule, and brain stem, are better preserved than other structures, although they are not usually entirely normal. Cerebellar white matter usually has a mildly abnormal signal and is not swollen.

Neuropathologic examination. Brain biopsy shows numerous vacuoles between the outer lamellae of myelin sheaths, suggesting splitting of these lamellae or incomplete compaction [van der Knaap et al 1996]. In addition, small vacuoles are observed in astrocytic endfeet [Duarri et al 2011].

Improving MLC

In children diagnosed with improving MLC due to heterozygous gain-of-function variants in *HEPACAM*, the initial disease course is the same as that in children with the classic phenotype. Early cognitive and motor development is normal in most individuals and mildly delayed in some.

Macrocephaly is present at birth or (more commonly) develops within the first year of life in 90% of individuals. After the first year of life, head growth trajectory usually either decreases or follows a line above and parallel to the 98th centile. In 40%-50% of affected children, the head circumference normalizes [Hamilton et al 2018].

Motor development. Apart from macrocephaly, the first clinical sign is usually delayed walking. Walking is often unstable, and the child falls frequently. After the second or third year of life, motor function improves or normalizes in most, and all children eventually achieve independent walking. Neurologic examination may become normal, but some children have persistent hypotonia and clumsiness. Regression does not occur.

Cognitive function is normal in approximately 75% of individuals; 25% have mild intellectual disability [Hamilton et al 2018]. Behavioral problems are observed in 30% and autism spectrum disorder in 25% of individuals. Developmental regression has not been observed to date.

Seizures. Epilepsy and status epilepticus may occur, but 90% of individuals have no history of seizures [Hamilton et al 2018].

Prognosis. Information regarding average life span is very limited. One child died in status epilepticus at age three years [Hamilton et al 2018].

In families with multiple affected individuals in more than one generation, the proband is usually the child and the affected parent is subsequently diagnosed. Parents with a heterozygous pathogenic variant in *HEPACAM* often have macrocephaly or a history of childhood macrocephaly but normal motor and cognitive function. Some parents have cognitive or behavioral problems or motor clumsiness. Considering the normal health of many parents, it does not appear that heterozygous *HEPACAM*-related improving MLC is associated with a shortened life span; however, no formal long-term studies have been performed to date.

Only two sibs have been reported to date with biallelic pathogenic variants in *AQP4*, and limited prognosis information is available [Passchier et al 2023].

Phenotype Correlations by Gene

Classic MLC. A review of 17 individuals with biallelic *HEPACAM*-related classic MLC revealed no phenotypic differences from individuals with *MLC1*-related classic MLC [Hamilton et al 2018].

The three individuals with *GPRC5B*-related classic MLC are phenotypically indistinguishable from individuals with classic MLC due to biallelic pathogenic variants in *MLC1* or *HEPACAM* [Passchier et al 2023].

Improving MLC. Only two individuals (sibs) have been described to date with biallelic pathogenic variants in *AQP4* [Passchier et al 2023], so it is currently unclear whether heterozygous *HEPACAM*-related improving MLC and *AQP4*-related MLC are phenotypically distinguishable.

Genotype-Phenotype Correlations

AQP4. Two sibs with biallelic *AQP4* pathogenic variants have been reported with improving MLC similar to heterozygous *HEPACAM*-related improving MLC [Passchier et al 2023].

GPRC5B. Three unrelated individuals with *de novo* heterozygous pathogenic variants in *GPRC5B* have been described [Passchier et al 2023]. For these individuals, brain MRI presentation and clinical course are indistinguishable from *MLC1*-related classic MLC and biallelic *HEPACAM*-related classic MLC.

HEPACAM. Most known biallelic and heterozygous *HEPACAM* pathogenic variants affect the extracellular or transmembrane domains of the protein [López-Hernández et al 2011, Elorza-Vidal et al 2020].

- In biallelic *HEPACAM*-related classic MLC, pathogenic variants in *HEPACAM* are widely distributed over the entire extracellular and transmembrane region of the protein, whereas in heterozygous *HEPACAM*-related improving MLC, pathogenic variants are clustered in the first extracellular immunoglobulin-like domain [López-Hernández et al 2011, Elorza-Vidal et al 2020].
- *HEPACAM* pathogenic variants associated with autosomal recessive classic MLC and *HEPACAM* pathogenic variants associated with autosomal dominant improving MLC do not overlap, although they may affect the same residue [López-Hernández et al 2011]. At present, it is unclear why some *HEPACAM* pathogenic variants are associated with autosomal recessive classic MLC and others with autosomal dominant improving MLC. Notably, only missense variants in *HEPACAM* have been reported in improving MLC [López-Hernández et al 2011, van der Knaap et al 2012, Elorza-Vidal et al 2020].

***MLC1*.** A review of 187 individuals with biallelic *MLC1* pathogenic variants revealed that disease severity and clinical course can vary significantly in individuals from the same family [Hamilton et al 2018]. There are no known genotype-phenotype correlations to date.

Nomenclature

Subtypes of megalencephalic leukoencephalopathy with subcortical cysts (MLC) were previously named according to the genetic loci associated with each subtype:

- **Classic MLC (MLC1, MLC2A, and MLC3)**
  - MLC1, associated with biallelic pathogenic variants in *MLC1*
  - MLC2A, associated with biallelic pathogenic variants in *HEPACAM*
  - MLC3, associated with heterozygous pathogenic variants in *GPRC5B*
- **Improving MLC (MLC2B and MLC4)**
  - MLC2B, associated with heterozygous pathogenic variants in *HEPACAM*
  - MLC4, associated with biallelic pathogenic variants in *AQP4*

Other names previously used for MLC:

- Leukoencephalopathy with swelling and a discrepantly mild course
- Leukoencephalopathy with swelling and cysts
- Infantile leukoencephalopathy and megalencephaly
- Vacuolating leukoencephalopathy

Penetrance

Classic MLC. The penetrance of biallelic pathogenic variants in *MLC1* or *HEPACAM* and heterozygous pathogenic variants in *GPRC5B* is expected to be complete.

Improving MLC. The penetrance of heterozygous pathogenic variants in *HEPACAM* is reduced [López-Hernández et al 2011]. The proportion of individuals with a heterozygous *HEPACAM* variant who exhibit or have exhibited clinical manifestations of improving MLC is unknown. The penetrance of biallelic pathogenic *AQP4* variants is unknown.

Prevalence

There are several populations where founder variants in MLC-associated genes have been identified (see Table 8).

Founder variants in *MLC1* have been identified in East Indian individuals from the Agrawal community [Leegwater et al 2002, Singhal et al 2003, Gorospe et al 2004], Libyan and Turkish Jewish individuals [Ben-Zeev et al 2002], Korean individuals [Choi et al 2017], and Egyptian individuals [Abdel-Salam et al 2016].

Genetically Related (Allelic) Disorders

Associations of *MLC1* variants with catatonic schizophrenia have been reported. Whether they have a role in development of this phenotype remains to be determined [Meyer et al 2001, Devaney et al 2002, Rubie et al 2003, Kaganovich et al 2004, Verma et al 2005, Selch et al 2007, Spijker et al 2010, Balestri et al 2017].

Contiguous gene deletions in the 11q24 region involving *HEPACAM* and adjacent genes lead to Jacobsen syndrome [Mattina et al 2009, Yamamoto et al 2015]. For some individuals with Jacobsen syndrome, MLC-like white matter abnormalities on MRI have been described [Yamamoto et al 2015]. White matter abnormalities in

Jacobsen syndrome have been reported to normalize in some individuals, suggesting similarity with improving MLC [Fujino et al 2020].

Differential Diagnosis

The differential diagnosis of macrocephaly and diffuse leukoencephalopathy is limited. Other disorders with white matter disease and swelling of the abnormal white matter are listed in Table 3. The clinical features and course of these disorders are usually different from those of megalencephalic leukoencephalopathy with subcortical cysts (MLC), and none of these disorders shares all the MRI features characteristic of MLC.

Note: If the head circumference of an infant is well within the normal limits at age one year, it is highly unlikely that the infant has MLC.

Table 3. Disorders of Interest in the Differential Diagnosis of Megalencephalic Leukoencephalopathy with Subcortical Cysts

Gene	Disorder	MOI	MRI Features
ASPA	Canavan disease	AR	In Canavan disease: • WM abnormalities are limited to the directly subcortical WM in some persons. • MRI typically shows involvement of thalamus & globus pallidus w/relative sparing of bilateral crescent formed by putamen & caudate nucleus (globus pallidus & thalamus are not involved in MLC). • Absence of the typical subcortical cysts seen in MLC
GFAP	Alexander disease	AD	In Alexander disease: • Frontal predominance of MRI abnormalities (predilection for anterior parts of brain is less clear in MLC) • Cysts usually located in deep frontal WM (different from MLC) • Mild signal abnormalities of basal ganglia & thalami (not seen in MLC) • Contrast enhancement of specific brain structures almost invariably seen (not seen in MLC) • Typical involvement of brain stem structures (signal abnormalities, tumor-like structures, atrophy) (not seen in MLC)
L2HGDH	L-2-hydroxyglutaric aciduria (OMIM 236792)	AR	In L-2-hydroxyglutaric aciduria: • Cerebral WM abnormalities are limited to directly subcortical WM in some persons. • Cerebral WM abnormalities are multifocal in some persons (invariably diffuse in MLC). • MRI typically shows involvement of basal nuclei (not seen in MLC). • Dentate nucleus is typically prominently affected (not in MLC).
LAMA2	Congenital muscular dystrophy type 1A (MDC1A) [1] (See *LAMA2* Muscular Dystrophy)	AR	MDC1A usually lacks the typical subcortical cysts seen in MLC.

AD = autosomal dominant; AR = autosomal recessive; MLC = megalencephalic leukoencephalopathy with subcortical cysts; MOI = mode of inheritance; WM = white matter

1. MDC1A is associated with prominent weakness and hypotonia (features not seen in MLC).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with megalencephalic leukoencephalopathy with subcortical cysts (MLC), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Megalencephalic Leukoencephalopathy with Subcortical Cysts: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neurologic	Neurologic assessment	• Assess for macrocephaly (esp if progressive). • Brain MRI in those w/megalencephaly to assess white matter & subcortical structures (See Surveillance.) • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl physical, occupational, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
	Neuropsychological assessment	Assessment of cognitive function
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MLC to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support. • Home nursing referral.	

MLC = megalencephalic leukoencephalopathy with subcortical cysts; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for MLC.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Megalencephalic Leukoencephalopathy with Subcortical Cysts: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Motor issues	PT to improve motor function	
Developmental delays	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist or epileptologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/behavioral difficulties. Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is individualized therapy targeted to each child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst. Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavioral management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary. Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Megalencephalic Leukoencephalopathy with Subcortical Cysts: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures, progression of head growth, changes in tone, & movement abnormalities.	
	Brain MRI to assess for white matter changes, subcortical cyst progression, & atrophy	Every ~5 yrs
Development	Monitor developmental progress & educational needs.	At each visit
	Eval w/developmental pediatrician	Annually &/or as needed

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

In individuals with classic MLC, minor head trauma may lead to temporary motor deterioration, seizures, or (rarely) coma. For this reason, contact sports and other activities with a high risk of head trauma should be avoided in affected individuals. Wearing a helmet should also be considered for situations associated with increased risk of head trauma.

Evaluation of Relatives at Risk

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

Pregnancy Management

Potential teratogenic effects of anti-seizure medication should be discussed with affected women of childbearing age, ideally prior to conception.

See MotherToBaby for further information on medication use during pregnancy.

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

Classic megalencephalic leukoencephalopathy with subcortical cysts (MLC) is most commonly caused by biallelic pathogenic variants in *MLC1* or *HEPACAM* and inherited in an autosomal recessive manner. Rarely, classic MLC occurs as an autosomal dominant disorder caused by a *de novo* heterozygous *GPRC5B* pathogenic variant.

Improving MLC most commonly occurs as an autosomal dominant disorder caused by an inherited or *de novo* heterozygous pathogenic variant in *HEPACAM*. Rarely, improving MLC is caused by biallelic pathogenic variants in *AQP4* and inherited in an autosomal recessive manner.

Note: *HEPACAM* pathogenic variants associated with classic MLC and *HEPACAM* pathogenic variants associated with improving MLC do not overlap, although they may affect the same residue [López-Hernández et al 2011]. In a few individuals with a pathogenic variant associated with autosomal dominant *HEPACAM*-related

improving MLC on one allele and a pathogenic variant associated with autosomal recessive *HEPACAM*-related classic MLC on the other allele, classic MLC was observed [Authors, personal communication]. In these individuals, risk to offspring depends on the transmitted pathogenic variant: offspring who inherit the allele associated with heterozygous *HEPACAM*-related improving MLC may be affected and offspring who inherit the allele associated with biallelic *HEPACAM*-related classic MLC will be asymptomatic carriers.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive MLC (i.e., a child with *MLC1*-related classic MLC, biallelic *HEPACAM*-related classic MLC, or *AQP4*-related improving MLC) are typically heterozygous for an autosomal recessive MLC-related pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an autosomal recessive MLC-related pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband [López-Hernández et al 2011] or as a postzygotic *de novo* event in a mosaic parent. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Individuals who are heterozygous for an *MLC1* pathogenic variant are typically asymptomatic.
- Individuals who are heterozygous for a *HEPACAM* pathogenic variant associated with classic MLC are asymptomatic. *HEPACAM* pathogenic variants associated with autosomal dominant improving MLC do not overlap with *HEPACAM* pathogenic variants associated with autosomal recessive classic MLC (see Genotype-Phenotype Correlations; also see **Note** under Mode of Inheritance).
- Individuals who are heterozygous for an *AQP4* pathogenic variant are asymptomatic to date.

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant associated with autosomal recessive MLC, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Intrafamilial variability has been observed in *MLC1*-related classic MLC. A review of 187 individuals with biallelic *MLC1* pathogenic variants revealed that in individuals from the same family, disease severity and clinical course can vary significantly [Hamilton et al 2018].
- Individuals who are heterozygous for an *MLC1* pathogenic variant are typically asymptomatic.
- Individuals who are heterozygous for a *HEPACAM* pathogenic variant associated with classic MLC are asymptomatic. *HEPACAM* pathogenic variants associated with autosomal dominant improving MLC do not overlap with *HEPACAM* pathogenic variants associated with autosomal recessive classic MLC (see Genotype-Phenotype Correlations; also see **Note** under Mode of Inheritance).
- Individuals who are heterozygous for an *AQP4* pathogenic variant are asymptomatic to date.

Offspring of a proband. The offspring of an individual with autosomal recessive MLC (i.e., *MLC1*-related classic MLC, biallelic *HEPACAM*-related classic MLC, or *AQP4*-related improving MLC) are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant associated with autosomal recessive MLC.

Carrier Detection

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

Note: The parents of many individuals with classic MLC are consanguineous. Carrier testing for reproductive partners of known carriers is appropriate, particularly if consanguinity is likely.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Many individuals with heterozygous *HEPACAM*-related improving MLC have a parent with macrocephaly or a history of childhood macrocephaly. Given the neurologic improvement that is observed in this phenotype, the parent is not at risk of neurologic regression. Whether having a heterozygous gain-of-function *HEPACAM* pathogenic variant leads to other manifestations late in life has not been investigated; however, to date no evidence suggests disease progression later in life.
- A proband with heterozygous *HEPACAM*-related improving MLC may have the disorder as the result of a *de novo HEPACAM* pathogenic variant. The proportion of individuals with *HEPACAM*-related improving MLC caused by a *de novo HEPACAM* pathogenic variant is approximately 20%.
- In the three individuals reported to date with *GPRC5B*-related classic MLC, the heterozygous pathogenic *GPRC5B* variant arose *de novo*.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with heterozygous *HEPACAM*-related improving MLC may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the autosomal dominant MLC-related pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the heterozygous *HEPACAM* or *GPRC5B* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the heterozygous *HEPACAM* or *GPRC5B* pathogenic variant but are clinically unaffected, the sibs are still at increased risk for heterozygous *HEPACAM*-related improving MLC or *GPRC5B*-related classic MLC because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant MLC (i.e., heterozygous *HEPACAM*-related improving MLC or *GPRC5B*-related classic MLC) has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the heterozygous *HEPACAM* or *GPRC5B* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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 or are carriers (or are at risk of being carriers) of MLC-related pathogenic variants.

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 pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for MLC are possible.

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.

- **Alliance MLC**
  Email: info@AllianceMLC.org
  www.alliancemlc.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
ulf.org

- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  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. Megalencephalic Leukoencephalopathy with Subcortical Cysts: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
AQP4	18q11.2	Aquaporin-4		AQP4	AQP4
GPRC5B	16p12.3	G-protein coupled receptor family C group 5 member B		GPRC5B	GPRC5B
HEPACAM	11q24.2	Hepatic and glial cell adhesion molecule		HEPACAM	HEPACAM
MLC1	22q13.33	Membrane protein MLC1	MLC1 database	MLC1	MLC1

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 Megalencephalic Leukoencephalopathy with Subcortical Cysts (View All in OMIM)

600308	AQUAPORIN 4; AQP4
604004	MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 1; MLC1
605908	MODULATOR OF VRAC CURRENT 1; MLC1
605948	G PROTEIN-COUPLED RECEPTOR, FAMILY C, GROUP 5, MEMBER B; GPRC5B
611642	HEPATOCYTE CELL ADHESION MOLECULE; HEPACAM
613925	MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 2A; MLC2A
613926	MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 2B, REMITTING, WITH OR WITHOUT IMPAIRED INTELLECTUAL DEVELOPMENT; MLC2B

Molecular Pathogenesis

MLC1. Membrane protein MLC1 (MLC1) is highly expressed in the human brain, as well as in leukocytes. Within the human brain, MLC1 is almost exclusively expressed in astrocytic endfeet in the perivascular, subependymal, and subpial regions. The localization of the protein, combined with the clinical phenotype of megalencephalic leukoencephalopathy with subcortical cysts (MLC), suggests a role for MLC1 in brain ion and water homeostasis [van der Knaap et al 2012]. MLC1 shares its endfeet localization with members of the dystrophin glycoprotein-associated complex, including aquaporin-4 [Boor et al 2007]. MLC1 has been shown to

interact with a variety of proteins potentially involved in brain ion and water homeostasis. These include the Na^+/K^+-ATPase, TRPV4, caveolin-1, and Kir4.1, among others [Brignone et al 2015].

MLC1 pathogenic variants show a low steady-state expression of MLC1 with a consequent reduction in surface expression [Teijido et al 2004, Montagna et al 2006]. Electrophysiologic studies reveal a reduction of volume-regulated anion channel (VRAC) activity in lymphoblasts from individuals with biallelic *MLC1* pathogenic variants. This results in impaired regulatory volume decrease upon hypotonic cell swelling [Ridder et al 2011]. Cell lines overexpressing normal MLC1 show enhanced VRAC activity, which is absent upon overexpression of mutated MLC1, supporting the role of MLC1 in VRAC regulation [Ridder et al 2011].

HEPACAM encodes hepatic and glial cell adhesion molecule (called either hepaCAM or glialCAM), a single transmembrane protein with two extracellular immunoglobulin domains that is predominantly expressed in the brain. GlialCAM colocalizes with MLC1 in astrocyte endfeet. However, glialCAM is also expressed in axons, on the outside of myelin sheaths, and in oligodendrocytes [Favre-Kontula et al 2008, López-Hernández et al 2011]. GlialCAM acts as a chaperone for MLC1, ensuring the localization of both proteins at astrocyte-astrocyte junctions in endfeet and in cultured astrocytes [López-Hernández et al 2011, Capdevila-Nortes et al 2013]. GlialCAM also acts as an auxiliary subunit for the chloride channel ClC-2. It increases ClC-2 mediated currents, changes their functional properties, and is necessary for ClC-2 localization to astrocyte-astrocyte junctions [Jeworutzki et al 2012, Hoegg-Beiler et al 2014]. GlialCAM also interacts with the gap junction subunit connexin 43 [Wu et al 2016].

All MLC-causing variants in *HEPACAM* affect the extracellular region of glialCAM. In cultured rat primary astrocytes, mutated glialCAM with either a dominant or a recessive pathogenic variant disrupts localization of MLC1 and glialCAM at astrocyte-astrocyte junctions. Coexpression of wild type glialCAM rescues the detrimental effect of glialCAM with a recessive variant on MLC1 localization, but it does not rescue the effect of the dominant variant of glialCAM [López-Hernández et al 2011]. Biochemical analysis shows that some dominant and recessive pathogenic variants disrupt the ability of glialCAM to homo-oligomerize [Arnedo et al 2014]. However, what causes a *HEPACAM* variant to be dominant vs recessive is still unclear.

GPRC5B encodes G-protein coupled receptor (GPCR) family C group 5 member B (GPRC5B). In the brain, GPRC5B is highly expressed in perivascular astrocyte endfeet, a location shared with MLC1 and glialCAM [Alonso-Gardón et al 2021, Passchier et al 2023]. GPCRs can be activated by different types of chemical or mechanical stimuli, or by interaction with other proteins. GPRC5B is considered an orphan receptor since its ligand has not been identified. An interaction of GPRC5B with MLC1 and glialCAM has been described [Alonso-Gardón et al 2021]. Volume regulation in lymphoblasts from GPRC5B patients is disrupted [Passchier et al 2023]. Knockdown of GPRC5B in astrocytes reduces VRAC activity [Alonso-Gardón et al 2021], while overexpression in astrocytoma cells increases VRAC activity [Passchier et al 2023]. Therefore, expression patterns and cellular mechanisms linked to GPRC5B overlap with those of MLC1 and glialCAM. The two dominant pathogenic variants that have been identified in *GPRC5B* are duplications of two neighboring amino acids in the fourth transmembrane region of the receptor (p.Ile176dup and p.Ala177dup) [Passchier et al 2023]. How these variants alter the function of the receptor is currently unknown.

AQP4 encodes the ubiquitous brain water channel aquaporin-4. Like the other proteins involved in MLC, aquaporin-4 is highly expressed in perivascular astrocyte endfeet and at other brain-fluid interfaces. At these locations, aquaporin-4, similar to MLC1, is part of the dystrophin glycoprotein-associated complex [Boor et al 2007]. The presence of large numbers of water channels at astrocyte endfeet enables fast water exchange between the extracellular space and the interconnected network of astrocytes and other glial cells [Nagelhus & Ottersen 2013]. These combined features increase the ability of astrocytes to rapidly adjust cell volume and increases their capacity for ion and water homeostasis, but simultaneously makes them more prone to pathologic swelling in situations of acute edema formation. Modulation of aquaporin-4 function or localization is being investigated as potential therapeutic strategy for the treatment of acute brain edema [Kitchen et al 2020].

The recessive pathogenic variant p.Ala215Thr in aquaporin-4 alters the second of two highly conserved Asn-Pro-Ala (NPA) motifs that form the narrow central part of the water channel. These motifs are crucial for selective water permeability and for localization of the channel to the plasma membrane [King et al 2004]. The p.Ala215Thr variant leads to protein misfolding, resulting in loss of membrane localization and water channel function [Passchier et al 2023].

Mechanism of disease causation

- **Loss of function.** *MLC1*, biallelic *HEPACAM* (classic MLC), and *AQP4* pathogenic variants
- **Gain of function or dominant negative.** Heterozygous *HEPACAM* (improving MLC) and *GPRC5B* pathogenic variants

Table 7. Megalencephalic Leukoencephalopathy with Subcortical Cysts: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
AQP4	1 pathogenic variant has been described to date.
GPRC5B	2 pathogenic variants have been described to date. Both localize to the fourth transmembrane region of the G-protein coupled receptor. Variants are amino acid duplications.
HEPACAM	Biallelic & heterozygous variants have been identified with classic and improving MLC, respectively.
MLC1	A few variants have been identified in the 5' untranslated region that negatively impact production of MLC1 [Authors, personal communication]. A fraction of identified variants in *MLC1* are splicing (most involve the canonical splice site). Deletions in 1 or more exons have been observed.

MLC = megalencephalic leukoencephalopathy with subcortical cysts
1. Genes from Table 1 in alphabetic order

Table 8. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
AQP4	NM_001650.5 NP_001641.1	c.643G>A	p.Ala215Thr	The only known pathogenic autosomal recessive variant in *AQP4* to date. It was identified in 2 sibs w/improving MLC [Passchier et al 2023].
GPRC5B	NM_016235.2 NP_057319.1	c.526_528dup	p.Ile176dup	1 of 2 known autosomal dominant pathogenic variants in *GPRC5B*. It was identified in 2 unrelated persons w/classic MLC [Passchier et al 2023].
		c.528_530dup	p.Ala177dup	1 of 2 known autosomal dominant pathogenic variants in *GPRC5B*. It was identified in 1 person w/classic MLC [Passchier et al 2023].
MLC1	NM_015166.4	c.-42C>T	--	Predicted to create new start codon in the 5' UTR of *MLC1* [Kariminejad et al 2015]

Table 8. continued from previous page.

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	NM_015166.4 NP_055981.1	c.135dup	p.Cys46LeufsTer34	Founder variant in East Indian persons from the Agrawal community (in the biallelic form) [Leegwater et al 2002, Singhal et al 2003, Gorospe et al 2004]
		c.176G>A	p.Gly59Glu	Common in Libyan Jews & also found in Turkish Jewish families; possible founder variant [Ben-Zeev et al 2002]
		c.278C>T	p.Ser93Leu	Common in Japanese persons [Shimada et al 2014]; also observed in Finnish, Turkish [Leegwater et al 2001], & Italian persons [Montagna et al 2006]
		c.824C>A	p.Ala275Asp	Founder pathogenic variant that accounts for 70% of *MLC1* variants in persons of Korean ancestry [Choi et al 2017]
		c.908_918delinsGCA	p.Val303GlyfsTer96	Common in persons of Egyptian ancestry who share specific haplotype, indicating founder effect [Abdel-Salam et al 2016]

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.
MLC = megalencephalic leukoencephalopathy with subcortical cysts; UTR = untranslated region
1. Genes from Table 1 in alphabetic order

Chapter Notes

Author Notes

The authors are happy to offer cDNA analysis of *MLC1* on lymphoblast cell lines of individuals with MLC without an identified molecular etiology in any of the known genes. If a molecular etiology is not identified, the authors are also willing to examine brain MRIs of these individuals to help determine whether the MRI is diagnostic of MLC and, if so, offer further genetic analysis to identify the genetic basis.

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