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Mucolipidosis IV

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Summary

Clinical characteristics

Mucolipidosis IV (MLIV) is an ultra-rare lysosomal storage disorder characterized by severe psychomotor delay, progressive visual impairment, and achlorhydria. Individuals with MLIV typically present by the end of the first year of life with delayed developmental milestones (due to a developmental brain abnormality) and impaired vision (resulting from a combination of corneal clouding and retinal degeneration). By adolescence, all individuals with MLIV have severe visual impairment. A neurodegenerative component of MLIV has become more widely appreciated, with the majority of individuals demonstrating progressive spastic quadriparesis and loss of psychomotor skills starting in the second decade of life. About 5% of individuals have atypical MLIV, manifesting with less severe psychomotor impairment, but still exhibiting progressive retinal degeneration and achlorhydria.

Diagnosis/testing

MLIV is suspected in individuals with typical clinical findings and elevated plasma gastrin concentration or polymorphic lysosomal inclusions in skin or conjunctival biopsy. Identification of biallelic pathogenic variants in *MCOLN1* confirms the diagnosis.

Management

Treatment of manifestations: Developmental and educational services including speech therapy; physical therapy and bracing for hypotonia and spasticity; intramuscular botulinum toxin injections or oral medications for muscle spasticity and rigidity as needed; anti-seizure medication as needed; surgical correction of strabismus; high-contrast black and white materials for those with visual impairment; topical lubricating eye drops, artificial tears, gels, or ointments for ocular irritation; feeding therapy and/or gastrostomy tube placement may be

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required for persistent feeding issues; management of constipation and bile reflux per gastroenterologist; treatment of renal failure per nephrologist; iron supplementation as needed.

Surveillance: Monitor those with seizures and assess for new neurologic manifestations at least annually; assessment of musculoskeletal complications as indicated; monitor developmental progress at least annually; annual ophthalmology examination; feeding and growth evaluation at least annually; cystatin C levels to monitor renal function at least annually; complete blood count and iron studies annually.

Agents/circumstances to avoid: Chloroquine may be contraindicated.

Genetic counseling

MLIV 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, and a 25% chance of being unaffected and not a carrier. Once the *MCOLN1* 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

Mucolipidosis IV (MLIV) **should be suspected** in any individual with the following clinical and laboratory findings.

Clinical findings

- Early onset of developmental delay whether static, as in cerebral palsy, or progressively declining with loss of previously acquired cognitive and motor abilities [Altarescu et al 2002]
- Dystrophic retinopathy with or without corneal clouding [Smith et al 2002]

Laboratory findings

- Elevated plasma gastrin concentration (due to achlorhydria) in virtually all individuals with MLIV (mean: 1507 pg/mL; range: 400-4100 pg/mL; normal: 0-200 pg/mL) [Schiffmann et al 1998, Altarescu et al 2002]
- Achlorhydria

Establishing the Diagnosis

The diagnosis of MLIV **is established** in a proband with suggestive findings and biallelic pathogenic (and likely pathogenic) variants in *MCOLN1* (see Table 1) or (if molecular genetic testing is unavailable and/or uninformative) elevated plasma gastrin levels. Identification of characteristic inclusions on skin biopsy or conjunctival swab may help direct diagnosis in some instances.

Note: Per ACMG variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular Genetic Testing

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see **Option 1**), whereas those with a phenotype indistinguishable from many other inherited disorders with developmental delay and/or dystrophic retinopathy are more likely to be diagnosed using genomic testing (see **Option 2**).

Option 1

Single-gene testing. Sequence analysis of *MCOLN1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: (1) Targeted analysis for pathogenic variant c.406-2A>G and a 6.4-kb deletion beginning in the 5'UTR and extending into exon 6 can be performed first in individuals of Ashkenazi Jewish ancestry (see Table 1). (2) The common 6.4-kb deletion cannot be detected by routine sequencing. Other methods such as gene-targeted deletion/duplication analysis or a genotyping assay specifically designed to detect this deletion (e.g., breakpoint PCR or allele-specific primer extension) must be employed.

A multigene panel that includes *MCOLN1* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by developmental delay, c**omprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Mucolipidosis IV

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method	
		Ashkenazi Jewish	Non-Ashkenazi Jewish
MCOLN1	Targeted analysis for pathogenic variants [3]	95%	6%-10% [4]
	Sequence analysis [5, 6]	77%-81%	99% [4]
	Gene-targeted deletion/duplication analysis [7, 8]	18% [9]	Unknown [9]

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. For c.406-2A>G and a 6.4-kb deletion beginning in the 5'UTR and extending into exon 6 (see Table 6). Note: Reported breakpoints for this deletion vary slightly; see HGMD.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.
6. Cannot detect 6.4-kb deletion, one the two pathogenic variants common in persons of Ashkenazi Jewish heritage
7. 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.
8. Required to detect the common 6.4-kb deletion observed in persons of Ashkenazi Jewish heritage and other novel (multi)exon deletions. Note that other genotyping assays specifically designed to detect the 6.4-kb deletion (e.g., breakpoint PCR or allele-specific primer extension) may be employed.
9. No data on detection rate of non-6.4-kb deletion gene-targeted deletion/duplication analysis are available.

Other Testing

Skin biopsy / conjunctival swab. In the past, identification of abnormal lamellar membrane structures and amorphous cytoplasmic inclusions in diverse cell types by electron microscopy on skin biopsy was used to confirm the diagnosis of MLIV [Bargal et al 2002]. Subsequently, demonstration of typical vacuolation by PAS staining of conjunctival cells obtained with a swab was used for diagnosis [Smith et al 2002].

Clinical Characteristics

Clinical Description

Mucolipidosis IV (MLIV) is a neurodevelopmental disorder with a gradual, late-onset neurodegenerative component. The phenotype in affected individuals can be either typical/severe (~95% of individuals) or atypical/mild (~5% of individuals) [Altarescu et al 2002]. Although individuals with MLIV generally survive to adulthood, life expectancy is reduced compared to healthy individuals by either secondary complications of severe neurologic disability or renal failure.

Typical MLIV

Individuals commonly present in the first year of life with axial hypotonia, delayed motor milestones, and/or corneal clouding. Because the combination of hypotonia and developmental delay are nonspecific, individuals with MLIV are frequently assigned a provisional diagnosis of cerebral palsy during their diagnostic odyssey. Corneal clouding is a more specific disease feature and identification by an ophthalmologist on slit lamp examination often leads to diagnosis by targeted genetic testing.

Neurologic findings. Axial hypotonia and delayed motor development are frequently the earliest neurologic features. Most individuals achieve independent sitting and the ability to combat crawl or scoot while in a seated

position, and several have learned to walk with the aid of a walker [Altarescu et al 2002]. Fine motor function is severely limited. Individuals may articulate a modified pincer or scissor grasp, but rarely a superior pincer grasp. Most individuals are able to feed themselves finger foods and a few have successfully used modified utensils.

Pyramidal and extrapyramidal tract signs manifest early in the course of disease. In the first decade of life, individuals exhibit a mixture of spasticity and rigidity with cogwheel or oppositional qualities. Dystonic posturing in the extremities is frequently observed. Hypertonicity is present in the upper and lower extremities and is generally symmetric. Decreased force on volitional activation of the extremities is consistent with upper motor neuron weakness, but worsening muscular hypertonicity suggests relative preservation of muscle and neuromuscular junction integrity.

Receptive language is better than expressive language; some individuals have used up to 50 signs to communicate. Individuals uniformly demonstrate intact social development with strong social engagement, a friendly disposition, and an enjoyment of music [Segal et al 2017].

Individuals typically exhibit dysarthria or anarthria, slow chewing, and restricted lateral tongue movement. Few individuals experience aspiration in the first decade of life and swallow studies are normal. Aspiration may emerge later in life requiring a tracheostomy or gastric tube placement [Altarescu et al 2002].

While individuals make some developmental gains in the first decade of life, caregivers consistently report worsening hypertonicity and weakness. By early adolescence, loss of psychomotor skills becomes apparent. Though previously described as mainly a static neurodevelopmental condition [Altarescu et al 2002]; serial brain magnetic resonance imaging volumetry and diffusion weighted imaging have demonstrated quantitative measures of progressive neurodegeneration that corroborate clinical reports [Schiffmann et al 2014].

Typical brain MRI abnormalities in individuals with MLIV include hypoplasia of the corpus callosum with absent rostrum and a dysplastic or absent splenium, signal abnormalities in the white matter on T_1-weighted images, and increased ferritin deposition in the thalamus and basal ganglia. Atrophy of the cerebellum is observed in older individuals [Frei et al 1998].

Epileptiform discharges on EEG are common but are infrequently associated with clinical seizures [Siegel et al 1998]. Three hertz spike-and-wave discharges and absence seizures are the most commonly reported epileptic phenomena in MLIV.

Eye findings. Individuals with typical MLIV have superficial corneal clouding that is bilateral, symmetric, and most visible in the central cornea [Smith et al 2002]. The corneal opacification is limited to the epithelium without stromal involvement or edema [Authors, personal observation], early reports of stromal abnormalities notwithstanding.

Vision may be close to normal at a young age. Over the first decade of life, progressive retinal degeneration with varying degrees of vascular attenuation, retinal pigment epithelial changes, and optic nerve pallor result in further decrease in vision [Siegel et al 1998, Altarescu et al 2002, Pradhan et al 2002, Smith et al 2002]. Bilateral bull's-eye maculopathy was observed in one individual [Smith et al 2002]. Visual acuity is difficult to test in most individuals with MLIV, but is decreased in almost all persons older than age five years. Virtually all individuals with MLIV develop severe visual impairment by their early teens as a result of the retinal degeneration.

Painful episodes consistent with corneal erosions are common, but appear to decrease in frequency and severity with age.

Other ocular findings are strabismus (>50% of individuals), nystagmus, ptosis, and cataract [Bach 2001, Smith et al 2002]. The pupillary response to light is usually sluggish without evidence of relative afferent pupillary defect [Smith et al 2002].

Growth. Birth weight and length are within normal range for the majority of individuals; however, growth restriction develops with age. One case series reported ten of 16 individuals with height below the third percentile and eight of 16 individuals with weight below the third percentile [Amir et al 1987]. The age at which growth restriction becomes apparent remains unclear.

Gastrointestinal features. Achlorhydria is uniformly present in individuals with MLIV. *MCOLN1* pathogenic variants impair apical-membrane trafficking of the gastric proton pump in parietal cells leading to decreased gastric acid secretion and elevated gastrin level [Chandra et al 2011]. In affected individuals, parietal cells are present in normal numbers but show lysosomal inclusion bodies and are defective in gastric acid secretion [Schiffmann et al 1998].

Renal findings. Progressive renal failure, which has been recognized in recent years, is now considered a feature of typical MLIV. It manifests itself in the second to third decade of life [Author, unpublished data]. Because of chronic muscle atrophy in MLIV, blood cystatin C level is the most sensitive way to diagnose renal insufficiency.

Iron deficiency occurs in about 50% of affected individuals due to poor absorption of dietary iron, and iron deficiency anemia, which is usually well tolerated, occurs in about 10% of affected individuals [Altarescu et al 2002].

Nonspecific facial features. The face is not typically coarse [Goldin et al 2004b], but has typical "hypotonic" features including a tented upper lip vermillion, anteverted nares, and open mouth [Pode-Shakked et al 2020].

Affected individuals do not have hepatosplenomegaly or specific skeletal abnormalities.

Atypical MLIV

Individuals with atypical MLIV are less severely affected than individuals with typical MLIV or have one organ system disproportionately affected [Altarescu et al 2002].

Some individuals attain the ability to walk independently or have isolated dystrophic retinopathy without neurologic dysfunction [Goldin et al 2008]. They develop slowly progressive ataxia, have mild eye abnormalities, and are usually of non-Ashkenazi Jewish descent [Altarescu et al 2002]. One female who presented with progressive visual impairment with corneal clouding with the appearance of cornea verticillata, retinopathy, normal psychomotor development, and behavioral abnormalities developed unstable gait in her twenties [Altarescu et al 2002]. Two other individuals with no neurologic deficit were diagnosed based on ocular findings [Dobrovolny et al 2007, Goldin et al 2008]. These individuals had all the other typical features of MLIV including achlorhydria and autofluorescent inclusions in cultured skin fibroblasts [Dobrovolny et al 2007, Goldin et al 2008].

Some present with a congenital myopathy with significant generalized hypotonia and elevated serum muscle creatine kinase concentration. Others present with static (non-progressive) motor and cognitive delay and minimal ocular abnormalities.

Genotype-Phenotype Correlations

Individuals of Ashkenazi Jewish ancestry usually have the severe form of MLIV.

A pathogenic variant that creates a new preferred splice site of *MCOLN1*, c.1406A>G (p.Phe454_Asn569del) was identified in a Canadian family from Newfoundland; it causes an atypical form of MLIV, in which affected individuals walk independently and have better communicative skills [Altarescu et al 2002].

Variants in the loop between the first and second transmembrane domain. Pathogenic variants found in the loop between the first and second transmembrane domain, one in the lipase domain and one eliminating one of

the four cysteines in the loop, possibly reduce the stability of mucolipin-1. Individuals with these pathogenic variants had a mild phenotype, an independent ataxic gait, and the ability to use their hands to feed themselves.

The typical, rather severe presentation associated with the c.694A>C (p.Thr232Pro) pathogenic variant in the same region may be explained by the fact that the abnormal protein does not reach the endocytic compartment and accumulates in the endoplasmic reticulum [Manzoni et al 2004].

Variants in the third transmembrane domain. In several individuals from the southeast United States, a c.1084G>T (p.Asp362Tyr) pathogenic variant was identified in the third transmembrane domain. This pathogenic variant was associated with a slower progression of the retinal disease and a relatively mild neurologic phenotype, although membrane preparations containing mucolipin-1 with this pathogenic variant had no channel activity [Raychowdhury et al 2004].

Variants in the fourth transmembrane domain. Several *MCOLN1* pathogenic variants are in the fourth transmembrane domain, including c.1221_1223delCTT (p.Phe408del), which causes the mildest MLIV phenotype known [Altarescu et al 2002].

Variants between the fifth and sixth transmembrane domain. Several other pathogenic variants are in the area encoding the presumed channel pore between the fifth and sixth transmembrane domain. Most of those were associated with a severe MLIV phenotype [Altarescu et al 2002].

Nomenclature

MLIV was classified as a mucolipidosis because of the initial impression of simultaneous storage of lipids and water-soluble substances.

Prevalence

The combined carrier frequency of the two pathogenic variants common in persons of Ashkenazi Jewish descent ranges from 1:100 to 1:127 [Bargal et al 2001, Edelmann et al 2002]. Of note, in a small group of 123 individuals, other investigators found a higher frequency [Wang et al 2001].

- The splice pathogenic variant (c.406-2A>G) is at least three times more common than the pathogenic deletion (6.4-kb del) [Edelmann et al 2002].
- The 6.4-kb deletion is particularly rare in the Israeli population (1:2,000) in comparison to its frequency in the New York metropolitan area (1:406) [Bargal et al 2001, Edelmann et al 2002].

Prior to the availability of molecular diagnosis of MLIV, individuals with atypical MLIV were thought to have cerebral palsy or isolated retinal dystrophy, suggesting that MLIV is underdiagnosed.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *MCOLN1*.

Differential Diagnosis

The earliest signs of mucolipidosis IV (MLIV) include axial hypotonia, developmental delay, and strabismus, which are nonspecific and often lead to a provisional diagnosis of cerebral palsy. However, the finding of corneal clouding in combination with these neurologic features is relatively specific and should trigger further workup for MLIV.

Eye Findings

Table 2. Disorders with Eye Findings of Interest in the Differential Diagnosis of Mucolipidosis IV

Ophthalmologic Phenotype	Gene(s)	Disorder	MOI
Corneal clouding	*ARSB*	MPS VI (OMIM 253200)	AR
	GALNS	MPS IVA	AR
	GLB1	GM1 gangliosidosis & MPS IVB (See *GLB1*-Related Disorders.)	AR
	GNPTAB	ML II & ML IIIα/β (See *GNPTAB*-Related Disorders.)	AR
	GNPTG	ML IIIγ	AR
	GNS *HGSNAT* *NAGLU* *SGSH*	MPS III	AR
	IDUA	MPS I	AR
Cornea verticillata (w/o retinal dystrophy)	*GLA*	Fabry disease	XL
Retinal dystrophy	*ALMS1*	Alström syndrome	AR
	BBS1 *BBS2* *BBS4* *BBS7* *BBS9* *BBS10* *BBS12* *MKKS* *MKS1* *TTC8* (~19 genes) [1]	Bardet-Biedl syndrome	AR
	CLN3 *CLN5* *CLN6* *CLN8* *CTSD* *CTSF* *DNAJC5* *GRN* *MFSD8* *PPT1* *TPP1*	Neuronal ceroid-lipofuscinoses (OMIM PS256730)	AR AD

AD = autosomal dominant; AR = autosomal recessive; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidoses; XL = X-linked

1. Listed genes represent the most commonly associated genes; at least 19 genes are associated with Bardet-Biedl syndrome (see Bardet-Biedl Syndrome).

Neurologic Findings

Because MLIV initially presents with impaired neurodevelopment in the absence of progressive features till later in life, individuals considered to have "cerebral palsy" should be evaluated for MLIV.

The neurologic abnormalities and the finding of widespread storage material in tissue biopsy could suggest other lysosomal storage disorders including mucolipidosis type I (OMIM 256550), mucolipidosis type II (see *GNPTAB*-Related Disorders), and the mucopolysaccharidoses (see Table 2).

The finding of white matter abnormalities and a thin dysplastic corpus callosum could suggest other inherited hypomyelinating leukodystrophies such as sialic acid storage disease (Salla disease). (See Free Sialic Acid Storage Disorders.)

Management

No clinical practice guidelines for mucolipidosis IV (MLIV) have been published.

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Mucolipidosis IV

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval by neuropsychologist • Eval for early intervention / special education
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Eyes	Ophthalmologic eval	To assess for vision deficits, corneal clouding, strabismus, cataract, retinal changes
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in patients w/ dysphagia &/or aspiration risk.
Renal	Blood cystatin C level	By early adolescence
Hematologic	• CBC • Iron studies	To assess for iron deficiency & anemia
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of MLIV to facilitate medical & personal decision making

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Family support/ resources	Assess: • Use of online family community established by the ML4 Foundation; • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

ADL = activities of daily living; CBC = complete blood count; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Mucolipidosis IV

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Hypotonia	Ankle-foot orthotics in individuals w/hypotonia & weakness of ankle dorsiflexion	PT & rehab can help strengthen core muscles & improve posture.
Spasticity & dystonia	• Orthopedics / physical medicine & rehab / PT/OT incl stretching to help avoid contractures & falls • Intramuscular botulinum toxin injections or oral medications for muscle spasticity & rigidity	• PT & rehab can help prevent permanent joint contractures. • Consider need for positioning & mobility devices, disability parking placard.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Abnormal vision &/or strabismus	• Surgical correction of strabismus • High-contrast black & white materials for those w/visual impairment	• Community vision services through early intervention or school district • Note: Corneal transplantation or scraping has not been successful because the donor corneal epithelium is eventually replaced by the abnormal host epithelium or the affected person's epithelium regrows.
Ocular irritation	Topical lubricating eye drops, artificial tears, gels, or ointments for management of intermittent ocular irritation seen frequently in younger children	• Use preservative-free drops only. • Consult ophthalmologist before treatment.
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Gastrointestinal	Establish care w/gastroenterologist for management of constipation & bile reflux (nonacidic in context of achlorhydria).	
Renal failure	Supportive care by nephrologist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Iron deficiency anemia	Iron supplementation as needed (e.g., oral ferrous sulfate)	Intravenous supplementation only in symptomatic persons

ASM = anti-seizure medication; OT = occupational therapy; 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.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - 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).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists such as a physical medicine and rehabilitation physician to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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.

Surveillance

Table 5. Recommended Surveillance for Individuals with Mucolipidosis IV

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	At least annually; more frequently if actively managing symptoms
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	Frequency dependent on eval & recommendations by physician or PT/OT
Development	Monitor developmental progress & educational needs.	At least annually; more frequently if actively managing symptoms
Eyes	Ophthalmology exam	Annually
Feeding	Evaluate feeding & growth.	At least annually; more frequently if actively managing symptoms
Renal	Monitor renal function w/cystatin C levels.	• Annually, or more frequently if active renal compromise is identified • Note: Creatinine levels are not sufficient to monitor renal function as muscle atrophy in MLIV will ↓ baseline levels.

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Hematologic	• CBC • Iron studies	Annually

CBC = complete blood count; OT = occupational therapy/therapist; PT = physical therapy/therapist

Agents/Circumstances to Avoid

Chloroquine may be contraindicated, based on published research in cultured skin fibroblasts from affected individuals [Goldin et al 1999].

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

Mucolipidosis IV (MLIV) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *MCOLN1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *MCOLN1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *MCOLN1* pathogenic variant, each sib of an affected individual has at conception 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 MLIV are not known to reproduce.
- No information is available regarding the ability of individuals with mild disease to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *MCOLN1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *MCOLN1* pathogenic variants in the family.

See Related Genetic Counseling Issues, **Population screening** for information about carrier testing in individuals of Ashkenazi Jewish descent who do not have a family history of MLIV.

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.

Population screening. Because of the high carrier rate in individuals of Ashkenazi Jewish descent, individuals of Ashkenazi Jewish heritage may choose to have carrier testing for the *MCOLN1* founder variants (c.406-2A>G and the 6.4-kb deletion). The combined carrier frequency of the two pathogenic variants common in persons of Ashkenazi Jewish descent ranges from 1:100 to 1:127 (see Prevalence).

Prenatal Testing and Preimplantation Genetic Testing

Once the *MCOLN1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MLIV 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.

- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
  Email: mps@mpssociety.org.uk
  www.mpssociety.org.uk
- **Mucolipidosis IV Foundation**

3500 Piedmont Road
Suite 500
Atlanta GA 30305
Phone: (877) ML4-5459 (654-5459)
Email: www@ml4.org
www.ml4.org

- **National MPS Society**
  Phone: 877-MPS-1001
  www.mpssociety.org
- **Norton & Elaine Sarnoff Center for Jewish Genetics**
  Phone: 312-357-4718
  Email: jewishgenetics@juf.org
  www.juf.org/cjg

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. Mucolipidosis IV: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MCOLN1	19p13.2	Mucolipin-1	MCOLN1 database	MCOLN1	MCOLN1

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 Mucolipidosis IV (View All in OMIM)

252650	MUCOLIPIDOSIS IV; ML4
605248	MUCOLIPIN 1; MCOLN1

Molecular Pathogenesis

The lysosomal storage of lipids and water-soluble substances in mucolipidosis IV (MLIV) is attributed to a transport defect in the late steps of endocytosis resulting from abnormal membrane components of endosomes. Endosomes shuttle lipids and proteins between the plasma membrane and the various cellular organelles. Nutrients bound to lysosomes for processing would be retained in these transition vesicles. Alternatively, it could indicate an increased rate of membrane recycling resulting from rapid degradation of malfunctioning protein complexes at the plasma membrane. Inability of cells to compensate for the missing cation channel function causes the defect in organization of white matter in the brain and reduces maintenance of cells in the retina and optic nerve. Inability to secrete gastric acid may be directly related to a defect in the operation of the acid-secreting H^+K^+ ATPase in stomach parietal cells.

Mechanism of disease causation. Loss of function

Table 6. Notable *MCOLN1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NG_015806	c.-1015_789del6434 (6.4-kb deletion)	--	Accounts for 18% of pathogenic variants in Ashkenazi Jewish persons [1]

Table 6. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_020533.2	c.406-2A>G	--	Accounts for 77% of pathogenic variants in Ashkenazi Jewish persons [2]
	c.694A>C	p.Thr232Pro	Assoc w/severe phenotype [Manzoni et al 2004]
	c.1222_1224delTTC	p.Phe408del	Causes mildest MLIV phenotype known [Altarescu et al 2002]
	c.1084G>T	p.Asp362Tyr	Assoc w/slower progression of retinal disease & relatively mild neurologic phenotype [Raychowdhury et al 2004]
	c.1406A>G [3] (g.9107A>G [4])	p.Asn469Ser	Causes atypical MLIV, in which affected persons walk independently & have better communicative skills [Altarescu et al 2002]
	c.1704A>T [5]	See footnote 5.	
	c.1615delG	p.Ala539ProfsTer41	Assoc w/mildest form of MLIV – isolated retinal degeneration & achlorhydria [Goldin et al 2008]

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. Deletion of exons 1 through 5 and part of exon 6; to date, only one individual homozygous for the 6.4-kb deletion has been identified [Bargal et al 2000, Bassi et al 2000, Sun et al 2000].
2. Approximately 60% of individuals with MLIV of Ashkenazi Jewish heritage in the US are homozygotes for the c.406-2A>G intronic acceptor splice site pathogenic variant. An estimated 33% are compound heterozygotes for this variant and the 6.4-kb deletion [Wang et al 2001, Goldin et al 2004a].
3. Base pair transition creates a new preferred splice acceptor site that results in a frameshift.
4. Variant designation that does not conform to current naming conventions
5. Near the donor site of intron 13; creates an alternative donor splice site that results in a frameshift [Dobrovolny et al 2007].

Chapter Notes

Author Notes

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Yulia Grishchuk obtained her PhD in Molecular Biology from Engelhardt Institute of Molecular Biology in Moscow, Russia. During her postdoctoral training at the Brain Mind Institute, EPFL, and University of Lausanne in Switzerland, she studied endocytosis and autophagy in neurotoxicity and neurodegeneration. She then joined Dr Slaugenhaupt's laboratory at Massachusetts General Hospital, where she continued her research of lysosomal dysfunction in neurodegeneration. Dr Grishchuk leads a laboratory working on therapy development for mucolipidosis IV.

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